Focus Issue.

The Management of Bipolar Spectrum Disorder

Guest Editor: Mark Agius.
Consulting Editor: Giuseppe Tavormina.
Editor-in-Chief: Professor Frank MC Besag.
ISSN 2047-1882 (Print) 2047-1890 (Online)

P7 “The heartland of psychiatry, revisited”
Guy Goodwin

P10 “The spectra of major and minor mood disorders”
Jules Angst

P237 “Craziness and Creativity”
Ahmed Hankir

P316 “Childhood bipolar disorder: diagnostic and treatment challenges”
Bernadka Dubicka
Focus Issue.
Cutting Edge Psychiatry in Practice:
The Management of Bipolar Spectrum Disorder

Guest Editor: Dr Mark Agius.
Consulting Editor: Dr Giuseppe Tavormina.
Editor-in-Chief: Professor Frank M.C. Besag.

Executive Group Members
Frank Besag (Chair)
Mark Agius
Uttom Chowdhury
Chinnaiah Yemula
Vishal Agrawal
Maxine Forrest
John Kedward
Gary Kupshik
Nadeem Mazi-Kotwal
Thilak Ratnayake

Editorial Board Members
Frank Besag
Mark Agius
Uttom Chowdhury
Chinnaiah Yemula
Vishal Agrawal
Ashok Bhiman
Alistair Burns
Carolyn Chew-Graham
Uttom Chowdhury
Gaurish Gaunekar
Chris Hollis
John Kedward
Gary Kupshik
Helen Lester
Nadeem Mazi-Kotwal
Thilak Ratnayake
Anthea Robinson
Samuel Stein
David Taylor
Ian Wong
Rashid Zaman

This journal is an initiative of South Essex Partnership University NHS Foundation Trust (SEPT)
Table of Contents

Introductory Articles

Foreward
Eugene Paykel

Introduction
Mark Agius

Part 1. Basic Concepts of the Bipolar Spectrum

An Introduction to the Bipolar Spectrum
Giuseppe Tavormina

The heartland of psychiatry, revisited
Guy M. Goodwin

The spectra of major and minor mood disorders
Jules Angst

Conversion from Unipolar to Bipolar Depression
Jonathan Rogers, Mark Agius

The temperaments and their relevance to bipolar spectrum disorders
Giuseppe Tavormina

Impulsivity in Bipolar Disorder
Mojca Zvezdana Dernovšek, Urban Groleger, Lilijana Šprah

Suicide and Suicide Prevention in Patients with Bipolar Disorders
Zoltán Rihmer

Is Bipolar Affective Disorder Underdiagnosed?
Shokoufa Kashani, Eva Bongards, Mark Agius

Unipolar Depression Versus Bipolar Disorder; An Overview
Gursharan Kashyap, Lucy Pauli

Overview of Bipolar Affective Disorder; Differences between Bipolar I Affective Disorder and Bipolar II Affective Disorder
Marina Mihaylova, Emil Mihaylov, Rakhee Vaja
# Part 2. Neurobiology of the Bipolar Spectrum

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain structural changes in bipolar disorders – interplay between illness and lithium treatment</td>
<td>59</td>
</tr>
<tr>
<td>Tomas Hajek</td>
<td></td>
</tr>
<tr>
<td>Lithium: The Complex Mechanisms of Action of the Simplest Metal</td>
<td>64</td>
</tr>
<tr>
<td>Luchezar Hranov</td>
<td></td>
</tr>
<tr>
<td>Neurocognitive impairment, psychosocial stress, and functional adjustment in bipolar disorder: Implications for disability policy</td>
<td>74</td>
</tr>
<tr>
<td>Boaz Levy, Emily Manove</td>
<td></td>
</tr>
<tr>
<td>The Bipolar Spectrum and Psychoneuroimmunology: Implications for Diagnosis and Treatment</td>
<td>89</td>
</tr>
<tr>
<td>Moritz Muehlbacher, Aye-Mu Myint</td>
<td></td>
</tr>
<tr>
<td>Mood Instability, Bipolar Disorder and Disadvantages of Antidepressants</td>
<td>98</td>
</tr>
<tr>
<td>Rudy Bowen, Verinder Sharma</td>
<td></td>
</tr>
<tr>
<td>Genetics of Bipolar Disorder: an Overview</td>
<td>104</td>
</tr>
<tr>
<td>Stefano Porcelli, Raffaele Salfi, Alessandro Serretti</td>
<td></td>
</tr>
<tr>
<td>Epigenetics of bipolar disorder</td>
<td>116</td>
</tr>
<tr>
<td>Peter Pregelj</td>
<td></td>
</tr>
<tr>
<td>Neurotransmitter and Intracellular Mechanisms of Bipolar Disorder; an explanation of Kato's Theory of Mood-stabilising Neurons</td>
<td>123</td>
</tr>
<tr>
<td>James Edmonds, Mark Agius</td>
<td></td>
</tr>
<tr>
<td>fMRI comparison between bipolar I and bipolar II disorders</td>
<td>131</td>
</tr>
<tr>
<td>Melissa Ng</td>
<td></td>
</tr>
</tbody>
</table>

# Part 3. Pharmacology of Bipolar Disorder

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroprotective and Neurotrophic Effects of Lithium on Bipolar Disorder</td>
<td>136</td>
</tr>
<tr>
<td>Cristian Vargas, Eduard Vieta, Carlos López-Jaramillo</td>
<td></td>
</tr>
<tr>
<td>The Place of Antidepressant Medication in the treatment of Bipolar Affective Disorder</td>
<td>146</td>
</tr>
<tr>
<td>Gursharan Kashyap, Clare Thakker</td>
<td></td>
</tr>
<tr>
<td>Antiepileptic drugs in the treatment of Bipolar Disorder</td>
<td>151</td>
</tr>
<tr>
<td>Mark Lyons, David Taylor</td>
<td></td>
</tr>
</tbody>
</table>
The Role of Atypical Antipsychotics in the Treatment of Bipolar Disorder
Jonathan Rogers, Rashid Zaman

Part 4. Diagnosing Bipolar Disorder

Treatment and early Intervention in Psychosis Program (TIPP)
Philippe Conus

Proving that a patient has bipolar disorder
Mark Agius, Helen Murphy

Bipolar disorder and Acute Mania
Richard Yasotharan

Bipolar III Disorder
Holly Cakebread

Rapid Cycling Bipolar Affective disorder: Diagnosis and management - A brief review
Madhavan Seshadri, Daniel Davies

Some somatic symptoms are important evidence for an early diagnosis of bipolar spectrum mood disorders
Tavormina Giuseppe

Mixed Affective States: A Diagnostic and Therapeutic Challenge
Saurab Singh, Jasmine Ho, Mark Agius

Part 5. Treatment of Bipolar Disorder

Treatment of Acute Mania: An article for the General Practitioner
Olivia Balding, Soosamma Varghese

Lithium therapy - from monitoring to shared care
Helen Wear, Clare Holt, Mark Agius

The Treatment of Bipolar Depression
Jenny Hopwood, Mark Agius

Psychotherapeutic interventions and bipolar disorder: impact of bipolar disorder on individual’s families and wider society.
Michelle Brandford, Sharn Tomlinson

Ongoing Management of Bipolar Disorder
Snehal Khajuria
Part 6. Recovery from Bipolar Disorder

Self-management in the treatment of bipolar disorders
*Benjamin Philip Martin*

Psychoeducation for Bipolar Disorders Patients: The “Porta Aberta” Programme
*Catarina Klut, Salomé Xavier, João Graça, Gonçalo Carreteiro and João C. Melo*

‘Craziness and Creativity’: A Review of Bipolar Disorder and the Artistic Temperament
*Ahmed Hankir, Mark Agius & Rashid Zaman*

‘The Melodies of Manic-Depressive Illness’: a Case Study of Bipolar Disorder
*Ahmed Hankir*

Review and Overview: Autobiographical Narrative and Psychopathology
*Ahmed Hankir*

Part 7. Comorbidities and Bipolar Disorder

Comorbidity of Bipolar Affective Disorder and Obsessive-Compulsive Disorder
*Laura Darby, Mark Agius & Rashid Zaman*

Migraine and Bipolar Disorder as CoMorbid Disorders
*Jonathan Holland, Mark Agius*

Bipolar Affective Disorder and Substance Abuse
*Anton Grech*

Bipolar Disorders and Borderline Personality Disorders: Two Sides, One Coin
*Sandro Elisei, Norma Verdolini, Serena Anastasi*

The Overlap of Pervasive Developmental Disorders and Bipolar Disorder in young people
*Mai Uchida, Emily Gray, Gagan Joshi*

ADHD and bipolar disorder among adolescents: Diagnostic traps for the unwary
*S. Rozencweig, Nicholas Zdanowicz, A. Myslinski, Christine Reynaert, Denis Jacques*

How to manage a patient with bipolar who is starting to develop cognitive decline as a result of dementia
*Krzysztof Krysta, Anna Sobieraj, Leontyna Wylężek, Mariusz S. Wiglusz, Wiesław J. Cubała*

Bipolar Affective Disorder and Epilepsy
*Mariusz S. Wiglusz, Mark Agius, Krzysztof Krysta, Wiesław J. Cubała*
Bipolar Disorder and Anxiety
Sophie Butler

Part 8. Bipolar Disorder in Different Situations

Relationship between postpartum mood disorders and bipolar disorder based on a case report of a patient with postpartum psychosis
Agnieszka Bratek, Julia Beil, Krzysztof Krysta, Anna Bocheńska

Childhood bipolar disorder: diagnostic and treatment challenges
Bernadka Dubicka

Bipolar Disorders in Adolescents
Nicholas Zdanowicz, Denis Jacques, David Tordeurs, Christine Reynaert

Correlates of disability in depressed older adults with bipolar disorder
Ariel Gildengers, Curtis Tatsuoka, Christopher Bialko, Kristin A. Cassidy, Philipp Dines, James Emanuel, Rayan K. Al Jurdi, Laszlo Gyulai, Benoit H. Mulsant, Robert C. Young, Martha Sajatovic

Treatment of bipolar disorder in pregnancy and post partum
Marjeta Blinc Pesek

Bipolar Disorder, Depression and Childhood Adversity
Jina Pakpoor, Mark Agius

Part 9. Final Summary Chapters –Lessons for GPs

Understanding The Bipolar Spectrum: Implications for Management and Diagnosis in Primary Care
Dean Hanafy, Mark Agius

Bipolar Spectrum: Consequences for the development of services
Mark Agius

The Bipolar Spectrum: Consequences for Neurobiology
Mark Agius, Shermayne Ng

Some useful web resources for depression and bipolar disorder
Sarah Chadwick

Bipolar Disorder – guidance on recognition in Primary Care
Daniel Dietch, Daniel Martin, Daniel J Smith, Carolyn Chew-Graham
Foreword

Eugene Paykel MD FRCP FRCPsych FMedsSci
Emeritus Professor of Psychiatry
University of Cambridge

Over the last 20 years there has been increasing recognition that bipolar disorder is often a very severe and potentially disabling psychiatric condition. This has been accompanied by an increase in research into many aspects, ranging from molecular genetics to treatment and outcome. The boundary between unipolar and bipolar affective disorder has become less clear than we once thought, as milder and sub-threshold bipolar forms have become recognised. The range of available treatments has expanded, with recognition of mood-stabilising effects of some antiepileptic drugs, and application of psychological approaches such as cognitive therapy and psychoeducation. The specific indications and best places in practice of some of the newer treatments are still in the process of becoming well defined. In the UK, as mental health specialist services have become focussed on severe disorders, patients with bipolar disorder have become important in clinical management for all members of the mental health team.

Dr Mark Agius, guest editor of this issue, has a very high profile in psychiatric postgraduate education. He organises many international symposia and meetings and he has a wide network of British and European contacts, whose expertise he has made full use of in this issue. The authors include the two best known senior academic experts on the disorder on this side of the Atlantic, Jules Angst and Guy Goodwin.

The topic coverage in this issue is very wide. The emphasis is particularly practical, for those who treat and manage patients with the disorder. Papers range through basic concepts, neurobiology, pharmacology, diagnosis, treatment, recovery, comorbidity, problems in different situations and lessons for general practitioners.

I am pleased to commend this issue as an excellent update for all involved in the treatment and management of patients with this often severe and recurrent disorder.
Introduction

Mark Agius  
Guest Editor

Bipolar Affective disorder is a very common condition in Mental Health Services in both Primary and Secondary Care. However, it is often not suspected and consequently it is both underdiagnosed and inappropriately managed. This is a cause for concern because patients who are inadequately treated for bipolar disorder can be at high risk of suicide. Patients with bipolar disorder are often misdiagnosed as having recurrent unipolar depression; the explanation for this is that although they often have recurring episodes of hypomania and depression, the hypomania is not identified by the doctor and misinterpreted as normality by the patient.

Hagop Akiskal has made the following comments about this situation. “Melancholia as defined today is more closely aligned with the depressive and/or mixed phase of bipolar disorder. Given the high suicidality from many of these patients, the practice of treating them with antidepressant monotherapy needs re-evaluation” (1).

The consequence of this was his development of the concept of the bipolar spectrum, describing among others Bipolar I, core manic-depressive illness and Bipolar II, depression with discrete spontaneous hypomaniac episodes (2), hence distinguishing both these conditions from unipolar depression. The development of the concept of the bipolar spectrum has led to the identification of subgroups of bipolar patients and the identification of groups of patients who have particular suicidal risk. It has also raised the possibility that some unipolar depressed patients may develop bipolar disorder. All these issues, and the consequent differences in treatment between unipolar and bipolar disorder are dealt with in this issue. What also arises is the fact that bipolar illness is linked to a number of co-morbidities which make it particularly difficult to treat. This difficulty is also discussed in the issue, together with bipolar disorder in different situations. We describe interventions in the psychological field which alleviate the distress caused by this disorder and promote patient resilience. Further, we discuss the consequences for the design of mental health services to deal with this disorder.

The bipolar spectrum is a group of clinical conditions. It is very important to work out the underlying neurobiology if we are fully to understand what is happening in bipolar disorder. We need to answer a number of questions. Does unipolar depression really develop into bipolar disorder? Is the bipolar spectrum a description of the progression of an illness from an early to a more serious late stage of the same illness? What are the biological processes involved? In this issue we also endeavour to present what we know about the answers to these important questions.

I thank all the contributors and my co-Editor Giuseppe Tavormina, as well as the CEPIP Editor-in-Chief Prof. Frank Besag and the CEPIP Editorial Board for making the production of this publication a very enjoyable task.

Mark Agius

References

Part 1. Basic concepts of the Bipolar Spectrum

An Introduction to the Bipolar Spectrum

Giuseppe Tavormina, M.D.
President of “Psychiatric Studies Center” (Cen.Stu.Psi.)
Piazza Portici, 11 - 25050 Provaglio d’Iseo (BS) – Italy
E-mail: dr.tavormina.g@libero.it

Abstract

Affective or mood disorders form part of a spectrum of bipolar disorders. Here we describe such a spectrum. We also describe the main diagnostic markers and give an overview of the need to achieve early diagnosis with appropriate treatment.

Key words: bipolar spectrum, affective disorders, early diagnosis, treatment.

Affective disorders, or disorders of the bipolar spectrum (including sub-threshold forms) are very common. Indeed, they are more common than it is usually believed, especially when we include the sub-threshold forms. Hence, these conditions are often underestimated epidemiologically, under-diagnosed, and ineffectively treated or untreated (Agius, 2007; Tavormina, 2007). Inadequate diagnosis and consequent inadequate treatment of these illnesses can lead to various public health issues, with serious consequences, including abuse of substances, employment difficulties, suicidal risk and problematic or criminal behaviour. (Akiskal-Rihmer, 2009; Tavormina, 2010).

Mood in a person who is euthymic is stable; in mood disorders, the mood “swings” between depression and euphoria/irritability and therefore in mood disorders there is “unstable mood”.

It is essential to emphasize that depressed mood is subject to the normal oscillation of the tone of mood. Hence patients should be only diagnosed as depressed when they complain of sadness or low mood for a period of at least two weeks. Often, a depressive episode is in fact only one phase of a broader “bipolar spectrum of mood”, in which instability of the mood is the main component. The average age of onset of an episode of instability of mood is usually relatively early, between 20 and 40 years. However a significant number of these illnesses start very early or very late (the first episode being in adolescence or after age 50). About 20% of the population presents a picture of “mood instability” (including the subsyndromal conditions or temperaments). Epidemiological studies have found an incidence of depression among women which is double that of men.

Here we present a classification of mood disorders, based on Akiskal’s original proposition of a spectrum of disorders, and the proposal of the present author (Tavormina, Agius, 2007), which ranges from bipolar I disorder at one end to unipolar depression at the other end, while including all the other types of instabilities between. We have excluded post-traumatic stress disorder for the sake of clarity, and we have accepted the subsyndromal ‘temperaments’ as being within the full spectrum. We have re-arranged the different states, when compared to our previous article, to indicate that items 1-6 are all conditions of the bipolar spectrum which carry high suicide risk, and hence need effective treatment, but of course, many patients with unipolar depression, whether recurrent or not also may have a high risk of suicide.

1. Bipolar I [mania/depression]
2. Rapid cycling bipolarity
3. Bipolar II [hypomania/depression]
4. Bipolar III [Bipolarity induced by anti-depressants]
5. Mixed Dysphoria (depressive mixed state)
6. Agitated depression (a mixed affective state)
7. Cyclothymia
8. Cyclothymic temperament
9. Hyperthymic temperament
10. Depressive temperament
11. Recurrent depressive Disorder
12. Unipolar Depression.
(Based on Tavormina, Agius, 2007).

Assessment of the patient

The main ‘markers’ which are important in the early diagnosis of mood disorders and which should be assessed during the clinical interview, are as follows.

A family history of bipolar disorders (or suicide).
Previous episodes of hypomania/ euphoria/ irritability.
A history of 3 or more depressive episodes in the last few years.
Acute initiation of the disorder or flare-up of the illness in certain seasons (especially winter and/or summer).
Previous episodes of cyclothymia (oscillations of mood which are constant and continuous).
The presence of comorbid anxiety (GAD, PAD, OCD, Social phobia and simple phobia: because the symptoms of anxiety should not be clinically considered separately from a disturbance of the bipolar spectrum).
Presence of frequent headache, muscle tension, stomach somatisations.
A history of substance abuse (periodic or continuous).
A history of disorders of appetite.

Clinical evaluation

In order to make a correct diagnosis of disturbance of mood within the bipolar spectrum it is essential to evaluate the longitudinal psychiatric history of the patient carefully, with particular attention to any sub-threshold symptoms and careful evaluation of the patient’s temperament and the family psychiatric history (Tavormina, 2007).

The main symptoms present in mood disorders are the following.

Hyperactivity (euphoria) alternating with periods of serious psychomotor retardation (apathy).
Depressed mood and/or irritability.
Antisocial behaviour.
Substance abuse (alcohol and/or drugs).
Disorders of appetite.
Suicidal ideation.
A sense of despair.
Anhedonia and widespread apathy.
Delusions and hallucinations.
Hyper/hypo-sexual activity.
Insomnia/ hypersomnia.
Reduced ability to concentrate.
Mental overactivity.
Gastrointestinal disorders, headaches, and various somatic symptoms.

It is essential at the beginning of the clinical interview to evaluate the present clinical situation which led the patient to consult the psychiatrist, and to assess what had led up to the present situation, including when the first symptoms of mood disturbance started, even though the first symptoms might have been very attenuated.

The co-presence of various types of somatic symptoms, as well as the presence of substance abuse should suggest the possibility of the presence of a condition within the bipolar spectrum.
It is extremely important to evaluate clinically the somatic symptoms described by the patient by conducting a physical examination (Tavormina, 2012). The chronic presence throughout life in these patients of some somatic symptoms, (especially: colitis, gastritis and headache) should draw the attention of clinicians (both psychiatrists and primary care physicians) to the possibility of the presence of an illness within the bipolar spectrum, and hence may be important in the early diagnosis of a bipolar spectrum mood disorder (Tavormina, 2011).

Evaluation of the characteristic temperament of the patient at the beginning of his history of mood disorder is an essential in making a correct diagnosis and providing the correct therapy. Rihmer and Akiskal (Rihmer, Akiskal, 2009) have commented: “The sub-threshold types of temperament have an important role in the evolution of clinical episodes of mood disorder in that they indicate the direction of the polarity and the formation of symptoms of acute mood episodes …… They also significantly affect the course and development of these pathologies, thus influencing the suicidal risk and other forms of self-destructive behaviours such as substance abuse and eating disorders”.

Mood disorders can cause substance abuse as an attempt to self-medicate. The abuse of substances (alcohol, cannabis, cocaine and cannabinoids, etc.) may, in turn, cause depression, dysphoria, anxiety and the so-called “amotivational syndrome”. The concomitant abuse of substances in patients with mood disorders can make such patients resistant to treatment and lead to a worse prognosis. Patients who present with substance abuse always need to be screened for the presence of bipolar spectrum disorders: abuse of substances needs to be considered as a possible symptom of bipolar spectrum disorder, not as a separate illness.

Concluding remarks

The consequences of the lack of recognition and consequent lack of treatment of a mood disorder can include higher risk of suicide, reduction in the expectation and/or the quality of life (personal, family and work), increased loss of working days, increased use of health care resources, including the resources needed to manage concurrent diseases; the mood can finally become chronic and the clinical picture can become worse. The pharmacological therapy of mood disorders may require polypharmacy with mood stabilisers (mainly: lithium, carbamazepine, valproate, gabapentin, oxcarbazepine, lamotrigine, topiramate, olanzapine or pipamperone) and antidepressants (mainly: SSRIs or SNRIs). One should never use antidepressants alone and/or in combination with benzodiazepines (nor should benzodiazepines alone be used for a long period), in order to avoid an increase in mood instability and evolution toward states of dysphoria (Agius, 2011; Tavormina, 2010, 2012). The correct maintenance therapy should be assessed on an individual case-by-case basis, depending on the clinical picture, and it should always include a mood stabiliser which may, if appropriate, be combined with low or small doses of an antidepressant. Frequent necessity of the patient to resort to the use of benzodiazepines is a tangible sign of clinical deterioration, which must require both patient and psychiatrist to consider the need for adjusting the dosage of maintenance therapy.

GP Comment

What have I learned from this paper?

As a jobbing GP, I found the concluding points helpful – the use of benzodiazepines is a tangible sign of clinical deterioration. However, finding a correct maintenance dosage within a primary care environment would be challenging. Re-classifications recommendations may cause confusion as which one should we follow. Currently a GP would refer to NICE guidelines which are dated July 2006. It highlights the importance of being aware & clinically recognising mood instability.

Dr Vishal Naidoo, GP.
References

The heartland of psychiatry, revisited

GUY M GOODWIN, DPhil, FRCpsych, FMedSci
University Department of Psychiatry, Warneford Hospital, Oxford

Correspondence to:
Guy M. Goodwin,
WA Handley Professor of Psychiatry,
University Department of Psychiatry
Warneford Hospital
Oxford OX3 7JX

Tel: 01865 226451
Fax: 01865 204198
e-mail: guy.goodwin@psych.ox.ac.uk

Abstract

In 2007 John Geddes and I published an editorial in the British Journal of Psychiatry in which we highlighted the adoption of schizophrenia as psychiatry’s heartland and its largely negative consequences for the practice of psychiatry as a distinctive medical specialty (1). It did not have a very wide impact. I received a few friendly emails (or maybe people even wrote letters then) but it has rarely been cited.

I suppose there was a kind of Schadenfreude, therefore, when it was made public that in 2011, in England and Wales, just 83% of the 478 first year (CT1) vacancies to train in psychiatry were filled. Earlier data showed that of those filling such posts, only 14% had been trained in the UK (2). This represented the lowest ratio of home qualified doctors training for any medical specialty. These findings suggest that psychiatry has become the least attractive specialty in medicine for UK graduates. And these are, of course, the graduates who will have encountered UK psychiatry as medical students.

It is certainly the case, and it was really what spurred me to make the connection in the first place, that recruitment of academically inclined doctors had declined to a trickle in a centre like Oxford that I know well. The Royal College of Psychiatrists, having slowly woken up to the problem, has now implemented a strategy to try and reverse the situation.

However, the other argument was that bipolar disorder is the heartland of psychiatry, whatever the parochial problems we face for psychiatric recruitment in this country. Of course, we had no desire to diminish the absolute importance of schizophrenia (I was asked quite seriously by one colleague if I disliked schizophrenic patients), just to restore the balance with bipolar disorder and to see how its challenges broaden the scope and interest of psychiatry as a medical specialty. It remains the case that, in almost every respect, bipolar disorder would have afforded psychiatry a model within which the medical role is easier to define than for schizophrenia, and the development of which could have informed psychiatric services in general. There could have been and still could be a better balance between medical, psychological and social care. We made this argument from a number of perspectives. First, the course of illness in bipolar disorder allows a much more meaningful distinction between the needs of patients for sympathetic inpatient respite care when acutely ill and for outpatient-based interventions when well. Second, its treatment is less amenable to one-size-fits-all social care, and bipolar disorder is more likely to challenge clinicians to understand the illness and its treatment in a therapeutic relation with individual and autonomous patients. Third, the use of rational pharmacology linked with the facilitation of behaviour change is the key modern activity of physicians treating all common illnesses.

The final point we made in 2007, was that treatment of bipolar disorder demonstrably requires medical expertise in which we should take pride. This argument for expertise can now be formalized.
on the basis of a pragmatic trial over 6 years in Denmark where specialized care for bipolar patients was shown to be superior to standard care (3). The need to develop expert services for bipolar patients is underlined by the developments in pharmacotherapy and the emphasis in treatments on education and behaviour rather than more conventional 'therapy'. There is a distinction between acute and long-term medication and there is active involvement by patients in managing acute exacerbations of symptoms. Psychological treatments complement the medical approach, and enhanced care is an objective for all patients. Therefore, prescribing for and managing bipolar patients requires the key elements of expertise: knowledge, skill and experience (4).

The broader implications of our failing model for psychiatric care, or at least for the place of psychiatrists within it, remain, however. The same mentality that neglects specialist diagnosis and treatment replaces it with something vacuous and imprecise. We previously expressed the view that our heartland must be fruitful, not a barren wilderness of good intentions. Consider the following amazing piece of prose (5):

New Ways of Working is what it says – new ways of working – rather than a single service model or structure that has to be adopted. It recognises that services catering for the different types of needs of service users across their lifespan and differing demographics and geography will need different configurations to manage their task most effectively. However, the underlying principles relating to using the skills of the workforce in the most productive way are common. It is about achieving cultural change; a shift in the way teams think about themselves, the skills of the individuals within them, and the reasons they are there. However, cultural change is difficult to achieve and it is difficult to measure the extent to which it has been achieved.

It has all the charm of a pamphlet extolling the virtues of a Soviet collective farm. When I get an outstanding medical student express an interest in psychiatry, would I be wise to have them read these inspiring words, ending as they do with a sentence that embodies exhaustion and futility?

The role of doctors will undoubtedly evolve as knowledge, and perverse ignorance become more universally available to all via the internet. The role of the psychiatrist must be to relate real advances in understanding and practice to the care that is actually delivered. At present it seems rather to be to sit in endless meetings and take responsibility for other people's decisions. It becomes more not less important that psychiatrists have an academic understanding of what they are doing and a clear role within the services in which they work. Re-discovering the need for expert treatment in bipolar disorder could be a good place to start.

**GP Comment**

**What have I learned from this paper?**

I found this article very thought provoking.

The management of bipolar disorder is similar to all long-term conditions as it requires effective teamwork and excellent communication between specialist secondary care, primary care, psychological and social care.

There is an undoubted need for specialist advice in diagnosis, drug treatment plus speedy access to care for acute episodes.

Facilitation of behavioural change, as for all long-term conditions treated in primary care, is a challenge. Also patients on lithium need regular blood tests.

A trusting relationship with the patient, teamwork and, most important, concordance of advice from all professionals and carers help to improve patient compliance and health outcome. Successful teamwork benefits professionals too, by increasing work satisfaction.
The challenge in the hurly-burly of the modern NHS is to devote time to team building. I hope all newly-appointed GP commissioners will seize the gauntlet and support the creation of effective teams.

It is very unfortunate that currently psychiatry is the least attractive speciality to pursue but let us hope prospective candidates will read this article, as they are vital members of the team!

Dr Anthea Robinson, GP, Bedfordshire.

References


Declarations of interest.

GG is a psychiatrist and holds a Honorary Consultant contract with the Oxford Health NHS Foundation Trust. He has received honoraria from AstraZeneca, BMS, Lundbeck, Sanofi-Aventis, Servier, holds shares in P1vital ltd; has served on advisory boards for AstraZeneca, BMS, Boehringer Ingelheim, Cephalon, Janssen-Cilag, Eli Lilly, Lundbeck, Otsuka, P1Vital, Roche, Servier, Shering Plough, Shire, Takeda, Wyeth and acted as an expert witness for Eli Lilly.

The opinions and views expressed in this article are those of the author and do not represent those of any other organisation.
The spectra of major and minor mood disorders

Jules Angst, M.D.
Zurich University Psychiatric Hospital.

Abstract

There is growing evidence supporting the concept of a diagnostic spectrum reaching from depression via bipolar II and bipolar I disorders to mania and of a severity spectrum from psychotic via major and minor syndromes to normal mood swings. By nature, lows in mood are more distressful than highs; as a consequence, bipolar disorders and mania/hypomania are under-reported and underdiagnosed. An early diagnosis of bipolarity is essential for correct treatment and can help reduce secondary substance use, prolong life, improve quality of life and reduce costs.

Key words: spectrum, mania, depression, bipolar disorders, diagnosis, comorbidity, mortality

Introduction

Because depression is very distressing, a depressed person is motivated to seek treatment and to describe their symptoms, which makes the condition relatively easy to diagnose. Hypomania, by contrast, is often experienced as a heightened state of well-being (enhanced mood, increased energy/activity) and is far less likely to be mentioned spontaneously in a consultation with the doctor. As a result bipolar disorder tends to be underdiagnosed; this is especially the case for bipolar II and minor bipolar disorders. It has been found that 8 to 10 years may intervene before patients with bipolar depression receive a correct diagnosis of their disorder. Moreover, recurrent unipolar depression (i.e. without hypomania or mania) remains an uncertain diagnosis lifelong. Each new episode carries the risk of a switch into hypomania; in a 25-year prospective study, the risk of a diagnostic change from depression to bipolar disorder was found to be 1.25% per year and to remain constant with age (1).

In terms of consequences, bipolar affective disorder is more severe than major depression, as measured by lifelong recurrence and comorbidity with other psychiatric disorders (especially anxiety and secondary substance use disorders), and the risk of developing dementia in old age. It is also more associated with certain somatic disorders, such as diabetes, hypertension and cardiovascular disease. Finally, mortality rates are higher in patients with bipolar disorder compared to those with depression, although the suicide risk is lower among patients with type I bipolar disorder (2).

Depressed patients are diagnosed as having bipolar disorder if they have experienced hypomania or mania at some time in their lives. In population studies, lifetime prevalence rates rise markedly with repeated interviews. In three large epidemiological investigations (NCS-NCS-R, EDSP and NEMESIS) (3-5) the first interview wave found lifetime rates of depression of between 11.8% and 17.1% and of bipolar disorder between 1.6% and 1.9% in the general population. At the second or third interviews, five to ten years later, the rates for depression had increased to between 21.2% and 28.1% and those for bipolar disorder to between 2.6% and 5.2% (6-8). These figures may well still be too low: a New Zealand study (five interviews up to age 32) reports a lifetime prevalence rate for depression of 41.4%. The authors found forgetting to be an enormous source of error in the reporting of lifetime rates (9). We are all forgetful, but the longer we know our patients the safer is the diagnosis. Re-analyses of the EDSP and NCS-R studies referred to earlier showed that about 40% of persons with DSM-IV MDD manifested signs of subthreshold bipolarity (10,11).

The correct diagnosis of bipolar illness is essential if we are to provide appropriate treatment, including long-term secondary prophylaxis; early diagnosis and treatment can also contribute significantly towards limiting the high human and economic costs arising from the non-recognition of these serious and highly comorbid disorders (12).
The spectra of mood disorders

The development of a validated bipolar spectrum concept, combining dimensional and categorical principles, can provide more precise diagnoses (including subthreshold groups), allow differential treatment of affective disorders, stimulate research and help reduce the under-recognition of bipolarity.

Today the term ‘bipolar spectrum’ is used in two complementary senses:

(a) a spectrum of severity, which embraces psychotic and non-psychotic major and minor bipolar disorders (including bipolar dysthymia, recurrent brief and minor depressions), cyclothymic disorders, hypomania and, at its problematic broadest, even borderline personality disorders and cyclothymic temperament;

(b) a proportional diagnostic spectrum, which considers the two components, mania and depression, first on the level of major mood disorders – major depression (D) bipolar II disorder (Dm), bipolar I disorder (MD), mania with mild depression (Md) and pure mania (M) (13) – and second on the level of minor mood disorders: minor depression and its chronic form dysthymia (d), minor bipolar disorder (md) and hypomania (m).

This proportional model is an extension of Kleist’s concept of bipolar disorder as a combination of the two monopolar disorders, depression and mania (14,15). This model has proved fruitful not only in incorporating bipolar I and bipolar II disorders but also in differentiating mania with or without mild depression (Md/M) from bipolar I disorder (MD). Mania with and without mild depression are especially found in adolescents (16). Mania differs from bipolar I disorder in terms of family history, course and suicide risk just as, on the subthreshold level, hypomania differs from minor bipolar disorder or cyclothymic disorder in terms of family history and temperament.

Both the severity and the proportional bipolar spectrum concepts are dimensional in nature, having no natural categorical subgroups. Diagnostic concepts of psychiatric syndromes are purely descriptive and cannot constitute diseases (17). Categories are obviously necessary for communication purposes and for treatment decisions, but epidemiological and clinical studies have demonstrated that depressive and hypomanic/manic symptoms and syndromes manifest on a continuous distribution from normal to pathological. Moreover, in a 20-year follow-up, patients with type I and type II bipolar disorders were found to spend about half the time in subthreshold affective conditions, and these were dimensional, involving the full range of symptom severity of depression and hypomania (18).

To this we should add a third dimension consisting of personality. Most healthy people experience depressive and hypomanic symptoms and many can be characterised by normal temperaments (depressive, hypomanic or cyclothymic) or the corresponding abnormal affective personality disorders (PD) as conceptualised by Kretschmer 1921 (19). Temperament and affective PD are basically inborn and, although closely associated with phasic or chronic affective disorders, should be clearly distinguished from them. Temperament and affective personality disorders are depicted as the basis of the two-dimensional spectrum (see Fig. 1).
Difficulties in diagnosing bipolarity

The dimensional nature of the mood spectrum raises the question of the correct cut-off levels for caseness (20). All human beings experience diurnal and seasonal mood changes. As with blood pressure, abnormality is difficult to define and changes with the advance of the frontiers of knowledge. It is generally agreed that the DSM-IV criteria for hypomania (21) are too strict (not sensitive enough) and not based on empirical evidence (not validated). All aspects of the definition of hypomania/mania are therefore under discussion in the preparation of DSM-5. For instance it is now proposed that the exclusion criterion of antidepressant-induced hypomania should be dropped. Furthermore increased activity/energy (hitherto restricted to elevated and irritable mood) is to be added to criterion A. For the diagnoses of subthreshold bipolar disorders, a reduced number of required symptoms as well as a minimum duration of 2 days are being considered. As with depression, brief spells of hypomania (1–3 days) are far more common than manifestations lasting 4 days or 1 week. In order to improve the recognition of bipolarity, we have proposed a subdiagnostic concept consisting of a few hypomanic symptoms of brief duration associated with a lifetime diagnosis of depression.

Today, psychiatry still lacks empirically validated definitions of hypomania and minor depression, which will allow early recognition of major and minor bipolar disorders. Up to half of all patients treated for depression were found to have “minor” or “subthreshold” conditions not meeting full DSM-IV criteria (22). Fortunately, DSM-5 will introduce operationally defined subthreshold conditions. The promising bipolar severity spectrum concept can be discredited, however, by uncritical generalisations and over-inclusiveness. Nevertheless, we can safely assume that the prevalence of bipolar disorders is seriously under-reported and that the burden of bipolar disorder, which the World Health Organisation ranks far lower than that of depression, will, as a consequence, have to be reassessed. The treatment of subthreshold bipolar disorders is a future topic of research; no controlled studies on drug treatment in this field have yet been performed. It would be unscientific to apply the
results from drug trials in major mood disorders to the treatment of minor disorders without new testing.

Finally, the mood spectrum is also embedded in the spectrum of functional psychoses, including schizophrenia, schizoaffective and affective disorders. Mood-incongruent affective psychotic disorders are the bridge to the schizophrenic spectrum. Moreover, in agreement with clinical genetic studies (23), modern molecular genetic studies demonstrate that there is no clear-cut distinction between schizophrenia and bipolar affective disorder; they share many clinical and genetic features (24).

Conclusions

There is growing clinical evidence that the spectrum approach, with its dimensional nature, offers a real alternative to the traditional Kraepelinian dichotomy of schizophrenia v. manic-depressive insanity (25) and the unipolar–bipolar dichotomy.

The proposed three-dimensional mood spectrum model unifies categorical classification, which is essential, with a dimensional view, which is true to nature; both are needed and both are empirically testable. Patients with minor mood disorders (minor bipolar disorder, minor depression, hypomania), many of whom seek treatment, deserve much more attention.

GP Comments

What have I learned from this paper?

Comment 1.

There is good evidence that there is a ‘spectrum’ of mood disorders from unipolar depression to forms of bipolar disorder. A three-dimensional model incorporating mood spectrum severity and personality is a helpful way of understanding this complexity. It is also interesting that some features overlap with schizophrenia.

It is important to appreciate that Bipolar II – of which there may be a number of undiagnosed patients on a GPs list – is not ‘bipolar lite’ and carries a higher suicide rate than Bipolar I. However, an important issue around diagnosing ‘milder’ bipolar spectrum illness (not Bipolar I or II) is that there is insufficient evidence to guide us in treatment.

Thus, the challenge for GP’s is recognising those patients with ‘depression’ who may be on the bipolar spectrum – being alert for hypomania and mania – whilst being cautious not to medicalise normal personality traits and reactions to stressful life events. In this respect, GPs are uniquely placed to re-evaluate our patients over time.

Dr Daniel Dietch, Lonsdale Medical Centre, London.

Comment 2.

In terms of consequences, BPD is more severe than major depression as measured by lifelong recurrence and comorbidity. I also learned that mortality is higher in patients with BPD than in unipolar depression. This highlights the importance, as a GP, of being vigilant for symptoms of bipolar in patients with depression, as correct diagnosis and management is of major importance.

Dr Damandeep Kochhar, FY II GP Trainee.
References


Conversion from Unipolar to Bipolar Depression

Jonathan Rogers2,4 & Mark Agius1,3,5

1. Department of Psychiatry, University of Cambridge, Cambridge, UK
2. School of Clinical Medicine, University of Cambridge, Cambridge, UK
3. South Essex Partnership University Foundation Trust, UK
4. Gonville and Caius College, University of Cambridge, Cambridge, UK
5. Clare College, University of Cambridge, UK

Abstract

Many studies have demonstrated that major depressive disorder has a tendency to convert to bipolar disorder, although it is possible that a reverse shift is masked by treatment. Conversion from unipolar to bipolar disorder generally takes place at a rate of 1% per annum but this may be higher in younger cohorts. Many factors predict conversion, including family history, symptomatology, personality and, in female patients, trigger by childbirth. Clinicians should therefore be aware of the possibility of conversion and conscious of the risk factors.

Key words: bipolar disorder, major depressive disorder, conversion, switching, depression

Presence of Conversion

The first question to ask when approaching this topic is whether unipolar depression does ever become bipolar disorder. Various studies claim to have testified to this phenomenon (1) as cited in (2), (3), (4), (5). In each of these, cohorts of patients with a confirmed diagnosis of major depressive disorder (MDD) were followed up and any change in their diagnosis to bipolar disorder noted. Akiskal et al. noted that in such studies the conversion rates to bipolar I (BP-I) vary from 0% to 37.5%, median 9.7% (1). There are several possible reasons for this large range of reported conversion rates. A particular potential methodological criticism of these studies, is that, since bipolar disorder consists of both depressive and manic (or hypomanic) episodes, a bipolar individual whose first episode happens to be depressive might receive a diagnosis of MDD before they experience their first episode of mania or hypomania; this would result in an apparent conversion due to a premature diagnosis of MDD. If the conversion took place within the first year of the depressive episode, the diagnosis of bipolar disorder might be easier to make and the confusion with the diagnosis of MDD would be less likely to occur; however, in longer studies it has been shown that the conversion sometimes takes place much later than 12 months after the initial depressive episode. A study by Goldberg et al. followed 74 adults who were hospitalised with unipolar depression over 15 years, demonstrating that conversions took place over the entirety of this period (6). Since robust diagnostic criteria were used in many of these studies, there appears to be good evidence to support that this was a genuine conversion from MDD to bipolar disorder rather than mere correction of misdiagnosis.

What is also interesting in this phenomenon is that conversion not only takes place from unipolar to bipolar depression but that it occurs between the smaller diagnostic entities within these conditions. In an important recent study, it was shown that patients with bipolar disorder not otherwise specified or cyclothymia tended to progress to BP-II, while those diagnosed with BP-II could convert to BP-I (7). It is possible that, rather than the MDD-BP conversion being a distinct event, it is the overriding direction of a continuous conversion along the unipolar-bipolar spectrum. It is, nevertheless, intriguing that this conversion is unidirectional; that is, it is common for MDD to become BP, but the reverse does not appear to take place. The reason for this is not obvious and should be subject to further research. One possibility is that it is merely an artefact of psychiatric medication and diagnosis, for it is not improbable to suppose that if a patient has reached the criteria for bipolar disorder but at some subsequent point ceases to experience manic or hypomanic episodes, the clinician will tend to assume that this is due to the effect of continuing mood stabilisers on their condition rather than considering that one facet of their illness had improved. This critique may have some merit, but a
helpful historical study by Angst and Sellaro, which discussed the natural history of bipolar prior to the introduction of mood stabilisers and antidepressants, notes poignantly that ‘bipolar disorder has always been highly recurrent and considered to have a poor prognosis’ (8). Hence, it is likely that there does exist a genuine preponderance in affective disorders away from unipolar depression and towards bipolar disorder.

**Chronology of Conversion**

We have already discussed how conversion from unipolar to bipolar depression does not always occur immediately; it is now appropriate to examine in greater detail how these conversions are distributed over time. In a study of outpatients with MDD, conversion took an average of 6.4 years from the start of the follow-up, with a range between 1 and 25 years (5). In fact, Akiskal et al. demonstrated that there is a conversion rate of around 1% each year in a study of 559 patients with MDD, who had a mean age in the low thirties at the start of the study (9) as cited in (2). It is not the case, however, that this rate is constant regardless of the study group, for Goodwin and Jamison have noted that this figure only applies to a mature cohort: in children and younger adults, conversion can be as high as 3-5% per annum (10). It would appear then that younger patients are in a more volatile state and should require a lower index of clinical suspicion for conversion than depressive adults.

The other aspect of conversion chronology to be considered is its relationship to the onset of depressive symptoms. In our own study (11), we conducted a retrospective analysis of 128 patients with confirmed bipolar disorder to ascertain the onset of depressive and (hypo)manic symptoms, based on patient reports. We found that there was a mean delay of 7.3 years (SD=7.9) from the onset of depressive to the first (hypo)manic symptoms. The variance of this figure demonstrates that the moment of conversion is not easily predicted, even when the time of first depressive symptoms is known. Since the first diagnosis given to many of these patients was MDD rather than BP, it is likely that this delay accounts for a diagnostic lag. In short, while much of the literature has already demonstrated that bipolar is a possible outcome for MDD, our study shows that MDD is also the most likely precursor to bipolar disorder, even if it is not always given this diagnosis.

**Predictors of Conversion**

While the actual time of conversion is highly variable, there are certain features of MDD patients that increase the statistical likelihood of switching to bipolar. In an important paper by Akiskal et al., in which 206 outpatients with depression switched to bipolar, six criteria were identified as being significant predictors of conversion, as follows: onset at or before 25 years of age, BP family history, strong family history of affective illness, precipitation by childbirth, hypersomnia with psychomotor retardation, and pharmacological mobilisation (5). The specificity of any one of these variables was poor, but taken together, any 3 of them gave an impressive diagnostic specificity of 98%. The authors poignantly note that conversion ‘tends to be limited to certain predisposed individuals with primary affective disorder’. The place of post-partum mental illness of any type as being liable to convert to bipolar has more recently been verified by a large study in which 14% of women with post-partum symptoms converted, while only 4% of the other women in the trial did so (12).

In addition to these predictors, other factors have been identified which may be elicited by a careful history and examination. First, bipolar-like symptoms among unipolar depressives have been implicated in predicting conversion. In particular, sub-threshold hypomanic symptoms in the presence of MDD have higher rates of conversion than those who have MDD without these symptoms (14). Second, pre-conversion personality has convincingly been shown to be significant in this regard, at least in conversion to BP-II. Akiskal and colleagues showed that patients who converted from MDD to BP had scored higher on neuroticism, orality, emotional reliance and were lower on ego resiliency and emotional stability; these authors also identified four new personality factors (mood lability, energy-activity, daydreaming and social anxiety), which similarly apportioned higher scores to BP-II converters. The authors memorably noted the ‘intimate interweaving of trait and state’, as they showed the importance of the clinician not limiting patient history taking to features that were clearly pathological. What was interesting about this research was that it showed no difference whatsoever between non-converters and BP-I converters (1). Since
other studies have not made this distinction, it still remains to be seen if other predictors of conversion
demonstrate a similar disparity.

Conclusions

From the published studies it is clear that MDD does convert to bipolar disorder, possibly passing
through various sub-classifications en route. Moreover, although it is hard to predict when a patient
will convert, a number of factors, related to their age, symptomatology, personality and family history
can be very accurate predictors of the likelihood of conversion taking place. Clinicians should be
aware of these factors when treating depressive patients, anticipating the possibility of conversion
and managing it appropriately if it does occur. Research is now required to take this practice to the
next level by formulating neurobiological predictors of conversion, as it is likely that combining
neuroimaging and genetic analysis with clinical measures would yield still greater accuracy.

GP Comment

What have I learned from this paper?

Patients who initially have what appears to be a clear diagnosis of depression may “convert” to bipolar
disorder and this could have important implications for treatment. Those who have a diagnosis of
depression need to be followed up and specific enquiry must be made about hypomanic or manic
symptoms.

Mayruja Santhirakumar, GP Trainee.

References

bipolar I An 11-year prospective study of clinical and temperamental predictors in 559 patients. Arch
Gen Psychiatry, 1995; 52: 114-23.
3 M. Strober, C. Lampert, S. Schmidt and W. Morrell. The course of major depressive disorder in
adolescents: I. Recovery and risk of manic switching in a follow-up of psychotic and nonpsychotic
the course of depressive illness: Phenomenologic, familial, and pharmacologic predictors. Journal of
Affective Disorders 1983; 5: 115–128.
6. J. F. Goldberg, M. Harrow and J. E. Whiteside. Risk for bipolar illness in patients initially hospitalized
along the Bipolar Spectrum: A Longitudinal Study of Predictors of Conversion from Bipolar Spectrum
11. J. Rogers, M. Agius and R. Zaman. Diagnosis of Mental Illness in Primary and Secondary Care with a
Hypomanic Symptoms in Progression From Unipolar Major Depression to Bipolar Disorder. Am J
14. R. Nadkarni and M. Fristad. Clinical course of children with a depressive spectrum disorder and
The temperaments and their relevance to bipolar spectrum disorders

Giuseppe Tavormina, M.D.
President of “Psychiatric Studies Centre”
Piazza Portici, 11 - 25050 Provaglio d’Iseo (BS) – Italy
E-mail: dr.tavormina.g@libero.it

Abstract

Temperament is a key factor when assessing a patient within the bipolar spectrum. Indeed, Akiskal and others have included the temperaments as conditions in their own right within the bipolar spectrum, describing them as ‘soft’ forms of bipolar condition within the spectrum. They can develop over time into a more clear bipolar condition, and hence are important in early diagnosis. In this article, the importance of the temperaments is discussed, and a technique is described for identifying the temperaments of individual patients.

Key words: bipolar spectrum, temperaments, early diagnosis.

Bipolar disorder can be considered a real chrono-pathology, in which there is a recurrent switch/shift of mood balance. [Akiskal et al, 1996]. Depression and mania are not only successive conditions, depression and mania are both successive and simultaneous conditions [Rhimer et al, 2009]. Bipolar spectrum disorders (BSD), including sub-threshold forms, are much more common than previously thought [Tavormina et al, 2007]. In order to diagnose BSD correctly, it is important to know the patient’s premorbid personality and past history: it is crucial to know the longitudinal history and the full family history. One major contribution by Akiskal [Akiskal 1989] to the assessment of patients in the bipolar spectrum is the identification of the underlying temperament as a condition in its own right within the bipolar spectrum, described as a ‘soft’ form of bipolar condition within the spectrum. An observational study of the diagnosis of 423 consecutive new patients over a period of four years led to the main observation of a high percentage of bipolar spectrum diagnosis [Tavormina 2009]. This has suggested a new classification of “the bipolar spectrum” (ten sub-types of bipolar spectrum mood disorders); these sub-types also include the temperaments, even if they are only sub-clinical aspects of the bipolar spectrum. The temperaments are continuous presentations of the character's mood-peculiarities, and also are subthreshold (subclinical) forms of the bipolar spectrum [Tavormina 2009]. Every patient with BSD already presented in their personal history of the illness subclinical evidence of one temperament (the evidence of this study was: hyperthymic temperament 35%, cyclothymic temperament 49%, depressive temperament 16%).

Following this classification, the following are the main temperaments within the bipolar spectrum.

Depressive Temperament

The following are the characteristics of a patient with this temperament: gloomy, humourless and incapable of fun, tending to worry, with frequent pessimistic cognitions, introverted, passive and lethargic, tending habitually to sleep long hours (more than 9 hours of sleep) or suffering from intermittent insomnia, constantly preoccupied with inadequacy, failure, or negative events, tending to be sceptical, self-critical, overcritical, complaining or prone to guilt.

Hyperthymic Temperament

The following are the characteristics of a patient with this temperament: cheerful, tending to overoptimism and exuberance, demonstrating mental overactivity, tending to be overtalkative, warm, extrovert, people seeking, overconfident, self-assured, tending to boastfulness or grandiosity, a habitually short sleeper [less than 6 hours of sleep], including weekends, having a high energy
level, tending to be full of plans and improvident activities, tending to be overinvolved, uninhibited, stimulus seeking, or promiscuous.

**Cyclothymic - irritable Temperament**

Main symptoms: biphasic dysregulation characterised by slight endoreactive shifts from one phase to the other, each phase lasting for a few days at a time, with infrequent euthymia; mental overactivity, insomnia or bad quality of sleep, somatization.

**Softly- unstable Temperament**

This is a “soft cyclothymic temperament”, characterised by: vague and fluctuating uneasiness, mood instability but of low grade, anxious traits, trait-state overlap.

All the temperaments may develop over time into a more clear bipolar picture. Whereas the other three temperaments had been described by Akiskal [Akiskal 1989], the softly unstable temperament has been first described by our group, based on our clinical observations. When this temperament develops to threshold forms of bipolar disorder, it presents a better prognosis than cyclothymic temperament development [Tavormina 2009].

Here we describe a technique for establishing the particular temperament which a particular patient may display.

It is essential then to bring out the characteristic temperament of the patient from the beginning of his history of mood disorder, starting from the time that he was about 20 years of age. In patients who are very young, this must be done with great clinical care.

In order to do this it is necessary to ask the patient a question with 3 choices: “Could it be considered that, at the age of about 20 years, you were a person of very lively character-hyperactive and extremely cheerful ... “, or “a person who always tended to be tense and irritable ... “, or “a person always tended to be taciturn, solitary and melancholy ... “.

The aim of this question is to identify by a positive response to the first choice a “hyperthymic temperament”, a positive response to the second choice a “cyclothymic temperament” or a positive response to the third choice a “dysthymic-depressive temperament”.

The subthreshold presence of the temperaments in the history of the patients with BSD allows us to consider this to be a crucial method for early diagnosis of bipolar spectrum mood disorders. It is very important to focus on the temperaments during the clinical interview, in order to be effective in the early diagnosis of mood instability. It is also important for early diagnosis to identify affective instability between episodes, the high frequency of somatic symptoms, stormy object relations and the complicated biographies which these patients describe.

**GP Comment**

*What have I learned from this paper?*

This article discusses the different temperaments found in those with bipolar disorder and their importance in early diagnosis of mood instability. It also reminds us of the significance of discovering the patient’s premorbid personality and longitudinal history of their illness; it gives practical questions that can be used to identify temperaments of individual patients.

*Dr Jenny Hopwood, GP Trainee.*
References


Figures

Patients in the bipolar spectrum out of 423 consecutive patients.

The percentages of the temperaments of 423 consecutive patients
Impulsivity in bipolar disorder

Mojca Zvezdana Dernovšek
University psychiatric clinic Ljubljana

Urban Groleger
University psychiatric clinic Ljubljana

Lilijana Šprah
Sociomedical Institute,
Scientific Research Centre of the Slovenian Academy of Sciences and Arts, Slovenia

Abstract

Impulsivity has for long time been neglected in bipolar mood disorder (BPD). The concept of BPD has changed beyond clinical presentations of bipolarity to include personality, affective temperaments and important comorbidities. These changes have allowed more focused research into the evolving concepts of impulsivity. Increased impulsivity has been associated with all phases of bipolar disorder (mania, mixed and depression) including inter-episode euthymic phases. The present concept of impulsivity differentiates “state” and “trait” impulsivity; both have been associated with bipolarity. Sub-traits of impulsivity (motor activation, attention, lack of planning) have been demonstrated to influence specific phases of bipolar disorder. Recent work on emotional processing and cognitive control offers additional insight into the role of increased impulsivity in bipolar disorder. Data suggests that impulsivity changes the presentation of acute BPD symptoms and increases the risk for aggressive and suicidal behaviour, influences the course of BPD, increases the risk of complications and worsens the long-term prognosis. Data on specific therapeutic effects on impulsivity are scarce in BPD. The authors have endeavoured to offer clinically relevant data on impulsivity and therapeutic implications for everyday clinical use.

Key words: impulsivity, bipolar disorder

Introduction

Impulsivity is conceptualized as inadequate control of thoughts and behaviour; it is broadly defined as acting without thinking (1). Impulsivity is a complex construct that involves biological, psychological, social and developmental factors on a continuum from normality (and health) towards pathology (and illness) (2). Impulsivity is not a diagnosis per se or a unified category of signs and symptoms or personal characteristics. Impulsivity is closely related to several psychiatric disorders; however, its role still has to be clarified (2). Impulsivity has great clinical and public health importance, since it is associated with worse outcome of mental disorders and therefore increases substantial morbidity, social, family and job impairments, accidents, suicides and violence (3). Biological and psychological diagnostics and treatments for psychiatric disorders should include methods aimed at assessing impulsivity during the treatment and prevention of relapses (2). BPD with depression, mixed episodes, mania and inter-episode periods of euthymic mood are characterized by mood and behavioural instability where actions precede thinking about consequences, reflecting the core feature of impulsivity. In this paper some insights into impulsivity in the context of BPD will be reviewed, as well as the interaction between them, which is highly relevant in clinical settings.

The concept of impulsivity

There are several definitions of impulsivity. Some of them are more straightforward, such as: (a) “swift actions without forethought or conscious judgment” (4); (b) “behaviour without adequate thought” (5); (c) “tendency to act with less forethought than do most individuals of equal ability and knowledge” (6). Other conceptualizations include also subtraits such as risk taking, lack of planning and making up one’s mind quickly (7). Patton et al. (8) postulated impulsivity as a three-dimensional construct, with
the following domains: (1) acting on the spur of moment (motor activation), (2) not focusing on the
Task at hand (attention) and (3) not planning and thinking carefully (lack of planning). This definition
was operationalized in the most widely used clinical scale for impulsivity assessment BIS-11 (8). There
are also several tasks available for impulsivity assessment in laboratory settings. They can be classified
into three broad categories: (a) “perseverance of a response that is punished or unrewarded” (9), (b)
“preference for small immediate reward over a larger delayed reward” (10), and (c) “making a response
that is premature or the inability to withhold a response” (11). From the social aspect, impulsivity can
be seen as learned behaviour where the child learns to react immediately to obtain what is desired for
gratification (12). According to several theories, two core motivational systems regulate this kind of
behaviour: (a) behavioural inhibition system (BIS) that deals with aversive motivation and avoidance
or withdrawal behaviour, and (b) behavioural activation system (BAS) that deals with appetitive
motivation and approach behaviour (13-14). This theory has been operationalized in the BIS-BAS scale,
widely used for the assessment of impulsivity in the general and clinical population (15).

Impulsivity can be also defined as a predisposition toward unplanned reactions to internal or external
stimuli without regard to the negative consequences (2). Two components of impulsivity can be
identified in this regard: impulsivity as a predisposition, vulnerability or “trait” of an individual, who
under certain psychological, social or psychopathological conditions might develop impulsive
behaviour, which can be defined as “state”. These two components of impulsivity might explain why
certain individuals in acute psychiatric episodes become more impulsive, disinhibited and aggressive
and others with the same clinical symptoms do not. A number of studies have demonstrated that the
presence of a mood disorder correlates with a significantly higher level of impulsivity (16-17).

Impulsivity and bipolar mood disorder

Although BPD has been traditionally considered a disorder with favourable long-term outcome,
several studies demonstrate that a large percentage of patients with BPD have a severe course, with
high rates of relapse, residual symptoms, cognitive and functional impairment, chronic course and
psychosocial disability, along with two to three times higher mortality than in the general population.
10-20% of patients with BPD commit suicide during an acute episode (mainly depression and mixed
episodes) and in the euthymic state (18). Impulsivity is a prominent aspect of BPD (19). Besides
influence on clinical symptoms of bipolar episodes, impulsivity also contributes to the complications
of BPD, including suicide (20-22), substance abuse (23-25) and aggressive behaviour (hostility,
agitation and overt aggression) (26).

Impulsivity is clinically obvious in manic and mixed episodes. Although clinical symptoms of manic
states may vary from patient to patient, impulsivity is ubiquitous (27). Depression, however, may
appear less strongly related to impulsivity than mania is, but this relationship is obvious at least in
suicidal behaviour (28). This increased level of impulsivity in depression illustrates the complexity
of the relationship between impulsivity and BPD: it may be related to manic symptoms (29) or to
hopelessness (21) or to the depression itself (17). Some studies reported a similarly elevated level of
impulsivity in patients with BPD regardless of the phase of illness (27), suggesting that impulsivity
might represent a stable component, which is not merely a manifestation of a mood state but a
characteristic of a patient with BPD also during the inter-episode euthymic phase (30). There are many
possible associations between impulsivity and BPD (2), which could be related to:

- susceptibility (vulnerability to develop bipolar disorder),
- episodes of illness: increased impulsivity may accompany episodes or appear earlier in the course of
  an episode than the diagnostic affective symptoms,
- risk of complications such as suicide or substance abuse,
- response to specific treatments of bipolar disorder,
- pathophysiology of the illness: combination of increased norepinephrine, decreased serotonin or
  impaired prefrontal cortex functions.
Research on impulsivity in bipolar disorder

There are numerous studies in which assessments of impulsivity in patients with BPD have been performed, employing different instruments and in different settings. Swann et al. (27) reported a higher level of impulsivity, as measured by the Barratt Impulsiveness Scale (BIS-11), in patients with BPD in comparison to controls, even when the patients were between episodes of mania and depression. Human laboratory measures used in this study correlated with the severity of manic symptoms but did not differ from measures of impulsivity in the control group. There was also a lack of correlation with depressive symptoms (27). The authors suggested that the trait-dependent component of impulsivity measured by BIS-11 could be related to serotonin deficiency (31) and the state-dependent component of impulsivity as measured by Continuous Performance Test (IMT-DMT) (11) could be linked with manic symptoms and noradrenergic function (27, 32). According to BIS-11 manic and euthymic bipolar patients showed similarly elevated scores compared to healthy controls (19). The similarity was explained by correlation between manic symptoms and IMT-DMT scores and attributed to subsyndromal manic symptoms in the seemingly euthymic phase (19).

Peluso et al. (26) measured impulsivity using BIS-11 across all bipolar illness phases (euthymic, depressed, mixed and manic states) and did not find significantly different impulsivity scores across all mood states. However, impulsivity BIS-11 scores were higher than in the control group on the total score and on all three subscales (non-planning, attention and motor). Swann et al. (17) demonstrated an increased total BIS-11 score in depressed, manic and mixed subjects compared to inter-episode subjects, but the increase of specific BIS-11 scores was dependent on affective state. According to their study, motor impulsivity appeared to be selectively related to mania, nonplanning impulsivity to depression and attentional impulsivity to both mania and depression. All three BIS-11 subscores were elevated in mixed states of BPD. Swann et al. (17) demonstrated that some symptoms of mania (hyperactivity, increased energy and accelerated speech) and some depressive symptoms (hyperactivity, hopelessness and anaerobia) correlated with increased impulsivity measured by BIS-11.

Increased motor impulsivity in mania relates to impetuousness and venturesomeness (33), the inability to delay a reward-related response (34) and impaired stop-signal reaction time (35). The core feature is inability to withhold or to modify motor responses. Corruble et al. (36) found an increase in all three BIS-11 subscales in unipolar depressive episodes; however nonplanning impulsivity is most strongly related to bipolar depression (17). A component of impulsivity appears to be intrinsic to the depressive state itself (17) and not just subtle manic or mixed symptoms in the bipolar depressive episode or euthymic phase (37).

Complications of impulsivity in bipolar disorder

Increased trait impulsivity was consistently linked to suicidal behaviour (38-40). In studies on suicides in patients with BPD the trait impulsivity or both state and trait impulsivity were demonstrated (41) with higher impulsivity scores in patients with BPD with a history of suicide attempts and also higher scores in those with multiple attempts compared to those with a single suicide attempt (42). Maser et al. (20) has demonstrated in a 14-year follow-up study that impulsivity was one of the best long-term predictors for suicide attempts and completion in affectively ill patients. According to Najt et al. (41) there is a positive link between both state and trait impulsivity in BPD that goes beyond acute illness episodes into euthymic phases but relates differently according to the presence of suicidality, impulse-control disorders, substance abuse or aggression (41).

There is a consensus that impulsivity closely relates to aggression (43). The diagnosis of mania seems to be over-represented among assaultive hospitalized patients; many studies described violent behaviour in manic patients prior to and during hospitalization (44-45). Barlow et al. (45) showed that patients with BPD had the highest risk (2.81 fold increase) for aggressive behaviour compared to all psychiatric inpatients. Similarly, the cumulative increase in total BIS-11 scores has been shown when substance abuse and BPD are present simultaneously in same patients (25). Therefore baseline or trait impulsivity may also serve as a common factor of vulnerability to comorbid substance abuse and BPD. Inter-episode patients with BPD and substance abuse show higher laboratory measures of impulsivity
(IMT/DMT) compared to those without substance abuse (25). So impulsivity may predispose an individual to both acute bipolar episodes and substance abuse that additionally increases the likelihood for new episodes through additionally increased impulsivity.

Anxiety disorders are frequently comorbid with BPD. A positive association between anxiety and impulsivity was found in various studies (46-47). Bellani et al. (48) show a direct association between anxiety and impulsivity on one hand, and anxiety and BPD on the other, adding to the understanding of the complex relationships between impulsivity and BPD.

**Impulsivity and euthymia in bipolar disorder**

Several studies have demonstrated increased impulsivity during euthymia in BPD. Also in some of our studies (49-50) we demonstrated an increased total impulsivity score along with increased attentional, motor and nonplanning BIS-11 subscores, as well elevated BAS scores (Behavioural activation system) in euthymic patients with BPD comparing to healthy individuals (51). Since Akiskal et al. (52) revived the concept of affective temperaments, many studies suggested an association with BPD (53-54), where certain affective temperaments represent a potential contributor to the bipolar spectrum (55). Signoretta et al. (56) reported association of cyclothymic disposition with lifetime psychopathology and impulsivity; Stanford et al. (57) reported a high correlation between impulsivity and irritability.

Some of our studies demonstrated a strong positive correlation between different aspects of impulsivity and cyclothymic, irritable and anxious temperaments in the group of euthymic outpatients with BPD which could indicate that those traits represent a relatively stable picture of BPD, which is maintained even during the remission phase (30, 49, 58). These findings are in line with the hypothesis that the relatively high level of impulsivity found in patients with BPD, persisting also during remission, may be a stable component, which is not merely a manifestation of mood state (16). The importance of increased impulsivity in euthymic inter-episode patients with BPD has been investigated further by examining the role of cognitive control processes in emotional information processing using the Emotional Go/NoGo task, a measure of cognitive inhibition (50, 59-60). We found that patients with BPD showed decrements in cognitive control processes as indexed by a reduced perceptual sensitivity to negative and neutral stimuli, more impaired response inhibition and slower processing of these stimuli. According to research results, increased impulsivity, increased emotional responses on various stimuli and diminished cognitive control with impaired cognitive and emotional processing all contributed to increased vulnerability of otherwise euthymic inter-episode patients with BPD.

**Linking impulsivity and bipolar mood disorder**

Impulsivity is strongly related to the course of BPD. Trait impulsivity is increased in manic, mixed and depressive episodes, influencing clinical symptoms and increasing the likelihood of behavioural disinhibition with irritability, agitation, and aggressive and suicidal behaviour. State impulsivity was compared to healthy controls in inter-episode euthymic patients with BPD demonstrating increased vulnerability for future episodes and complications that further increase the likelihood of a more severe course of BPD. The components of trait impulsivity are associated with certain affective temperaments (stable personality characteristic), emotional processing and cognitive control and processing, influencing the behaviour of an individual in various life circumstances as well as under stress. State impulsivity may increase under similar conditions including psychopathology (substance abuse, anxiety, abnormal reactions to environmental factors). Increases in both trait and state impulsivity may together reach the threshold for new bipolar episodes influencing the course of BPD. The model of these interactions is presented in picture 1.
Various studies have tried to demonstrate therapeutic effect on impulsivity across different psychiatric diagnostic categories (2). Studies have demonstrated the efficacy of SSRIs in decreasing impulsivity in patients with personality disorders and schizophrenia, lithium and antiepileptic drugs in organic brain disorders, autism in adults, conduct disorders and dementia, and risperidone in different patient populations. There are no relevant studies in bipolar patients (2). No psychotropic drug has an official indication for “impulsivity”. However, atypical antipsychotics are widely used in low doses to diminish both anxiety and impulsivity in real-life psychiatric settings. Belli et al. (61) recently published a review of the use of psychotropic drugs in patients with borderline and bipolar disorder and found data to support the use of mood stabilisers (valproate and lamotrigine) and atypical antipsychotics (olanzapine and quetiapine but also clozapine and risperidone) to reduce impulsivity in this patient.
population (61). Until now, no drug has demonstrated ability to treat impulsivity; the effect is limited to impulsivity reduction. It is, however, not clear whether psychotropic drugs reduce state impulsivity, trait impulsivity or both.

Psychosocial and psychotherapeutic interventions are effective adjuncts to pharmacotherapy but there are almost no data on their influence on impulsivity (2, 61). The number of studies is small and the observed outcomes are life functioning, satisfaction, quality of life, treatment adherence and the number of relapses. The literature on the efficacy of insight-oriented psychotherapies is scarce and not systematic. Most popular for BPD are psychosocially-oriented approaches: interpersonal and social rhythm therapy, cognitive behaviour therapy (CBT), family-focused therapy and individual or group psychoeducation (62). CBT has been demonstrated to reduce impulsivity in different populations (drug abusers, delinquents, chronic psychiatric patients and preschool impulsive children) (2). It is, however, again not clear which impulsivity has been reduced; furthermore, specifically bipolar patients have not been included in the review.

In our study neurocognitive functioning was examined in euthymic patients with BPD who attended 6 workshops of psychoeducation (63). The patients with BPD were found to be emotionally less labile, with increased impulsivity, more prone to potentially rewarding action and avoiding potentially more dangerous situations, had impaired selective attention, and in general, poorer cognitive control of emotional stimuli and worse recognition of basic emotional facial expressions. Attendance at workshops did not significantly affect the neurocognitive deficits, with the exception of clinically improved subjects.

Conclusions

The impact of impulsivity on the outcome of BPD and comorbidity is so important that complex interplay of state and trait impulsivity should be assessed in each patient with BPD. There are some simple and affordable research and clinical instruments for assessment of impulsivity; these should be used in everyday clinical practice, especially when bipolar patients reach the euthymic phase, to determine their “trait” impulsivity. State impulsivity in acute BPD can be expected, especially when trait impulsivity is high. So far data on treatment aimed at impulsivity are scarce and no clear recommendations can be offered. However psychotherapeutic and psychoeducational work might be effective on factors influencing impulsivity and therefore improve the long-term course of bipolar disorder.

GP comment

What have I learned from this paper?

This article highlights how impulsivity is increased in patients with a mood disorder. It has been linked to higher suicide behaviour rates. Impulsivity is comprised of 2 components: trait and state. This explains why some patients are more vulnerable to impulsive characteristics during acute relapses. It is therefore important to ascertain these components during assessment, particularly when patients are in the euthymic state. Although pharmacotherapy has been shown to prevent impulsivity it has not been able to treat it. Psychotherapeutic and psychoeducational resources could be effective in achieving this.

Dr Snehal Khajuria BSc (hons) MBBS , GP trainee.

References


29. Swann AC, Moeller FG, Steinberg JL, Schneider L, Barratt ES, Dougherty DM. Manic symptoms and
30. Dolenc B. Affective temperaments and trait impulsivity in the group of bipolar outpatients and healthy volunteers: could it also be relevant in the early diagnostic picture of bipolar mood disorder? Rev Psychol 2010; 17 (2): 91-5.
51. Dolenc B, Šprah L, Dernovšek MZ. Motivational systems and trait impulsivity in euthymic outpatients with bipolar mood disorder and healthy volunteers: P01-203. In: 19th European


Suicide and suicide prevention in patients with bipolar disorders

Zoltán Rihmer, MD, PhD, DSc.
Department of Clinical and Theoretical Mental Health, and Department of Psychiatry and Psychotherapy, Semmelweis University, Faculty of Medicine, Budapest, Hungary
Tel: (36-1) 325-1498
Fax: (36-1) 355-8498
E-mail: rihmerz@kut.sote.hu

Abstract

Bipolar disorders are quite prevalent but frequently underdiagnosed and undertreated. The early recognition and appropriate treatment is particularly important, since out of all psychiatric illnesses, (untreated) bipolar disorders carry the highest risk of both attempted and completed suicide. Studies show that suicidal behaviour in patients with bipolar disorders is state and severity dependent; that means that suicidality markedly decreases or vanishes after clinical recovery. However, since the majority of mood disorder patients never commit suicide and more than half of them never attempt suicide, special clinical characteristics of the disorder as well as some familial and psychosocial factors should also play a contributory role. Considering the clinically explorable suicide risk factors in patients with bipolar disorders (family and/or personal history of suicidal behaviour, early onset, severe depressive episode/hopelessness, agitated/mixed depression, bipolar II diagnosis, rapid cycling, comorbid Axis I and Axis II disorders, adverse life situations, lack of social and medical support, cyclothymic temperament, impulsive aggressive personality features, etc.), there is a good chance that suicidal behaviour is predictable. There is also much evidence that (successful) acute and long-term pharmacotherapy of bipolar patients reduces the risk of attempted and completed suicide by more than 80 percent, even in this high-risk population. Recent studies also show that supplementary psychosocial interventions (psychoeducation, and targeted psychotherapies) further improve the results.

Key words: bipolar disorders, suicidal behaviour, suicide prevention, antidepressants, mood stabilizers, suicide risk factors, psychosocial interventions

Suicidal behaviour, particularly completed suicide, which is the most dangerous complication of untreated major psychiatric illness, is one of the most tragic human events. Although suicide is very complex, multi-causal behaviour, involving several medical-biological, psychosocial and cultural components, a history of untreated major mood disorders (particularly in the presence of previous suicide attempt) constitutes the most important risk factor. However, because the majority of mood disorder patients never complete (and about 50% of them never attempt) suicide, other familial-genetic, personality and psychosocial risk factors also play a significant contributory role (1, 2, 3, 4).

Psychological autopsy studies from several different countries of the world have consistently shown that around 90% of consecutive suicide victims have one or more Axis I (mostly untreated) major psychiatric disorders at the time of their death, and major mood disorders (59-87%), schizophrenia/schizoaffective disorder (10-12%) and substance-use disorders (10-15%) are the most common principal diagnoses (4, 5, 6, 7, 8). On the other hand, it has been estimated that 15-19% of severe (mostly hospitalized) patients with major depression would die by suicide (6, 9). In their meta-analysis of studies on suicide risk in psychiatric disorders, Harris and Barraclough analysed separately the risk of suicide in unipolar major depression and in bipolar disorder (10). They found that the risk of suicide was about 20-fold for patients with index diagnosis of unipolar major depression, and the same figure for bipolar disorder was 15. However, these three studies (6, 9, 10) cannot provide a precise estimate of separate suicide risk in unipolar and bipolar disorder, i.e. they overestimate the risk for unipolar depression and underestimate it for bipolar disorders. The main issues are that the index diagnosis
frequently changes during the long-term course from unipolar depression to bipolar disorder (11, 12, 13, 14) and in the studies (performed several decades ago) reviewed by the mentioned authors the diagnostic category of bipolar II depression (depression with hypomania but not with mania) which is quite a common form of bipolar disorder (12, 15, 16) has not been considered separately; it is very likely that the majority of bipolar II patients in these studies were included in the unipolar major depressive subgroup. Indeed, a recent long-term follow-up study showed that the rate of completed suicide was about double in bipolar disorder (types I and II combined) than in unipolar depression (17). Another recent population-based epidemiological study also found that 28% of bipolar (types I and II combined) and 11% of unipolar major depressive disorder patients reported a lifetime history of suicide attempt (18).

Risk of suicidal behaviour in patients with bipolar disorders

Since specific diagnostic subtypes of major mood disorders (unipolar, bipolar I and bipolar II) show several differences from both clinical and research perspectives (6; 11; 18; 19; 20; 21), it is logical to assume that each subgroup might have its own different suicide risk.

1. Completed suicide

The different risk of suicide in the three main subgroups of major mood disorders was first reported by Dunner et al. (1976) who found that 3% of the 73 unipolar, 6% of the 68 bipolar I and 18% of the 22 bipolar II patients died by suicide during their 1-9 year follow-up study (19).

In their recent long-term prospective follow up study (average 11 years) on 1983 unipolar major depressives and 843 bipolar (I+II) patients, Tondo et al. found a five-fold higher rate of completed suicide in bipolar I and II than in unipolar patients (0.25% of patients/year vs. 0.05% of patients/year) (22). They also found that the ratio of attempted to completed suicide in bipolar II, bipolar I and unipolar depression was 5, 11, and 10, respectively, indicating that the lethality of suicide attempts was far highest in bipolar II patients. The higher lethality of suicide attempts of bipolar II than bipolar I and unipolar patients has been supported by the study of Sani et al. (17). During the long-term (up to 35 years) follow-up study on 4441 formerly hospitalized psychiatric patients the authors also found that bipolar II patients had the highest risk for suicide; the authors reported that 2.8% of 1163 bipolar I and 4.2% of 602 bipolar II patients completed suicide while the rate for 1142 unipolar major depressive patients was 1.9% (17). Similarly, in the STEP-BD study (4360, mostly pharmacologically-treated bipolar patients, mean follow-up 18 months) the rate of completed suicide was more than two-fold in bipolar II (0.34%) than in bipolar I patients (0.14%, 23).

The results of the two published psychological autopsy studies where the prevalence of bipolar II, bipolar I and unipolar depression have been analysed separately, show that among the 125 consecutive suicide victims with primary major depression at the time of suicide, 44% had bipolar II depression, 2% had bipolar I depression and 54% had first episode or recurrent unipolar depression (24, 25). Because the lifetime prevalence rates of DSM-III/IV bipolar II illness in the population are relatively low compared with unipolar major depression (2-5% and 15-17%, respectively) (26, 27), these results, in agreement with other findings (17, 23), also suggest that among the three different subgroups of major mood disorders bipolar II disorder carries the highest risk of committed suicide.

2. Attempted suicide

In addition to the high mortality rate due to suicide, up to 50% of patients with bipolar disorder attempt suicide at least once during their life (3, 8, 28). Considering only the ten studies, in which unipolar, bipolar I and bipolar II patients were analysed separately, and summarizing the data (3), it can be seen that the rate of previous suicide attempts is lowest in unipolar major depression (13 %) highest in bipolar II patients (33%), and intermediate in bipolar I patients (28%). Re-analysing the ECA database, Judd and Akiskal (29) also reported that the rate of prior suicide attempt(s) was higher in bipolar II (34%) than in bipolar I (24%) patients, while the same figure for unipolar major depression was 16% (30). The long-term prospective study by Tondo et al. also found that the rate of suicide attempts during follow-up was more than double in bipolar (I+II) than in unipolar patients. However,
the annual rate of suicide attempts was highest in bipolar I (1.52%), compared with bipolar II (0.82%) and unipolar (0.48%) depression in this study (22).

The results of a German ten-year prospective longitudinal study showed that 32% of 33 bipolar II, 17% of 65 bipolar I and 6% of 286 pure unipolar major depressive patients attempted suicide during follow-up (31). In the Finnish Jorvi Bipolar Study 16% of the 90 bipolar I and 25% of the 101 bipolar II patients reported at least one prior suicide attempt at the index episode (32). Similar findings were reported from South-Korea; 17% of the 71 bipolar I and 36% of the 34 bipolar II patients reported the history of suicide attempt (33). Analysing the specific diagnostic subtypes of consecutive suicide attempters with current DSM-IV major depressive episode, it has been also found that bipolar, and particularly bipolar II patients were relatively overrepresented both in Budapest (34) and in Rome (35).

In contrast to the studies, mentioned above, analysing the NCS-Replication database, Angst et al. found that the history of lifetime suicide attempts was the highest in bipolar I (66%), lower in bipolar II disorder (50%) and lowest in unipolar major depression without subthreshold bipolarity (30%) (28). However, in patients with unipolar major depression with subthreshold hypomanic symptoms, the rate of patients with prior suicide attempt was intermediate between pure unipolar major depression and bipolar II disorder (41%).

3. Clinically explorable suicide risk factors

Bipolar patients with comorbid anxiety, substance-use, and personality disorders as well as with DSM-IV atypical depressive features are also at an increased risk of attempted or completed suicide (3, 4, 8, 21, 30, 34, 36, 37). Beside the highest lethality of suicide attempts (22; 17), the major sources of the highest suicide risk in bipolar II patients may be the very high rate of atypical depression, comorbid anxiety disorders (37, 38; 39), substance-use disorders (38, 40) and depressive mixed states/agitated depression (2, 12, 17, 41; 42). The importance of depressive mixed states in predicting suicidal behaviour is supported by several recent studies (12; 43; 44; 45; 46) and current findings also show that cyclothymic/irritable affective temperaments, that are characteristic also mainly for bipolar II disorder, also increase the risk of suicidal behaviour (47).

Family history of suicide (19; 48; 49), past suicide attempt(s), early onset of the illness, impulsive, aggressive personality features, childhood physical and sexual abuse as well as recent adverse life events, and permanent psychosocial stressors (3, 4, 5, 8, 12, 43, 46; 47, 50, 51), have also been shown to be risk factors for attempted or completed suicide, particularly in the frame of major depressive, mixed depressive or dysphoric manic episodes. In a study on 211 patients suffering from recurrent unipolar major depression or bipolar (I+II) disorder, hospitalized after suicide attempt, it was found that family history of suicide was significantly associated with diagnosis of bipolar disorder and looking for the features associated with serious suicide attempt, bipolar disorder was the only associated diagnosis (52).

It should be noted, however, that in the majority of cases many suicide risk factors are present and they have an additive effect on the self-destructive behaviour; the higher the number of risk factors the higher the suicide risk (2, 3, 4, 8, 43).

Despite of the fact that up to 66% of suicide victims contact different levels of health care (mostly GPs and psychiatrists) 4 weeks before suicide, the rate of adequate pharmacotherapy among depressed suicide victims is disturbingly low (24, 53; 54; 55). While the current prevalence of DSM-III/DSM-IV or ICD-10 major depression in primary care practice is around 8-10%, the majority of depressed patients are not recognised by their GPs. Moreover, the rate of adequate antidepressant pharmacotherapy among diagnosed depressives was less than 20%. However, studies performed 5-10 years later, reported much higher rates of recognition and treatment of depression in primary care practice (62-85%) and 33-50% of them were treated with antidepressants (56, 57).

Since successful acute and long-term pharmacotherapy of mood disorders relieves not only the clinical symptoms, but parallel with this also decreases or eliminates suicidality, appropriate acute
and long-term treatment of mood disorders is a key issue in suicide prevention. GPs and psychiatrists play a crucial role in suicide prevention via early recognition and appropriate management of suicidal patients. (4, 53, 54, 58, 59, 60). Table-1. shows the clinically most important suicide risk factors in bipolar disorders.

**Suicide prevention in bipolar disorders**

Since suicidal behaviour is a multi-causal phenomenon with many biological, psychological and cultural components, its prevention should also be complex. Bipolar disorder, a major precursor of suicidal behaviour, is quite prevalent, but frequently underdiagnosed. Considering both the bipolar I and II manifestations, the lifetime prevalence is between 3 and 5% (6, 16, 26, 27). Since bipolar disorders usually show a peak onset between 15 and 25 years of age, but there is 8-10 years of delay in correct diagnosis (6, 16, 20, 27), early detection of bipolar, the nature of the mood disorder, including the soft manifestations as well, is the first step in suicide prevention. Misdiagnosis of bipolar depression as unipolar depression results in treatment with antidepressants alone, and this can worsen the course of the illness, because of inducing mixed depressive episodes, hypomanic or manic switches, or rapid cycling, therefore increasing the chance of suicidal behaviour (16, 41, 45, 61, 62, 63).

The role of health care in the suicide prevention of bipolar patients is summarised in Table 2. As suicide behaviour in bipolar patients occurs mostly during severe pure or mixed depressive episodes and less frequently in the frame of dysphoric (mixed) mania, but practically never during euphoric mania and euthymia (i.e. suicidal behaviour in bipolar patients is a state-dependent and severity-dependent phenomenon) (3; 4, 21;), it is logical to assume that effective acute and long-term treatment has a strong protection against suicidal behaviour and probably against other complications such as secondary substance-use disorders, marital instability, loss of job, cardiovascular morbidity/mortality, violent behaviour, etc.

1. **The role of psychopharmacotherapy in suicide prevention of bipolar patients**

Successful acute pharmacotherapy of depressive or mixed episodes can only prevent the risk of suicidal behaviour connected with a given episode; therefore it is only the adequate long-term (prophylactic) therapy that can provide ongoing protection in patients with bipolar illness.

a. **Lithium and antiepileptic mood stabilizers**

The place of lithium and antiepileptic mood stabilizers in the treatment of manic states and in the prevention of recurrences in bipolar patients is well documented (6, 64, 65, 66). Recent data also indicate that the combination of lithium (and other mood-stabilizers) with antidepressants reduces the risk of hypomanic or manic switching when bipolar depression is treated with antidepressant monotherapy (62, 67).

In a comprehensive review of 45 randomized, controlled and open clinical studies (including 34 studies also providing data without lithium treatment) involving a total of 85,229 person-years of risk exposure Baldessarini et al. reported about 80 percent risk reduction for attempted and completed suicides in either unipolar or in bipolar patients with long-term lithium treatment (58). The risk reduction was similar for suicide attempts and for completed suicides. The incidence-ratio of attempts to suicides increased 2.5 times with lithium treatment, indicating reduced lethality of suicidal acts. This marked anti-suicidal potential of lithium seems to be more than the simple result of its episode-prophylactic effect, as it has been demonstrated that during the long-term lithium prophylaxis of 167 recurrent bipolar or unipolar affective disorder patients with at least one prior suicide attempt, a significant reduction in the number of suicide attempts was found not only in the excellent responders (92%), but also in the moderate responders (78%) and poor responders (70%) (68). The clinical consequence of this finding is that, in the case of lithium non-response, when the patient has one or more suicide risk factor, instead of switching lithium to another mood stabilizer, the clinician should retain lithium (even on a lower dose) and combine it with another mood stabilizer.
In a 34-38 year long naturalistic follow-up study including 220 formerly hospitalized bipolar I and bipolar II patients, Angst et al. found that patients who received long-term pharmacotherapy (lithium, neuroleptics, antidepressants) tended to live longer and to have significantly (2.5-fold) lower suicide rate (13.1% vs. 5.2%) than untreated bipolar patients (69). The authors also found significantly lower rates from all natural deaths among treated vs. untreated patients.

In a randomized, open-label, prospective 2.5-year-follow-up study Thies-Flechtner et al. investigated the number of suicide events in 175 bipolar, 110 schizoaffective and 93 recurrent depressive patients (70). The patients were randomly assigned to lithium, carbamazepine or amitriptyline. There were 14 serious suicide events (9 completed suicides and 5 serious attempts) during the study, and 7 out of the 14 events (6 suicides and 1 attempt) were among the bipolar patients. Most of the 14 suicide acts happened in the carbamazepine group (4 suicides and 5 attempts), and none of the 14 suicidal patients were taking lithium. These findings also support the strong anti-suicidal effect of lithium that may be related to its well-known anti-aggressive and serotonin-agonistic activity (6, 68).

The anti-suicidal effect of lithium in bipolar and unipolar major mood disorder patients has been also supported from an epidemiological perspective. Investigating the lithium levels in drinking water in 18 municipalities in Japan in relation to the suicide mortality in each municipality, the authors found that lithium levels were significantly and negatively associated with suicide rate averages for 2002-2006 (71). Very similar results were published recently from Austria (72).

In a retrospective chart review study of 140 outpatients with bipolar disorders treated continuously for a minimum of 6 months during a 23-year-period of private practice, Yerevanian et al. found a more than two-fold reduction in non-lethal suicidal behaviour during, compared with after, discontinuation of mood stabilizers (lithium, valproate or carbamazepine) (73). The frequency of non-lethal suicidal behaviour was not different during treatment with lithium, compared with valproate or carbamazepine.

In a naturalistic, retrospective chart review study of 405 bipolar patients seen in a large US Veterans Administration health-care system, Yerevanian et al. analysed the risk of suicidal behaviour of the patients followed for a mean of 3 years (74). As there was only one completed suicide in this study the analysis was restricted only to suicide attempts and serious suicidal ideation resulting in hospital admission. The findings showed that mood stabilizer monotherapy (lithium, divalproex, carbamazepine) reduced the risk of suicidal behaviour by more than 90 percent. Lithium and antiepileptic mood stabilizers showed similar benefits in this respect.

In a population-based retrospective “real world” cohort study on more than 20,000 patients with bipolar I or bipolar II disorder Goodwin et al. compared the risk of suicide and suicide attempts during lithium treatment with that during divalproex or carbamazepine treatment (75). There was no exposure to lithium, divalproex or carbamazepine during 45% of all person-years of the follow-up (mean: 2.9 years). In this observational study, where milder or non-suicidal cases were probably over-represented among patients who had never been treated with any mood stabilizer, a 42% reduction in suicide death among patients taking lithium was found, when compared to those who were not treated with any mood stabilizers. After adjustment for age, sex, comorbid disorders and concomitant use of other psychotropics, the authors found that the risk of suicide deaths and suicide attempts resulting in hospitalization was about twice as high during treatment with divalproex and with carbamazepine than during treatment with lithium. These results are in good agreement with the findings of Thies-Flechtner et al. who reported that among patients treated for bipolar disorders the risk of suicidal behaviour was lower during lithium treatment than during treatment with carbamazepine (70).

Using linkage of national registers, Søndergard et al. investigated the association between continued mood-stabilizing treatment and suicide among all patients discharged nationwide from hospital psychiatry as inpatients or outpatients during 1995 and 2000 in Denmark with an ICD-10 diagnosis of bipolar disorder (n=5926) (59). The results showed that patients who continued treatment with mood stabilizers (lithium, divalproex, lamotrigine, oxcarbazepine and topiramide) had a significantly
decreased rate of suicide compared to patients who purchased mood stabilizers once only and the rate of suicide decreased consistently with the number of additional prescriptions. Although long-term treatment with lithium and antiepileptic mood stabilizers was associated with similar reduction in the suicide mortality, these results suggest that lithium may have some superiority in preventing suicide.

Analysing the 12,662 Oregon Medicaid patients diagnosed with bipolar disorders and treated with mood stabilizers between 1998 and 2003 Collins and McFarland found that the adjusted hazard ratios (versus lithium) for suicide attempts was significantly higher for divalproex users \((p=0.001)\), and for completed suicide for gabapentin users \((p=0.001)\) (76). However, a recent, small-scale, double-blind, 2.5 year long trial on bipolar I and II patients showed no significant difference in the frequency of suicide attempts in patients treated with lithium or valproate (77).

b. Antidepressants and antipsychotics

The role of typical and atypical antipsychotics in the acute treatment of mania, mixed states and psychotic depression is well considered (6, 65, 66). Recent results suggest that some atypical antipsychotics (olanzapine, quetiapine, and aripiprazole) have long-term mood-stabilizing effects in patients with bipolar disorders (78, 79, 80, 81), but their putative specific anti-suicidal effects need further studies.

Antidepressants have limited value in the long-term treatment of bipolar disorders because of their mood-destabilizing effects (45, 61, 65, 66). However, mood stabilizers reduce the risk of the mood switch (62, 66, 67). The study by Yerevanian et al. also showed that during the long-term pharmacotherapy of bipolar patients the risk of suicidal behaviour is highest in patients with antidepressant and antipsychotic monotherapy (82, 83), lowest in patients with mood stabilizer monotherapy (74) and the risk of patients with combination therapy (mood stabilizers + antidepressants or antipsychotics) showed an intermediate position with similar risk of suicidal behaviour to bipolar patients during the period “off” any psychotropics (74, 82, 83). The clinical implications of these findings is that clinicians who add antidepressants or antipsychotics to mood stabilizers to treat breakthrough depression or mania during the long-term treatment of their bipolar patients should consider that antidepressants and antipsychotics may increase the risk of suicidal behaviour; therefore, they should keep their patients on these supplementary medications as short a time as possible and the main component of the long-term pharmacotherapy should be the mood stabilizer monotherapy.

2. Psychosocial interventions in suicide prevention of bipolar patients

Recently, more and more effective psychosocial interventions in the field of bipolar disorders were developed, primarily for patients who showed insufficient response to acute and long-term pharmacotherapy, who could not tolerate drugs or who were noncompliant with the treatment (84, 85). The main targets of these interventions are: preventing medication non-compliance with psychoeducation or with cognitive-behavioural therapy, lifestyle modification, teaching patients and relatives to identify early symptoms of relapse and obtain treatment as early as possible, and modification of family and other interpersonal conflicts (84, 86, 87, 88). These psychosocial techniques specifically designed for relapse/recurrence prevention in bipolar patients are effective either alone, or mostly in combination with mood stabilizers (see for review: 84, 85, 86). The interaction between pharmacotherapy and psychosocial interventions is quite complex as successful episode-preventive medication with mood stabilizers in bipolar patients counteracts dysfunctional cognitions (including lowered self-esteem), and adjunctive cognitive therapy helps to optimize the long-term course of bipolar illness (89).

Mental health professionals and physicians are, of course, unable to prevent all suicides and it is not only healthcare workers who are responsible for suicide prevention. However, our present pharmacological and psychosocial interventions are effective enough to minimize the chance of suicide in patients with bipolar disorder that represent the highest risk of self-inflicted death.
GP Comment

What have I learned from this paper?

Bipolar disorder carries one of the highest rates of suicide of any psychiatric disorder. The risk is especially raised in those with unrecognized illness or in those who are undertreated, especially with mixed states, which are common but difficult to diagnose. All patients who make a suicide attempt should have a careful assessment for bipolar disorder and it is noteworthy that bipolar II has a higher suicide risk than bipolar I, due to the relentless depressive symptoms in bipolar II. However, the challenge is to identify when ‘depression’ is actually bipolar depression.

Lithium appears to be protective against suicide and even if patients appear well, lithium should not be stopped unless there has been a very careful assessment by the patient’s psychiatrist. GPs and other healthcare professionals should endeavour to provide high levels of support, holistic care and compassion for these patients. Outcomes are good and there is hope where there is psychosocial support and expert management.

Dr Daniel Dietch, Lonsdale Medical Centre.

References


and antidepressants. Comprehensive psychiatry, 24, 249-258.


Table 1

Clinically significant suicide risk factors in bipolar disorders

<table>
<thead>
<tr>
<th>Diagnostic subtype</th>
<th>Bipolar II &gt; bipolar I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early onset of the illness</td>
<td>(&lt; 25 years)</td>
</tr>
<tr>
<td>Previous/current suicidal ideation</td>
<td></td>
</tr>
<tr>
<td>Previous suicide attempt</td>
<td>Violent &gt; nonviolent</td>
</tr>
<tr>
<td></td>
<td>High lethality &gt; low lethality</td>
</tr>
<tr>
<td>Current clinical features</td>
<td>Severe depression, hopelessness, insomnia, guilt</td>
</tr>
<tr>
<td>DSM-IV atypical features</td>
<td>Mixed depressive episode/agitation</td>
</tr>
<tr>
<td></td>
<td>Dysphoric (mixed) mania or hypomania</td>
</tr>
<tr>
<td></td>
<td>Mixed affective episode</td>
</tr>
<tr>
<td></td>
<td>Rapid cycling course,</td>
</tr>
<tr>
<td></td>
<td>First episode depression, predominantly depressive polarity</td>
</tr>
<tr>
<td></td>
<td>Comorbid anxiety/anxiety disorders, substance-use and personality disorders</td>
</tr>
<tr>
<td></td>
<td>Cyclothymic/irritable affective temperament</td>
</tr>
<tr>
<td></td>
<td>Impulsive/aggressive personality features</td>
</tr>
<tr>
<td>Family history of suicide</td>
<td>in first- and second degree relatives</td>
</tr>
<tr>
<td>History of childhood physical and/or sexual abuse</td>
<td></td>
</tr>
<tr>
<td>Permanent adverse life situations, acute psychosocial stressors</td>
<td></td>
</tr>
<tr>
<td>Lacking adequate acute and long-term treatment/care</td>
<td></td>
</tr>
<tr>
<td>Noncompliance or reduced compliance with the acute and long-term treatment</td>
<td></td>
</tr>
</tbody>
</table>

Table 2

Suicide prevention strategies in bipolar disorders

The role of health care

I. Elimination of acute suicide danger
   (emergency hospitalization, sedation, anxiolysis, crisis-intervention)
II. Improving the diagnosis and treatment of bipolar disorders with particular regard to the soft clinical manifestations
   1. Education of health care workers, patients, relatives and gate-keepers
   2. Adequate acute and long-term treatment/aftercare
      (pharmacotherapy, non-pharmacological interventions such as psychoeducation,
psychotherapy, cognitive therapy, family counselling/family therapy etc.)

III. Improving the patients’ compliance
    (psychoeducation, psychotherapy, cognitive therapy, regular contact, etc.)

IV. Reducing the stigma against bipolar disorders and suicide via media
Is Bipolar Affective Disorder Underdiagnosed?

Shokoufa Kashani, Eva Bongards, Mark Agius, South Essex University Partnership Foundation Trust, UK
2 School of Clinical Medicine, University of Cambridge, UK
3 Christ’s College, University of Cambridge, UK
4 Department of Psychiatry, University of Cambridge, UK
5 Clare College, University of Cambridge, UK

Abstract

This article reviews the epidemiological evidence that bipolar affective disorder is often underdiagnosed and hence ineffectively treated. In order to mitigate this problem, all patients with depression should be systematically assessed using a full longitudinal history in order to detect hypomanic symptoms, as well as a family history. This is expected to lead to more appropriate diagnosis, and consequently treatment, of bipolar affective disorder.

Key words: bipolar affective disorder, unipolar depression, underdiagnosis, misdiagnosis.

Introduction

There has been much discussion as to whether or not bipolar affective disorder is underdiagnosed. In this review, the term ‘underdiagnosis’ will be used as referring to patients who actually have bipolar affective disorder but are not identified when the DSM-IV (1) or ICD-10 (2) criteria are applied. According to the DSM-IV criteria, bipolar affective disorder is defined as episodes of low mood interspersed with episodes of high mood, which are further characterised: in bipolar I disorder, the high moods consist of full mania lasting at least one week, while in bipolar II disorder, high moods consist of hypomania lasting for a minimum of four days. It is vital to realise that this definition is arbitrary, and that many patients have shorter symptomatic episodes, for example, hypomania lasting two days. Such patients are, at present, not considered to fulfil the full criteria for bipolar affective disorder and are therefore referred to as ‘subsyndromal’ for this condition. In line with the proposed arbitrary nature of the existing criteria, a study conducted by Angst (3) demonstrated that they are indeed artificial and hence potentially changeable parameters. He showed that the proportion of bipolar patients in a population of depressed patients could vary depending on the criteria. Additionally, many others have argued that bipolar affective disorder is underdiagnosed (4) (5) (6) (7).

Bipolar disorder is often misdiagnosed and underdiagnosed

Initial reports of underdiagnosis of bipolar affective disorder by Knutsen (4) and Schwartz (5) focused on the relatively easy misdiagnosis of bipolar I disorder as schizophrenia. The diagnosis of bipolar I disorder or schizoaffective disorder following a prior diagnosis of schizophrenia usually occurs as a result of a change in symptom patterns due to the natural evolution of the disorder (5). On the other hand, the diagnosis of bipolar affective disorder following prior diagnosis of unipolar depression is often far more difficult to achieve; this can be due to inadequate history taking and assessment of the patient (6).

Ghaemi et al. have shown that the time from initial presentation to diagnosis of bipolar affective disorder can be, on average, up to nine years for all bipolar patients. This figure is derived from the six years it can take for bipolar I disorder to be diagnosed, the eleven years it can take for bipolar II disorder, and the 12 years it can take for conditions at the ‘softer end of the bipolar spectrum’, also often described as ‘bipolar affective disorder not otherwise specified’, to be diagnosed (17). Hirschfeld et al. (7) presented the results of a survey carried out by the National Depressive and Manic-Depressive Association of a large group of patients who had been diagnosed with bipolar affective disorder. Over one third of respondents stated that they had sought professional help within one year of onset of symptoms. It was reported that 69% of bipolar patients had initially been misdiagnosed.
with a different condition and that the most frequent misdiagnosis had been unipolar depression. In addition, over one third of respondents stated that they had waited ten years or more before being accurately diagnosed. Furthermore, the results showed that those who had been misdiagnosed had consulted a mean of four physicians prior to receiving the correct diagnosis. Despite often under-reporting manic symptoms, more than half of the patients believed that it was the lack of understanding that their physician had of bipolar affective disorder which had delayed the diagnosis. Moreover, bipolar affective disorder was reported to have a profound negative impact on the patients and their families, in terms of social relationships, employment and careers. Patients stated that although the illness had manifested early in life, several years had passed before an accurate diagnosis was achieved.

Another important report of underdiagnosis of bipolar affective disorder is the GAMIAN-Europe/BEAM survey I of self-help groups, which showed that many patients who have bipolar affective disorder describe long durations of untreated illness (DUI) before diagnosis (8). Patients gave details of the following effects of this: worse clinical response, reduction of the effect of lithium treatment, poorer social adjustment, higher numbers of hospitalisations, increased risk of suicide and increased development of co-morbidities. Vazquez-Barquero et al. also report long DUI in bipolar affective disorder (9). According to Judd et al. (10) (11), the main reason for this, i.e. long DUI and misdiagnosis, is that on average, bipolar patients experience manic symptoms and symptoms of mixed states only 9% and 6% of their lifetime, respectively, while they are depressed 32% of the time, i.e. the vast majority of their symptomatic lives. Furthermore, the Stanley Foundation Bipolar Treatment Outcome Network reported that the first symptom in approximately half of the patients with bipolar affective disorder is depression (12). Bearing the above in mind, as well as the common clinical experience that many patients consider episodes of hypomania to be pleasant days, it is not surprising that bipolar affective disorder is often mistaken for unipolar depression, particularly at initial presentation.

Several ways of identifying more patients with bipolar affective disorder have been described

In order to screen for bipolar affective disorder in the community in 85,358 US citizens over the age of 18, Hirschfeld et al. developed the ‘Mood Disorder Questionnaire’ (13). They found the prevalence of bipolar I and bipolar II disorders to be 3.7%. Of all the patients thus diagnosed with bipolar affective disorder, only 19.8% had previously been identified to have the condition, 31.2% had been misdiagnosed with unipolar depression, and 49.0% had not received a diagnosis of either bipolar affective disorder or unipolar depression.

Benazzi (14) described another method of diagnosing bipolar II disorder. 111 outpatients with depression were interviewed for a history of hypomania and hypomanic symptoms using the Structured Clinical Interview for DSM-IV (SCID), modified by Benazzi and Akiskal. Bipolar I patients were excluded from the analysis, since their diagnosis was considered definitive. Benazzi then systematically assessed all past hypomanic symptoms, especially overactivity (14). The modification which he introduced was that the wording of the questions could be changed to increase understanding, and subsyndromal hypomania was defined as an episode of overactivity (increased goal-directed activity) plus at least two hypomanic symptoms (14).

Benazzi’s results showed that 68 of the 111 patients (61.2%) HAD bipolar II disorder, while only 43 patients had ‘true’ major depressive disorder. Of the latter group of patients, 39.5% (15.3% of the entire sample) showed evidence of subsyndromal hypomania (14). Those patients who were diagnosed with major depressive disorder but had subsyndromal hypomania had a median of four symptoms; the most common hypomanic symptom being overactivity. Overall, 76.5% of the patients were shown to have a bipolar spectrum disorder. Furthermore, it was noted that overactivity had higher sensitivity than elevated mood for predicting a diagnosis of bipolar II disorder.

Similar results were obtained by Tavormina et al. (15). They assessed 300 consecutive new patients presenting to an Italian private practice, by taking a full longitudinal history and a family history. Of the 300 patients who were assessed, 238 were found to lie on the bipolar spectrum. However, none of them were diagnosed with bipolar I disorder. 26% of their patients had bipolar II disorder, 21%
cyclothymia, 4% irritable cyclothymia, 3% were said to have a cyclothymic temperament, 5% had mixed dysphoria and 28% had agitated depression. However, only 9% were diagnosed with unipolar recurrent depression and 4% with a major depressive episode.

Based on this evidence, Agius et al. (16) decided to reassess patients registered with a community mental health team (CMHT) in Bedford, United Kingdom. They reassessed all patients with unipolar depression and recurrent depressive disorder, 456 patients in total, by taking a full longitudinal history and a family history. If this was indicative of bipolar affective disorder, they also used the Mood Disorder Questionnaire to validate their results. They found that whereas in November 2006 the CMHT had had 41 bipolar patients (8.9% of patients), 63 with recurrent depressive disorder (13.8% of patients) and 73 with one or more depressive episodes (16.0% of patients), by September 2007, there were 65 bipolar patients (14.3% of patients in the CMHT), 64 with recurrent depressive disorder (14.1% of patients) and 74 with one or more depressive episodes (16.3% of patients). Thus, over a period of ten months, the percentage of bipolar patients in the team increased by 5.4%, but the proportion of patients with unipolar depressive disorder in the CMHT did not change significantly. The conclusion reached was that if one were to screen patients systematically for bipolar affective disorder, the proportion of bipolar patients in a secondary care outpatient sample would increase.

Effects of underdiagnosis on treatment

The concept of bipolar affective disorder is often misinterpreted, leading to inconsistent diagnosis and treatment. In order to determine the consequences of underdiagnosis of bipolar affective disorder, Ghaemi et al. (17) assessed the records of 85 patients seen in an outpatient clinic within one year, who had diagnoses of affective disorders. Past diagnostic and treatment information was obtained by taking systematic psychiatric histories from the patients. The diagnosis of bipolar affective disorder was based on the DSM-IV criteria. A SCID-based interview was used to assess patients. The authors found that bipolar affective disorder was misdiagnosed as unipolar depression in 37% of patients on initial presentation to a mental health professional after their first (hypo)manic episode. Therefore, antidepressants were used earlier and more frequently than mood stabilizers, leading to likely overuse of the former and under-use of the latter. As a result, 23% of this sample of initially misdiagnosed patients experienced a worse, rapid-cycling, bipolar course, which was attributed to antidepressant use. Ghaemi et al. concluded that bipolar affective disorder tended to be misdiagnosed as unipolar major depressive disorder and that use of antidepressants in bipolar affective disorder was associated with a worse course of the illness (17). They also suggested several possible reasons for the observed underdiagnosis of bipolar affective disorder, such as patients’ poor insight into and recognition of (hypo)mania, failure of clinicians to take into account family members’ views when making the diagnosis, and physicians’ lack of understanding and therefore inadequate detection of (hypo)manic symptoms (6) (18) (19). Since Ghaemi et al. felt that the difference between the number of patients who had bipolar affective disorder and the number of patients diagnosed with it may also reflect disagreement among clinicians about the breadth of the bipolar spectrum; they suggested using the term “bipolar spectrum disorder” as a substitute for a more specific, more excluding diagnosis (6). The term is envisaged to place more emphasis on antidepressant-induced manic symptoms and family history, and also includes forms of bipolar illness that are not type I or II. In line with what is discussed above, Ghaemi et al. furthermore recommended more aggressive use of mood stabilizers and decreased use of antidepressants (17) (18) (19).

Can using self-report questionnaires alone lead to overdiagnosis of bipolar affective disorder?

Despite the convincing results just presented, difficulties have been encountered when basing diagnosis of bipolar affective disorder on self-report questionnaires alone. Zimmerman et al. (20) interviewed 700 psychiatric outpatients using the SCID. The patients also completed a self-report questionnaire, which asked whether they had previously been diagnosed with bipolar affective disorder by a healthcare professional. Furthermore, every patient’s first-degree family history was sought. Less than half of those respondents who reported previously to have been diagnosed with bipolar affective disorder received a diagnosis of bipolar affective disorder based on the SCID.
Furthermore, patients diagnosed with bipolar affective disorder based on the SCID had a significantly higher risk of having suicidal thoughts than patients who reported a previous diagnosis of bipolar affective disorder that was not confirmed by the SCID. Patients who reported a previous diagnosis of bipolar affective disorder that was not confirmed by the SCID did not have a significantly higher risk of having suicidal thoughts than those patients who were negative for bipolar affective disorder by self-report as well as the SCID. Zimmerman et al. concluded that, although underdiagnosing bipolar affective disorder was a problem, using a screening tool as the sole method of assessing patients may lead to overdiagnosis of the condition. In other words, they argued that the SCID was a more accurate method of identifying bipolar affective disorder. Self-report questionnaires could lead to overdiagnosis, and those patients who were identified as having bipolar affective disorder by the self-report questionnaires but not by the SCID did not have a higher risk of having suicidal thoughts, despite being identified by the self-administered questionnaires, so that there was no advantage in identifying them as bipolar.

Can broadening of the term ‘bipolar affective disorder’ to ‘bipolar spectrum disorder’ lead to overdiagnosis?

Concerns have, indeed, been raised more generally regarding overdiagnosis of bipolar affective disorder. One argument is that overdiagnosis may stem from the “promulgation of the concept of the soft bipolar spectrum disorder” (21) (22) (23). Regardless, we need to emphasize that this is not the issue we are addressing in this review. We refer to underdiagnosis of bipolar affective disorder as misdiagnosis or complete lack of diagnosis of patients who meet the present DSM-IV or ICD-10 criteria for bipolar affective disorder. Indeed, we concur with Zimmerman (24) (25) and others, such as Iordache (26), that it is necessary for patients to fit the current DSM or ICD criteria to be able to be diagnosed with bipolar affective disorder, a) in order for the condition not to be overdiagnosed and b) for epidemiological data to give an accurate representation of the prevalence and incidence of the disorder. We are also conscious of Zimmerman’s notable finding that many patients who are inappropriately diagnosed with bipolar affective disorder in fact have other important mental health conditions (24) (25).

Conclusion

Clearly, accurate diagnosis of bipolar affective disorder is a central issue in psychiatry. Only if we diagnose the condition accurately will we be able to devise the best possible management plans to reduce morbidity, as well as, importantly, mortality by suicide. Only then shall we be able to explain a diagnosis to our patients that finally makes sense to them, and support them in achieving their career- and other goals. As argued in this review, accurate diagnosis can only be achieved through thorough patient assessment and appropriate application of existing diagnostic criteria, which will also help us finally to treat some of those patients who were incorrectly diagnosed with resistant depression more effectively.

GP Comment

What have I learned from this paper?

I was surprised by the large number of patients who receive a diagnosis of unipolar depression, who may in fact have bipolar II disorder. When patients with depression present to primary care, there is a huge amount of ground to cover in the short consultation to assess current symptoms, risks, offer support and discuss treatments; asking about previous hypomanic episodes might be overlooked. However, as we follow these patients up at regular intervals we have the ideal opportunity to revisit the history and try to elicit any history of possible hypomanic-sounding episodes. The PHQ9 questionnaire, which is often used to screen for depression in primary care, does not include questions about manic symptoms so perhaps these could be incorporated.

Abigail Davis, GP Trainee.
References

Unipolar Depression versus Bipolar Disorder; an Overview

Gursharan Kashyap 1
Lucy Pauli 2, 3

1 South Essex University Partnership NHS Foundation Trust
2 Clare College Cambridge
3 Clinical School University of Cambridge

Author Participation: GK produced the data and an original draft.
LP edited the data and the draft.

Abstract

The case is made for the importance of diagnosing unipolar depression and bipolar disorder as two separate conditions. Differences in the natural history and course of the disorders, their symptomatology and response to treatment are described. The correct diagnosis and treatment of these conditions is of great importance in determining outcome.

Key Words: mania, bipolar illness, unipolar depression.

Bipolar disorder was previously known as manic-depressive disorder. The term "bipolar affective disorder" was used for the first time in DSM III in 1980. Bipolar disorder is characterised by alternating episodes of mania and depression or mixed episodes (which include both manic and depressive symptoms in the same episode). Mania and depression thus represent the two opposite poles of affective malfunction. Recurrent unipolar depression [F33 in ICD 10], on the other hand, is characterised by episodes of depression followed by a return to the euthymic state; the manic pole of affective malfunction is not represented at all.

It is important to recognise that bipolar disorder and unipolar depression are separate conditions. There are different psycho-biological contributors, including different aetiological factors; there are also different hypotheses with regard to their origin. In addition, there is a difference in their heritability (bipolar 80% and unipolar depression 46%) (1, 2), age of onset, and typical presentation. Overall, bipolar depression causes much more morbidity than unipolar depression, including marked functional impairment and social and economic loss (3). Bipolar disorder tends to be more severe, enduring and complex than unipolar depression; it is different in its nature, course and prognosis (4). The depressive phase of bipolar disorder was previously thought to be similar to unipolar depressive disorder. However, over time, evidence has shown that there are notable differences in the characteristics of the depressive phase of bipolar disorder and unipolar depression (as will be discussed below). It is therefore important to recognise that even the depressive illness of bipolar disorder is a distinct entity, which is now frequently referred to as ‘bipolar depression’.

Moreover, in a study of excess mortality in bipolar and unipolar disorders in Sweden, Osby et al. (4) reported that bipolar disorder raises the suicide risk 20 fold compared with the general population. Goodwin and Jamieson (5) stated that the lifetime bipolar suicide rate is around 19% (5). Suicide usually occurs in the depressive phase of the illness (6).

With so many variables playing significant roles and contributing to the depressive symptoms in these two disorders it is likely that the treatment of acute depression in these two different disorders will also be different, as discussed below.

Unipolar depression is well-recognised. However, it is unusual to diagnose a patient with unipolar mania (7). A patient presenting with mania will usually be diagnosed as having bipolar disorder since it is usually possible to demonstrate previous depressive episodes. Unipolar mania has, however, been...
Solomon et al. (8) described 7 patients with a diagnosis of bipolar disorder who had not had an episode of depression in the previous 20 years (8). Yazici et al., who defined unipolar mania as 4 episodes of mania with a depression-free follow-up period of 4 years, found an incidence of 16.3% in their study (7).

One factor that hinders straightforward diagnosis is the fact that patients might be able to cope with hypomanic or mild manic phases or, indeed, might not mind experiencing these periods of elevated mood, but tend to seek expert help in the depressive phases (9). The fact that patients do not present with mild mania and that the depressive episodes usually last longer than the hypomanic ones may lead clinicians to assume that the patient has unipolar depression. In order to ensure a correct diagnosis, specific enquiry needs to be made about mild manic/hypomanic episodes in the assessment of the patient. It is, therefore, important to look for clues that might indicate that a patient has bipolar disorder rather than unipolar depression. There are no investigations that will differentiate bipolar depression from unipolar depression, nor are there any clear-cut clinical features that can distinguish between them in a patient who has had only depressive episodes. However, there are certain features that may assist the clinician in making the correct diagnosis. Depression, especially of mixed type or atypical type, should raise the suspicion of bipolar disorder. An early onset and atypical presentation of depression is linked with Bipolar II disorder (10). Bipolar depressive episodes are more frequently associated with hypersomnia (10), increased appetite (10), diurnal variation of mood and occurrence of psychosis (11). Overall, the duration of bipolar depressive episodes is significantly shorter than unipolar depressive episodes (12). Bipolarity is also suggested by failure of multiple antidepressants in the past, occurrence of frequent episodes of depression and sudden relapse, preceded by an initial quick response to an antidepressant (13). The MDQ (Mood Disorder Questionnaire) has a high specificity of around 90% and a reasonable sensitivity of around 70% in diagnosing bipolar affective disorder (14). Perlis et al. (15) have pointed out that there are additional subtle differences, such as fear in bipolar depression compared to sadness in unipolar depression. Irritability, distractibility, and racing thoughts are commonly seen in bipolar II depression (16).

Akiskal (11) has stated that psychotic features, psychomotor retardation, abrupt onset or offset of depression, reversal of neurovegetative symptoms, tempestuosity, impulsivity, a family history of bipolar disorder or completed suicide, as well as clinical worsening of symptoms, possibly due to treating a mixed affective episode with antidepressants leading to emergence of symptoms, such as increased sexual drive and worsening insomnia, are all important clues to the identification of bipolar depression (11).

The diagnosis of a patient with unipolar depression may also need to be reassessed after the patient receives antidepressant therapy. The description of bipolar disorder III, which is mania precipitated by the administration of antidepressant medication in a person who was previously diagnosed as having unipolar depression (17), illustrates how the diagnosis may need to be changed during the course of the disorder. This change of diagnosis has implications both for treatment and prognosis.

In order to diagnose bipolar disorder correctly it is important to understand the typical course of the condition. Perugi et al., in a systemic retrospective study of 320 patients with bipolar I disorder, found that this usually started with acute depression (18). The acute depressive episode may be followed by another episode of depression or by mania. Acute bipolar depressive episodes can last for variable periods. They are usually shorter but more severe and aggressive compared with unipolar depressive episodes, consequently leading to greater functional and psychosocial impairment. Bowden (19) confirmed that bipolar disorder usually starts with depressive episodes early in life and patients usually spend most of their illness time in the depressive phase. This is especially so in bipolar I disorder (20). However, the course of disorder can be more complicated than this, such as in rapid cycling bipolar. Rapid cycling is the occurrence of at least 4 major mood episodes (depressive, manic, hypomanic, or mixed) during the previous year in a patient with a diagnosis of bipolar I or bipolar II disorder. Rapid cycling was included in the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) in 1994 after a meta-analysis by Bauer and colleagues (21) and is still surrounded by controversy as to whether it represents a temporary or permanent change in course. It carries a higher risk of functional impairment, severe depression and treatment resistance; it is associated with an overall...
poorer prognosis compared with non-rapid-cycling bipolar disorder (22). Analysis of the STEP-BD trial suggested rapid cycling might be a temporary phase in the course of bipolar illness and that antidepressant use could worsen the cycling (23).

Altshuler et al. (24), reported that, compared with unipolar depression, the depressive illness of bipolar disorder does not resolve fully and there are often subclinical and subsyndromal symptoms of depression (24) present that do not respond to antidepressants, signifying that there is a relative resistance to antidepressants in bipolar disorder. Furthermore, when in partial remission, patients can continue to have ongoing chronic subclinical symptomatology of depression, which is enough to cause functional impairment, increasing the risk of relapse to a full-blown depression (25).

Unfortunately, many patients still receive an incorrect diagnosis. Hirschfeld et al. (26), reporting the results of the national depressive and manic-depressive association survey, stated that 69% of patients with bipolar disorder are misdiagnosed primarily as major depressive disorder and for more than one third of patients there was a delay of around 10 years before they were eventually diagnosed as having bipolar disorder. The patients in this category, who were misdiagnosed as having depression and were treated with ineffective antidepressants, tended to follow an unfavourable course (30). This is important to note because the use of antidepressants in bipolar disorder has been discredited (27). Until recently it was assumed that the treatment for the acute depressive episode of both unipolar and bipolar depression was antidepressant medication. The evidence showing that antidepressant medication can change the course, nature, severity and prognosis of bipolar affective disorder has been presented in a separate paper in this volume (see paper entitled “The Place of Antidepressant Medication in the Treatment of Bipolar Affective Disorder”). In summary, the judicious use of antidepressant medication during the depressive phase only, and always in combination with mood stabilisers, is recommended by the NICE Guidelines, although several studies have now recommended mood stabilisers as the mainstay of treatment of bipolar depression. Certain mood stabilisers such as quetiapine and lamotrigine have been shown to be specifically effective in bipolar depression. Muzina et al. (27) have suggested that giving antidepressants to a patient with bipolar disorder can be detrimental since bipolar type II patients usually respond favourably to lithium if they have not previously been exposed to antidepressants. In addition, discontinuation of antidepressants can enhance lithium response (28).

It is important that the distinction between unipolar and bipolar depression be made appropriately since, if we consider a broader definition of bipolar disorder, the research suggests that up to 50% of recurrent major depression (especially the subgroups with atypical presentation, early onset and non-response to antidepressant medication), might actually fall into the bipolar group (30). This has important implications for the treatment and prognosis of the patient.

**GP Comment**

**What have I learned from this paper?**

This paper explains that unipolar and bipolar depression are distinct conditions. The authors detail aspects of the history that help to identify bipolar depression, including alternating episodes of mania and depression, atypical depression (e.g. hypersomnia, increased appetite, psychosis), a strong family history, early age of onset, profound morbidity and functional impairment. It is important that this distinction between unipolar and bipolar depression is made as it has important implications for treatment and prognosis.

Dr Jenny Hopwood, GP Trainee.
References.


Overview of Bipolar Affective Disorder; Differences between Bipolar I Affective Disorder and Bipolar II Affective Disorder

Marina Mihaylova, South Essex Partnership University Trust.
Emil Mihaylov, South Essex Partnership University Trust.
Rakhee Vaja, School of Clinical Medicine University of Cambridge, Newnham College Cambridge.

Abstract

Bipolar affective disorder is one of a group of mood disorders, which also includes unipolar depression and dysthymia. Bipolar disorder has been classified into two main subtypes, bipolar I and bipolar II. It is important to diagnose patients with the correct subtype of bipolar disorder, as treatment and management differs between the two. Misdiagnosis leading to inappropriate treatment carries the risk of harm to others or suicide, most notably in patients with bipolar I. Bipolar I and bipolar II disorder can be largely thought of as similar conditions but at different poles on a spectrum of severity. In fact, a diagnosis of bipolar II disorder is sometimes amended to the more severe bipolar I disorder in a proportion of patients. This paper aims to explore the similarities and differences between the two conditions, as differentiation between the two conditions can often be difficult.

Key Words: bipolar I affective disorder, bipolar II affective disorder.

Introduction

Bipolar affective disorder is a common psychiatric condition previously known as manic–depressive disorder. It is episodic in nature, with fluctuation between depression and elevated mood. The lifetime prevalence of bipolar I disorder varies from 0.4%-1.6% (1). and for bipolar II it is approximately 0.5% (1). With an estimated prevalence of around 1% in the population some research in the USA has pointed out that this does not include people who have symptoms of bipolar disorder but are sub-threshold for the diagnosis criteria outlined in the DSM (Diagnostic and Statistical Manual of Mental Disorders) (1). The study found that prevalence could be as high as 6.4% if all people suffering symptoms are included (2). Although there is no simple ‘cure’ for bipolar disorder, the management of the condition centres on symptom control, and this can be challenging at times. There may be situations of diagnostic uncertainty when first presented with the symptoms; over a five-year period about 5-15 % of individuals with bipolar II disorder will develop a manic episode and their diagnosis has to be changed to bipolar I (1). With the change in diagnosis, the approach to management also needs to change, in order to minimise risk. Symptoms of each condition are described in more detail below.

Comparison of bipolar I and II disorders

The American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM IV), 1994, (1) provides the criteria to distinguish between bipolar I and bipolar II. The following information is from the DSM.

Manic/hypomanic episodes

While bipolar I disorder is characterised by periods of mania, patients with bipolar II disorder have episodes of hypomania, which is less severe than mania (1). The presentation of mania is so florid, distinctive and clear that the diagnosis is usually straightforward (1). In hypomania, the symptoms are not so obvious and additional information is often required to ensure that the right diagnosis is made. At times, the distinction between mania and hypomania can be difficult to make, however, distinguishing the two is important because the risk of harm to the patient (e.g. suicide/self harm/consequences of high risk activities) increases significantly with mania (1). See table 1 for a comparison of symptoms seen in mania and hypomania.
Both manic and hypomanic episodes start suddenly and develop rapidly. They are often triggered by a stressful event. According to DSM IV, a manic episode is defined by a distinct period during which there is an abnormally and persistently elevated, expansive or irritable mood, which lasts at least one week (or less if hospitalization is required) (1). The definition of a hypomanic episode is similar, the main difference being that the mood change is sufficient to be noticeable but not to cause a great deal of impairment in social function or require hospitalisation, unlike in mania (1). In some cases, hypomanic episodes can develop into mania.

In manic episodes of bipolar I, inflated self-esteem is typically present and may be one of the first symptoms that makes the psychiatrist suspect this disorder. It can also be present in a milder form in hypomania. This ‘grandiosity’ in manic episodes may become delusional, and other psychotic symptoms such as hallucinations can occur; this is termed affective psychosis (1). These additional psychotic symptoms are rarely present in hypomania.

In both conditions the amount of sleep is reduced, which goes along with increased level of energy. Manic speech is the hallmark of the disorder. The patient speaks non-stop and very quickly; it is like a waterfall of words, powerful and unstoppable. The patient’s thoughts jump from one topic to another (1). If the flight of ideas is severe, the speech may become disorganized and incoherent. When an attempt is made to interrupt a patient in mania this can provoke irritability and aggression (1). The speech in hypomania is often louder and more rapid than usual but it is not typically difficult to interrupt (1). Flight of ideas is not common. In Bipolar I, there is a significant increase in goal-directed activities, which very often lack touch with reality and which other people find strange (1). In hypomania individuals often become more creative and productive but their activities are not bizarre (1).

The patient is seldom aware of the change in their mood during the manic/hypomanic episode; it is something that is usually recognised by people around them. However, retrospectively patients often regret their behaviour and actions during the episode and are aware that they were not behaving in a way that was normal for them.

**Depressive episodes**

One or more major depressive episodes can be seen in both bipolar I and bipolar II disorders but in bipolar II, such an episode is a requirement for the diagnosis (1). If a major depressive episode presents in the context of Bipolar I disorder, it is more likely to coexist with psychotic symptoms, possibly owing to the greater severity of bipolar I (1). Therefore, in any patient who has a psychotic depressive episode, the possibility of bipolar disorder should be considered and specific enquiry should be made regarding any history of possible manic or hypomanic episodes.

Some patients also have panic attacks during depressive episodes, as well as appearing anxious and developing phobias. For some patients, the symptoms manifest themselves physically as pain in the abdomen, joints, head or other parts of the body.

A study in Sweden showed that training for better recognition of depression, as part of bipolar disorders as well as major depressive disorder, significantly reduced the rate of depressive suicide in the period after the training (3). This shows that early recognition and treatment of depressive episodes can decrease probability of the worst outcome from this aspect of the disorder.

**Mixed episodes**

Bipolar I disorder can, less commonly, present as a mixed episode. The DSM-IV criteria for a mixed episode are: 1) the presentation must meet the criteria for both a manic episode and for a major depressive episode nearly every day during at least a one-week period; 2) the mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others; 3) the
symptoms are not due to the direct physiological effects of a substance or a general medical condition (1).

The 5th edition of Diagnostic and Statistical Manual of Mental Disorders, DSM-5 will be released soon. While the DSM IV defined mixed episodes separately from episodes of hypomania, mania and depression, the new classification will experiment with allowing symptoms of the opposite pole to be recognised if they arise during an episode, even if they are insufficient to qualify as a mixed episode. Identification of subthreshold non-overlapping symptoms of the opposite pole will done using a “mixed features” specifier to be applied to manic episodes in bipolar disorder I (BD I), hypomanic, and major depressive episodes in BD I, BD II, bipolar disorder not otherwise specified, and major depressive disorder. This may have an impact on future treatment and demographics of the disorder (4).

Psychosocial effects

The manic episodes of bipolar I disorder tend to cause more disruption to the life of the patient than the hypomanic episodes of bipolar II disorder; people with hypomania often continue going to work, even though they are prone to make mistakes. People in mania cannot function at all; their occupational functioning is completely impaired. In between episodes, the majority of patients with both forms of this disorder return to a fully functional level. However a proportion of patients continually experience mood instability and difficulties in functioning between episodes; this happens in 20-30% of those with bipolar I, and in 15% of those affected by bipolar II (1). The associated cognitive impairment is one of the reasons why many people with bipolar disorder may find it difficult to keep jobs (5).

Effects of age

For all forms of bipolar disorder the episodes tend to become more frequent with age and more difficult to treat. This could be because advancing age is associated with changes in the sleep-wake cycle and this can precipitate either a hypomanic or a manic episode.

Gender differences

As there are two aspects to the disorder, mania and depression, either of these changes in mood can present first. If a male develops any form of bipolar affective disorder, the first episode is more likely to be manic, while in women, it is more likely to be depressive. Bipolar I disorder is thought to be equally distributed among both sexes, while bipolar II is more common in women.

Neurobiology

While bipolar II disorder is commonly described as being a milder form of bipolar I disorder on a spectrum, recent research comparing neurological activity in the ventral striatum in the two disorders has shown that this region is significantly more active in bipolar II disorder during reward anticipation compared to bipolar I and normal controls (6). This could suggest that bipolar II disorder represents a more extensive change in neurological processes, or a different aetiology compared to bipolar I disorder. However very little is known about the neurobiology of the disorders and more research is required to elucidate mechanisms affected in the brain.

Diagnosing bipolar disorder

It is recognised that it can be difficult to make a diagnosis based on a limited time period of history, which is why time is a helpful diagnostic tool throughout management.

The DSM IV classification contains the criteria to diagnose bipolar disorders. For the diagnosis of bipolar I disorder, one single manic or a mixed episode is sufficient. In order to make a diagnosis
of bipolar II disorder there must be one or more major depressive episodes and at least one clear hypomanic episode. In both conditions the mood disturbance must be accompanied by at least three additional symptoms. These symptoms include: inflated self-esteem or grandiosity, decreased need for sleep, pressure of speech, flight of ideas, distractibility, increased involvement in goal-directed activities or psychomotor agitation and excessive involvement in pleasurable activities with a high potential for painful consequences. If the mood is irritable (rather than elevated or expansive) at least four of the additional symptoms must be present. Together with these symptoms there is an impairment in social, occupational or other important areas of functioning in both conditions, but to a greater degree in bipolar I than bipolar II.

Differential diagnoses must be considered for patients presenting with mood disturbances. The main feature to establish in any case is whether the change has been caused by any medications or other substances (substance-induced mood disorder). Another possibility is that it is an element of another medical condition that the patient may have. A diagnosis of bipolar I or II cannot be considered if such causes can explain the mood changes.

In addition, it can be particularly difficult to distinguish between bipolar I and II if the predominant change is increase in irritability, as this could be a feature of a depressive, manic, hypomanic or mixed episode, as seen in table 1. Irritability also overlaps into a number of other conditions, including major depressive disorder or dementia in the elderly, or even just a change in life circumstances leading to a reasonable reaction in keeping with the individual's personality.

For symptoms of increased excitability, as well as distinguishing between a manic, hypomanic or a mixed episode, other causes could include ADHD (especially when symptoms were present in childhood), or a euthymic period of time in patients who have chronic major depressive disorder.

**Conclusion**

Bipolar affective disorder is a complex and challenging condition. In some cases the diagnosis is relatively straightforward. There is a gradation between bipolar I and bipolar II disorder, where bipolar I is the more complete form of this disorder. It therefore follows that, although the risks are similar between the two, they are of greater degree in bipolar I. In particular both conditions carry an important risk of suicide (2,3), which can be decreased by effective treatment with mood stabilisers.

**GP Comment**

*What have I learned from this paper?*

I enjoyed reading this excellent clear summary of bipolar I and II. As a generalist, we often expect patients with bipolar to have 'bipolar I', so it is useful to consider the more subtle presentation of bipolar II to help detect this as early as possible. This article highlighted to me how helpful a collateral history can be regarding hypomanic episodes and these episodes could present to a GP indirectly, as concern expressed by a relative about another patient on the list. By being alert to the condition, as I will be now, we can help to diagnose it sooner.

Dr Abigail Davis, GP Trainee.

**References**

3. Rihmer Z, Rutz W, Pihlgren H. Depression and suicide on Gotland. An intensive study of all suicides


Table 1: Comparison of different mood states

<table>
<thead>
<tr>
<th>Table 1: Comparison of different mood states</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mania</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Most associated disorder</td>
</tr>
<tr>
<td>Mood</td>
</tr>
<tr>
<td>Psychomotor effects</td>
</tr>
<tr>
<td>Duration</td>
</tr>
<tr>
<td>Severity:</td>
</tr>
<tr>
<td>Noticed by others</td>
</tr>
<tr>
<td>Requires hospitalisation</td>
</tr>
<tr>
<td>Psychotic symptoms</td>
</tr>
<tr>
<td>Self-esteem</td>
</tr>
<tr>
<td>Distractibility</td>
</tr>
<tr>
<td>Speech</td>
</tr>
<tr>
<td>Flight of Ideas</td>
</tr>
<tr>
<td>Goal directed activities</td>
</tr>
<tr>
<td>Sleep</td>
</tr>
<tr>
<td>Energy</td>
</tr>
<tr>
<td>Weight</td>
</tr>
</tbody>
</table>

Information from the Diagnostic and Statistical Manual of Mental Disorders DSM IV

*Bipolar affective disorder I
Part 2. Neurobiology of the Bipolar Spectrum

Brain structural changes in bipolar disorders – interplay between illness burden and lithium treatment

Tomas Hajek MD, PhD
Department of Psychiatry, Dalhousie University, Halifax, Canada
Prague Psychiatric Centre, Department of Psychiatry and Medical Psychology, 3rd School of Medicine, Charles University, Prague, Czech Republic

Abstract

Structural imaging findings in psychiatric disorders, including the mood disorders, have been inconsistent, with rare replications and frequent contradictory findings. The argument that is presented here is that it is ultimately the clinical variables which will allow us to clarify the seemingly confusing neuroimaging findings. This can be demonstrated in the example of hippocampal volumes in bipolar disorders (BPD). Whereas cumulatively, bipolar patients show preserved hippocampal volumes, when studies are subdivided, based on exposure to lithium (Li), BPD subjects not exposed to Li show smaller hippocampal volumes than controls, who have smaller hippocampal volumes than Li-treated participants. In addition, hippocampal volumes in BPD seem to be negatively associated with the illness burden (duration of illness, numbers of episodes) but only among participants with limited exposure to Li. This neuroprogressive nature of illness translates into increased risk of neurodegenerative disorders in patients with BPD, a risk that may be alleviated by Li treatment.

Key words: bipolar, neuroprotection, neurodegenerative, hippocampus

The structural findings in patients with psychiatric disorders, including mood disorders, have generally been inconsistent. They have rarely been replicated and there are frequently contradictory results. Clinical variables, such as duration of illness, numbers of episodes, family history, the presence of comorbid conditions, as well as exposure to medication may all impact neuroimaging findings, sometimes in opposing directions (1-3). Considering the number of factors affecting the brain structure in bipolar disorders (BPD), it is not difficult to find neuroimaging abnormalities in these patients. What is more difficult is the interpretation of the findings. Neuroanatomical changes in BPD may either represent inherited risk factors for the illness or emerge as secondary to the burden of illness (duration of illness, numbers of episodes), comorbid conditions or medication exposure. I will make the argument that it is ultimately the clinical variables, which will allow us to clarify the seemingly confusing neuroimaging findings. Conversely, more careful consideration of clinical heterogeneity in research design of imaging studies might make neuroimaging more relevant for everyday clinical practice of psychiatry. These issues can be demonstrated in the example of hippocampal volumes in BPD.

Smaller hippocampal volumes relative to controls are among the most replicated neuroimaging findings in patients with major depressive disorder (4). In contrast, eight previously published meta-analyses found preserved hippocampal volumes in patients with BPD (5-12). The cumulative absence of hippocampal volume abnormalities among BPD subjects is unexpected, considering the clinical overlap between unipolar and bipolar depression. There is no clinical or laboratory feature of unipolar depression, which would not also be reported in patients with bipolar disorders. In addition, depression in BPD is typically the main manifestation of the illness (13), is more likely to recur (14), and may start earlier (15) than unipolar depression.

Patients with unipolar and bipolar depression, however, differ broadly in terms of medication exposure. Although Li shows antidepressant properties even in unipolar depression (16), it is predominantly used as a mood stabilizer in bipolar disorders (17). Neuroprotective effects of lithium
have been well documented in tissue cultures and animal models (18;19), with some suggestion of similar effects also in human subjects (20-24). Could it be that hippocampal volume changes in BPD are masked by exposure to the putative neuroprotective effects of Li (18;19)?

To test this hypothesis we performed a meta-analysis of studies, which subdivided patients based on the presence or absence of Li treatment. BPD subjects who were currently not treated with Li had significantly smaller bilateral hippocampal volumes relative to healthy controls who, in turn, had significantly smaller hippocampal volumes than Li-treated BPD participants (25). These findings explain the negative results of previous meta-analyses, where the substantially larger hippocampal volumes in the Li-treated subjects could have masked the smaller hippocampal volumes in the non-Li subgroups. However, the interpretation of results as an effect of Li is difficult. It was unclear, in a number of included studies, whether or not the patients were compliant, or whether they were treated with a sufficient dose of Li for a sufficient duration of time. In addition, none of the included studies controlled for the illness burden (duration of illness, numbers of episodes). This is important as hippocampal volume decrease is associated with illness burden (26;27) and is unlikely to be present in the early stages of illness. Investigating the effects of Li on hippocampal volumes thus requires maximizing the burden of illness.

To address these limitations, we studied bipolar patients with high burden of illness (10 years of illness and at least 5 episodes) and either no current or chronic, ongoing, regularly-monitored Li treatment for at least 2 years. Among BPD participants selected for substantial illness burden, only those not treated with lithium had lower hippocampal volumes than controls. BPD patients with similar illness burden and ongoing Li treatment had hippocampal volumes comparable to controls. Since the Li and non-Li groups in our study did not differ in relevant clinical variables, patient-related factors were unlikely to underlie the results. It seems more likely that the observed differences were related to differential exposure to Li (28). In addition, our previous studies showed preserved hippocampal volumes in unaffected subjects at genetic risk for BPD (29) or in Li-naïve bipolar patients early in the course of illness (28;29), suggesting that hippocampal volume changes in BPD are not pre-existing but rather develop only later in the course of the illness (see Figure 1). These results provide an indirect support for negative effects of illness burden on hippocampal volumes in bipolar disorders and for neuroprotective effects of lithium.

The findings also raise a number of clinical questions. Does the putative neuroprogressive nature of BPD translate into increased rates of neurodegenerative disorders? Does Li alleviate this risk? Could it even be used to treat neurodegenerative disorders? Analyses of the Danish population databases showed increased rates of dementias in patients with mood disorders relative to general population or patients with other chronic conditions (diabetes, osteoarthritis) (30;31). Interestingly the risk of dementia further increased with numbers of episodes of mood disorders (32).

Two small, uncontrolled studies have looked at effects of Li on the risk for dementia. A study using general medical practice database suggested that a greater proportion of patients with the diagnosis of dementia were treated with Li relative to patients without the diagnosis of dementia (33). In this study prescription of Li could have been a marker for the presence of mood disorders, which increase the risk of dementias. This potential confounding factor would be better addressed by comparing mood disorders in patients with and without Li treatment. Such a study showed that Li-treated bipolar patients over 60 years of age had lower rates of dementia than bipolar patients not treated with Li, despite absence of differences between the groups in illness burden (34). An epidemiological study demonstrated that whereas patients with a single prescription of lithium had an elevated risk of dementias, repeated prescriptions of lithium brought the risk down to that of the general population level (35).

The above-mentioned studies are difficult to interpret as they do not control for patient-related or prescriber-related confounding factors. Physicians may be, for example, less likely to prescribe Li to patients showing cognitive impairment or such patients may be less likely to tolerate Li. This would artifactually decrease the rates of Li-treated patients with dementias. The best way to control these confounders and to demonstrate anti-dementia properties of Li would be to use a prospective,
A single 10-week, multicentre, placebo-controlled, single-blind study of patients with mild Alzheimer disease (AD) reported no significant benefits of Li treatment on either cognitive performance or cerebrospinal fluid (CSF) concentrations of disease-related biomarkers (36). Interestingly, a single site analysis of data from this study did find increases of BDNF in Li-treated patients (37). The study was criticized, on the basis of the dosage and duration of treatment. Also the potency of any given medication to prevent AD and to treat a full-blown dementia would likely differ. Thus it may be preferable to test the effects of lithium in subjects who are at an increased risk for developing AD. Encouragingly, a single 12-month, double-blind, placebo-controlled trial in subjects with amnestic mild cognitive impairment showed slowing of cognitive decline, a significant decrease in CSF concentrations of phospho-tau, with a trend for decrease in beta amyloid (38).

To summarize, it seems that bipolar disorders negatively affect the structure of the brain. The neuroprogressive nature of illness translates into an increased risk of neurodegenerative disorders in patients with BPD, a risk that further increases with the numbers of episodes of mood dysregulation. Li-treated patients have mostly preserved brain structure, even in the presence of a marked burden of illness. These putative neuroprotective effects of Li seem to also alleviate the risk of neurodegenerative disorders on a population level, an effect that requires repeated prescriptions of Li. In contrast, controlled studies did not show persuasive effects of Li in treating patients with full-blown AD, although there are promising findings in subjects with mild cognitive impairment.

These findings also have broader implications. The notion that mood disorders have a neuroprogressive component and leave measurable “scars” in the brains of patients has marked consequences for our conceptualization and treatment of these conditions. Similarly, these results change our views about the pharmacodynamic properties of psychiatric medication. At least for lithium, it seems that the effects are not only about modulating the synaptic transmission/software of the brain, but rather about changing its very hardware or rather wetware.

Acknowledgement: The studies described here were supported by funding from the Canadian Institutes of Health Research, the Nova Scotia Health Research Foundation, the Dalhousie Clinical Research Scholarship to Dr. Hajek, and grants from the Ministry of Health (Grant No. NR8786) and the Ministry of Education (MSMT 1M0517) of Czech Republic.

Figure 1: Effects of illness burden (duration of illness, numbers of episodes) and exposure to Li on hippocampal volumes. The yellow/orange cluster denotes a significant hippocampal volume decrease in non-Li relative to control participants (corrected p < 0.05). For details, please see reference (28).

GP Comment

What have I learned from this paper?

I have always conceptualised that the hippocampus stores the memories needed to co-ordinate an effective thinking response and is central to performance and wellbeing. Lithium also has an unequivocal antisuicidal effect (BMJ Editorial 2013 347: f 4449 by Ann Berghoffer). This paper helps me to re-evaluate the role of lithium in the treatment of BPD. Lithium has a valued role in the clinical treatment of BPD and is a first-line treatment where primary and secondary care need to work together, explaining the benefits, together with the need for careful monitoring and follow through. This paper helps me to explain the benefits.

Dr David Beales FRCP MRCGP DCH DRCOG Dip Psych, GP with a Special Interest in Behavioural Medicine, Ropley.
References


32. Kessing LV, Andersen PK: Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? J Neurol Neurosurg Psychiatry 2004; 75:1662-1666


Lithium: the complex mechanisms of action of the simplest metal

Luchezar Hranov. Department of Psychiatry, Medical University of Sofia, Bulgaria.

Abstract

Lithium enhances neuronal resilience and hampers long-term neuronal (and by extension, mental) deterioration. Its “mood stabilising” properties are due to multi-level actions on the intracellular signal transduction pathways affecting the function of G proteins, of some intracellular messengers (mioinositol, MARKS, Bcl-2, ER stress proteins, calmodulin-synapsin1-synaptotagmin complex), and of some key enzymes (adenily cyclease, protein kinases A, Cά and Ce, GSK-3, ERK, MAP-kinase). In the long run, mood-stabilising agents enhance blockade of excitotoxic/apoptotic pathways, phosphorylation and rearrangement of microtubular proteins, and regulation of the expression of genes implicated in processes involved in neuroplasticity, neuroprotection, even neurogenesis. Long-term “stabilisation of mood” has taught us the lesson that pharmacologic enhancement of neuroprotective/neurotrophic mechanisms carries a high promise for effective interventions not only in bipolar affective disorder and schizophrenia but in brain damage, dementias and other neurodegenerative diseases, and even in stress-induced mental disorders.

Key words: lithium, bipolar disorder, signal transduction, neuroplasticity.

Introduction

Lithium (Li+) is the lightest of the alkali metals, with a density only half that of water. It is used medically under the form of a cationic salt: lithium carbonate or citrate. As with many other drug therapies, the medicinal properties of lithium were discovered serendipitously and utilized long before its mechanisms of action could begin to be studied. Aretaeus of Cappadocia (AD 81 – 138) observed and documented cases of agitated insanity accompanied by mood elation and defined these states as “worsening of melancholia”. He prescribed drinking water from certain alkaline springs containing lithium. The prescription was confirmed about 3 centuries later by his disciple Soranus of Efesus (1). In the 19th century, lithium salts were used therapeutically as part of popular tonics such as 7UP, as soporifics and as gout remedies.

Lithium was the first antimanic treatment discovered and it brought along the birth of the psychopharmacology revolution (4). The introduction of lithium salts for the treatment of bipolar affective disorder (BPD) by John Cade in 1949 revolutionised the pharmacotherapy of severe psychiatric illnesses. This landmark discovery not only relieved millions of suffering individuals but also changed the public and scientific perception of psychiatric disorders and triggered still ongoing attempts to define pathophysiological mechanisms for their origin and treatment (25).

Cade’s work was followed up and validated by a series of European studies (39, 40). Over time, lithium became the gold standard for the management of the bipolar spectrum and the first of the so-called “mood stabilizers”. A mood stabilizer is defined as a drug that benefits one or more primary mood states of BPD, is effective in the acute and maintenance phase of treatment, does not worsen any aspect of the disease (including enhancement of “switching”), and eventually reduces the number of illness episodes and prevents deterioration (16). By definition, such a stabilisation IS NOT ONLY control over acute full-blown/subsyndromal illness episodes but also dampening of mood lability, reducing disease progression, decreasing aggression and suicidality, improving functioning and enhancing cognition. Such complex effects could hardly be accomplished by a single pharmacological mechanism.

Exposure to lithium evokes a wide spectrum of behavioural, physiological, and developmental responses in diverse organisms. These effects have been explored in the hope of elucidating the...
mechanisms of lithium therapeutic action (14). Lithium exerts multiple effects on numerous biological processes, such as embryonic development, haematopoiesis, glucose metabolism, heart function, and endocrine regulation (44). The therapeutic impact of lithium is much more complex than it may seem. Several other beneficial effects of lithium have been observed in psychiatry such as anti-aggressive effects in adults and children, symptomatic improvement of hyperactivity in schizophrenia, and behaviour benefits in mentally retarded patients. Moreover, lithium has been found to be useful in a broad range of neurological disorders (headaches, epilepsy, stroke, amyotrophic lateral sclerosis, fragile X syndrome, Huntington's chorea, Parkinson's disease and Alzheimer disease), endocrine disorders (hyperthyroidism, thyroid carcinoma, diabetes mellitus, inappropriate secretion of the antidiuretic hormone), haematological disorders (neutropenia, thrombocytopenia), dermatological disorders (seborrhoeic dermatitis), allergic disorders (asthma), and infectious diseases (AIDS-related dementia) (44).

Many drugs have been designed, by evolution or synthesis, to interact with a single specific protein receptor or enzyme. During the last 50 years, many biochemical actions of lithium have been identified, providing the basis for numerous hypotheses that were proposed to explain its mechanism of therapeutic action. Such an approach targeted to isolated sites of action makes it exceedingly difficult to integrate the often opposing actions of lithium at different sites into a single general biological mechanism. Recent research suggests that understanding how lithium works in the treatment of BPD requires a very different way of thinking about drug action. It now seems likely that multiple sites affected by lithium contribute to its mood-stabilizing action. Some of the numerous effects of lithium that have been identified may each provide a necessary, but individually insufficient, component of the therapeutic response. Thus, they should be conceptualised as being only facets of the very complex therapeutic effect of lithium (18).

**Bipolar affective disorder (BPD)**

BPD is a major health problem with potentially devastating consequences for affected individuals, their families and society. Recent studies have clearly shown that, although it has been regarded as a remitting disorder with a generally favourable long-term outcome, this may only represent the situation for a minority of patients. BPD is recognized by the World Health Organization as a leading debilitating neuropsychiatric disorder that affects about 1.3% of both sexes globally (34). The poor prognosis of these patients is illustrated by high rates of relapse, lingering residual symptoms, chronicity, cognitive and functional impairment, forensic complications, diminished quality of life and psychosocial disability. Patients with BPD I are prone to coexisting substance abuse, cardiovascular disease, diabetes mellitus, thyroid dysfunction, and have a 5¬ to 17-fold higher suicide rate than the general population. There is evidence that the illness is self-perpetuating and each episode increases the risk of future recurrence (2). In untreated patients, the disorder typically worsens owing to cycle acceleration; the frequency of episodes increases due to shortening of the length of symptom-free intervals. An increase in the number of episodes correlates with decreased cognitive abilities and deficits in social functioning.

Accompanying the observations about the poor clinical course and outcome for many patients, there has also been a growing appreciation that BPD is a disorder in which regional reductions in CNS volume, as well as reductions in the numbers and/or sizes of glia and neurons in discrete brain areas do really exist (2). It has been demonstrated that the neuronal density (especially of non-pyramidal GABAergic interneurons) in the dorso-lateral prefrontal cortex is decreased, the volume of the subgenual anterior cingular cortex is smaller than in healthy controls, and the third ventricle is often enlarged in BPD patients (10, 22, 26). The marked reduction in glial cell counts in the subgenual prefrontal cortex, orbital cortex, dorsal anterolateral prefrontal cortex, amygdala, basal ganglia, and dorsal raphe nuclei may contribute to impairments of neuronal structural plasticity by reducing the neuronal energy supply and by reduced glial-mediated clearing of excessive synaptic glutamate (15, 26, 31). Although the precise cellular mechanisms underlying these morphometric changes remain to be fully elucidated, the data suggest that BPD is associated with impairments of structural plasticity and cellular resilience (28, 31). It is not known whether these deficits constitute developmental abnormalities that may confer vulnerability to abnormal mood episodes, compensatory changes to
other pathogenic processes, or are the sequelae of recurrent affective episodes per se. Structural damage is present before the first illness episode and progresses throughout the course of the disorder; that is why there is incomplete inter-episode recovery, many relapses and progressive pervasive functional deterioration (16). More recent evidence suggests that BPD affects intercellular signalling cascades, leading to impairments in structural and functional neural plasticity (32).

Accumulating evidence of the behavioural effects of lithium led to its approval by the FDA in 1970 for the treatment of mania in bipolar disorder; it still continues to be the mainstay of drug treatment. Its clinical applications include initial treatment of new manic episodes, long-term stabilisation of mood in BPD, and adjunctive therapy/prophylaxis in unipolar recurrent depression (13). Lithium has been proven to be effective in reducing both manic and depressive symptoms and in reducing the rate of suicide in bipolar patients (13).

The therapeutic action of lithium in BPD appears not to result from an effect at a single target site, but is rather an integrated complex of events which effectively adjusts neuronal activity at multiple levels (19). It is the integration of the multiple effects of lithium which is necessary to achieve the neurochemical balance and neuroanatomical stability facilitating the complex processes of mood recovery and stabilisation. Yet, it remains unclear how many of the multiple biochemical and molecular effects may explain the mechanism of the therapeutic benefit of lithium on BPD.

Mechanisms of action of lithium

With the passage of years it has been found that lithium induces multiple biochemical and molecular effects on neurotransmitter-receptor-mediated signalling, ion transport, signal transduction cascades, hormonal and circadian regulation, and gene expression (16). As neuroscience has developed over the past 50 years, the central paradigm for lithium action has shifted from monoamine metabolites via neurotransmitter receptors, second messengers, third messengers (transcription factors) to neuroprotection and neurogenesis, and in each of these lithium was found to have at least one major effect (8). Nevertheless, the precise underlying biochemical mechanisms of this drug are still not well understood and remain poorly defined (8, 12). Jope (19) has produced a summary of the manifold effects of lithium in the brain, as follows.

Lithium:
- adjusts neurotransmitter balances.
- adjusts basal and/or stimulated fluctuations in second messenger systems.
- adjusts basal and/or stimulated fluctuations in transcription factors.
- modulates expression of specific genes.
- protects neurons from toxic insults.
- modifies cytoskeletal function.

Importantly, rather than having unidirectional effects, lithium acts at multiple sites to adjust the balance between opposing influences (19). Moreover, an activity-dependent accumulation of lithium may be crucial for its therapeutic specificity and its ability to regulate synaptic function.

Neurotransmitter effects

Lithium was found to influence, to some extent, virtually every neurotransmitter. It reduces dopaminergic activity, enhances cholinergic and GABAergic neurotransmission, and blocks receptor supersensitivity in all major neurotransmitter systems (13). The levels of dynorphin, substance P, tachykinin, neuropeptide Y, and neurokinin A in certain brain regions are also increased following lithium treatment (19).

Accumulating evidence indicates that lithium has direct effects on glutamatergic neural transmission. Lithium stimulates glutamate release via activation of the N-methyl-D-aspartate (NMDA) receptors. Acute treatment increases synaptic concentrations of glutamate which, upon chronic lithium administration, leads to an increase in and stabilisation of glutamate uptake transporter capacity.
Several lines of evidence suggest that lithium alters neuronal excitability at hippocampal CA1 synapses, leading to enhanced excitatory postsynaptic potentials. This effect has been attributed to an increase in presynaptic excitability as well as to increases in synaptic efficiency. Alternatively, the effect of lithium on synaptic enhancement at CA1 synapses may arise from its ability to potentiate currents through the AMPA subtype of inotropic glutamate receptors by selectively increasing the probability of channel opening (38).

It is still not clear which, if any, neurotransmitter synthesis, uptake, and release processes contribute to the therapeutic action of lithium. It is possible that it is the adjusted balances (generally increased GABA/glutamate and acetylcholine/ catecholamine activity ratios), rather than actions on a single neurotransmitter, that facilitate mood recovery and stabilization (19).

**Enzyme interactions**

Several enzymes have been shown to be directly inhibited by lithium at therapeutically relevant concentrations. These include inositol monophosphatase (IMPase); inositol polyphosphate a-phosphatase; bisphosphate 3'-nucleotidase; fructose 1,6-bisphophatase; glycogen synthase kinase and phosphoglucomutase. Lithium also affects some enzymes involved in energy metabolism, such as hexokinase, pyruvate kinase, cholinesterase, tryptophan hydroxylase, and glycogen synthetase. Plenge (33) proposed the theory that lithium inhibits enzymes which have essential cofactor cations, such as Na+, K+, Ca++, Mg++, and Zn++ by displacement of these cations from the enzyme molecule. Decrease of the hippocampal Na+-K+-ATPase activity (and thus, of Ca++ turnover) remains a viable contributory factor in the actions of lithium.

**Signal transduction systems**

Numerous studies have demonstrated that lithium increases basal levels of cyclic adenosine monophosphate (cAMP) but impairs receptor-coupled stimulation of cAMP production. Overall, it appears that these actions of lithium reduce the magnitude of fluctuations in cAMP levels by increasing the lowest basal levels and decreasing maximal stimulated increases, thus stabilising the activity of this signalling system (19). A primary action of cAMP is to stimulate the activity of cAMP-dependent protein kinase A (PKA). Lithium inhibits PKA-induced phosphorylation of cytoskeletal proteins which may contribute to long-term modulation of neuronal structure and function. The major adverse effects of lithium therapy - hypothyroidism and nephrogenic diabetes insipidus - have been postulated to arise from the effects lithium has on thyroid-stimulating-hormone-sensitive adenylate cyclase, and on antidiuretic hormone (vasopressin)-sensitive adenylate cyclase, respectively (41).

Lithium is a potent inhibitor of inositol monophosphatase, the enzyme that converts inositol monophosphates to free inositol (43). Reduced inositol levels following lithium administration are most conspicuous in the hypothalamus and the astrocytes (19). The “inositol depletion hypothesis” posited that only the most active neurones in the central nervous system would be affected by lithium as they would be the cells most rapidly depleted of available inositol (3). The primary second messengers produced by the phosphoinositide signal transduction system are inositol trisphosphate (IP3), and diacylglycerol (DAG). The IP3 arm of the system releases intracellular calcium from internal stores which then activates calcium and/or calmodulin-dependent protein kinases. The DAG arm of the system produces activation of protein kinase C (PKC) which has various critical substrates. The PKC family of 12 isoymes regulates glucose transport, ion conductance, neural excitability, neurotransmitter release, gene expression, dendrite spine morphology and plasticity (11). PKC isoforms differ in structure, subcellular localization, tissue specificity, mode of activation, and substrate specificity (36). They are translocated from cytosol to membrane upon activation by DAG and phosphorylate NMDA and AMPA receptors.

The PKC inhibitor tamoxifen has demonstrated a robust anti-manic efficacy (11, 48, 49). Chronic application of lithium reduces specifically the levels of isotypes PKCa and PKCe (24). PKC activity
increases in the prefrontal cortex following stress or stimulant use and is decreased by chronic treatment with lithium. Excessive activation of PKC dramatically impairs cognition in mammals. Six-week treatment with lithium abolishes this effect.

Long-term treatment with lithium reduces significantly the levels of one of the major substrates of PKC, MARCKS (myristoylated alanine-rich C kinase substrate). MARCKS plays a key role in transducing extracellular signals to alterations in the conformation of the actin cytoskeleton which is crucial to morphogenesis and secretion. Its down-regulation following chronic lithium administration may alter membrane structure and stabilise aberrant neuronal activity in different brain areas (24).

Lithium activates the intracellular activated protein kinase/extracellular signal-related kinase (MAPK/ERK) signalling pathway which is used by neurotrophins, neurotransmitters, and neuropeptides to exert their neurotrophic and neuroprotective effects through specifically enhancing progenitor cell proliferation and differentiation, neuronal process growth and regeneration, neuronal survival, and long-term synaptic remodelling and plasticity (17). The final result is phosphorylation and activation of the transcription factor CREB (cAMP response element binding). CREB regulates the expression of many different genes, including B-cell lymphoma 2 (bcl-2) and brain-derived neurotrophic factor (BDNF) to enhance neuroprotection and neuronal survival mechanisms (27).

Lithium may modulate the production of nitric oxide and, in addition, may inhibit phospholipase A2, an enzyme that mediates the production of arachidonate which, in turn, leads to reduced activation of PKC, alterations in cell growth and apoptosis (pre-programmed cell death), and changes in the production of eicosanoids. Thus, lithium may affect central inflammatory processes and exert immunostimulant and antimicrobial activity (42).

**Mitochondrial function**

Mitochondria play a critical role in regulating energy production via oxidative phosphorylation and regulation of intracellular calcium, and are also critical mediators of cellular apoptosis (36). Increasing evidence suggests that they may also be integrally involved in general processes of synaptic plasticity (35).

Many lines of evidence link BPD to a fundamental abnormality in oxidative energy generation. Both brain and somatic energy generation are altered, and high rates of deletions in mitochondrial DNA are seen, as well as a reduction in the activity of complex 1 of the mitochondrial chain. Increased lipid peroxidation, a consequence of uncompensated oxidative stress, is consistently documented in BPD. Oxidative damage results in damage to membrane phospholipids, leading to alteration in fluidity and aggregation of oxidised protein, which may result in impairment of mood-stabilising neurones, and can ultimately lead to neuronal cell death by apoptosis (2). Chronic lithium treatment reduces oxidative stress.

Altered calcium dynamics is the most reproducible biological measure in the pathophysiology of BPD. A large movement of calcium into the mitochondria will exceed the mitochondrial capacity to export protons, potentially interrupting adenosine triphosphate synthesis and the activation of the permeability transition pore with release of cytochrome C, thus initiating cellular apoptosis. In addition, excessive production of reactive oxygen species (or free radicals) triggered by mitochondrial dysfunction may lead to oxidative stress, regardless of whether or not this is related to lower antioxidant capacity. Lithium affects beneficially key enzymes on the mitochondrial membrane via its neuroprotective actions, described below (35).

**Transcription factors and gene expression**

Many of the genes putatively involved in the pathogenesis of BPD are regulating 1) cellular signalling; 2) critical cytoskeletal proteins; 3) trophic effects and cell survival; 4) metabolic events and cell death (29). The underlying deviant brain growth, organization and ageing, resulting from their dysfunction, are likely to determine the lifetime course of psychopathology (9).
Transcription factors fulfil the critical functions of transmitting and regulating signals to the nucleus, allowing cells to respond to a changing environment through alterations in gene expression. They may be selectively influenced by lithium both as a result of modulation of the activities of specific signalling systems and as being specific targets for lithium (19). Lithium modulates the activity of several transcription factors (AP1, CREB, NF-κB) and increases mRNA levels for c-fos genes and for nitric oxide synthase 2, thus modulating gene expression. The net effect is an overall stabilisation and minimisation in the magnitude of signal fluctuations at the level of gene expression (19).

Neuroplasticity, neuroprotection and cytoskeletal remodelling

“Neuroplasticity” subsumes diverse processes of vital importance by which the brain perceives, adapts to, and responds to a variety of internal and external stimuli (49). Loosely defined, neurotrophic effects augment proliferation, differentiation, growth, and regeneration of neurons while neuroprotective effects slow or halt the progression of neuronal atrophy or cell death following the onset of insult, disease, or clinical decline (8, 17).

Lithium may enhance cellular resilience and plasticity in dysfunctional synapses and neuronal circuitry implicated in psychiatric disorders (17). The neurotrophins are a family of regulatory factors. They are known to mediate the differentiation and survival of neurons, as well as the modulation of synaptic transmission and synaptic plasticity. Increasing evidence suggests that neurotrophic factors inhibit cell death cascades by activating the extracellular-regulated kinase (ERK) signalling pathway (36). Lithium increases mRNA and protein levels of neurotrophins such as BDNF, glial cell-line derived neurotrophic factor (GDNF), neurotrophin 3 (NT-3), and vascular endothelial growth factor (VEGF) in cultured cells and brain regions. Nevertheless, the majority of the neuroprotective and neurotrophic effects of lithium appear to occur through its influences on two key proteins in the brain, bcl-2 and GSK-3β.

The bcl-2 (B-cell lymphoma/leukaemia-2) family includes both pro-apoptotic and anti-apoptotic proteins embedded in the inner mitochondrial membrane, although they may also be present in nuclear membranes and in the endoplasmic reticulum (26). The expression and/or activation of pro-apoptotic bcl-2 family members (e.g. bad and bax) may increase mitochondrial membrane permeability, while anti-apoptotic members (e.g. bcl-2 and bcl-xl) have the opposite effect (26). Bcl-2 is considered to be a neural “protector” by virtue of its ability to inhibit neural cell death by apoptosis and necrosis precipitated by numerous noxious stimuli. It also promotes neurite sprouting and influences the genetic control of axon growth. Bcl-2 seems to have multiple protective mechanisms of action including antioxidant effects, enhancement of mitochondrial reuptake of intracellular calcium and attenuation of the release of calcium from the mitochondrion amongst others (42).

The transcription factor PEBP2P (polyoma enhancer binding protein 2P) is one of the genes identified thus far to have markedly increased expression and functioning following lithium treatment. The end result is a dramatic increase in the levels of the neuroprotective protein bcl-2. Such increases have been registered predominantly in the frontal cortex (particularly in layers II and III), the hippocampus and the striatum (6). Interestingly, lithium also increases the expression of bcl-2-associated athanogene (bag-1), which is known to attenuate glucocorticoid receptor nuclear translocation, to activate the ERK/MAP kinases, and to potentiate the anti-apoptotic functions of bcl-2 (50).

Lithium exerts a direct inhibitory effect on glycogen synthase kinase (GSK-3), a multifunctional and highly active serine/threonine kinase that regulates diverse signalling pathways (e.g., the phosphoinositide 3-kinase pathway, the Wnt pathway, PKA, and PKC), and the ensuing neuronal cytoskeletal rearrangements may be a significant consequence of lithium administration. In general, increased activity of GSK-3 is pro-apoptotic, whereas inhibiting GSK-3 prevents apoptosis. In mammals, two closely related isoforms - GSK-3α and GSK-3β - are present. The GSK-3β isoform is highly expressed in neural tissue where its expression is regulated during development. GSK-3 isoforms are important regulators of glycogen synthesis, gene transcription, axonal remodelling in developing neurons, cytoskeletal modelling and organization, growth of neural tissue, synaptic and neuronal plasticity, cellular structure and resilience, and apoptotic processes (20, 21). Its downstream
targets include transcription factors like c-Jun, proteins bound to microtubules (Tau, microtubule-associated protein 1B, kinesin light chain), cell cycle mediators (cyclin D), and metabolic regulators (glycogen synthetase, pyruvate dehydrogenase) (36). Following exposure to stressful conditions GSK-3 can have multiple effects that could impair neural plasticity and in potentially lethal conditions could facilitate the apoptotic process. These include actions of GSK-3 that both contribute to apoptosis and actions that block anti-apoptotic processes (21).

The inhibition of GSK-3β by lithium can induce significant changes in microtubule assembly resulting in significant neuroplastic changes in discrete brain regions and alterations in interneuronal connectivity. In fact, GSK-3 inhibition directly influences gene transcription, leading to anti-apoptotic effects and improved cell structural stability (7).

GSK-3 also directly regulates the dopaminergic, glutamatergic, and serotonergic neurotransmitter systems. It has been suggested that GSK-3 regulates behaviour by affecting β-catenin, glutamate receptors, circadian rhythms, and neurotransmission (23). All of these have been implicated in the pathophysiology of severe mood disorders, and all of them are affected by lithium treatment.

**Neurotrophic effects**

N-acetyl aspartate (NAA) is an amino acid localised exclusively in mature neurons. It is deemed to be a marker of neuronal viability and function. Abnormally low levels of NAA in CNS diseases like amyotrophic lateral sclerosis, mitochondrial encephalopathies and HIV dementia have been shown to normalise with remission of the CNS symptoms. Chronic lithium treatment increases levels of NAA in rodent brain, human neuronal cells in culture, as well as in vivo in human bipolar patients and healthy volunteers. The lithium-induced increases in NAA seem to occur mainly in the frontal and temporal lobes. Interestingly, there is no correlation between the increase in NAA and the lithium levels (42).

Chronic behavioural stress shortens apical dendrites in the CA3 region of the hippocampus in rodents. Lithium treatment initiated 2 weeks before the stress and continued throughout a 3-week period of stress attenuated these stress-induced reductions in apical dendritic lengths (45).

Several additional reports and meta-analyses have documented increased total hippocampal volume in patients treated with lithium compared with unmedicated patients (47). Pooled imaging data showed cerebral volume reductions in BPD that were significantly associated with illness duration. Bipolar patients who were not on lithium therapy showed significant decrease in cerebral and hippocampal volumes, whereas patients treated with lithium showed significantly increased hippocampal and amygdala volumes (15). Recent studies using high-resolution magnetic resonance imaging have convincingly shown that the amygdala volume is smaller in unmedicated bipolar patients and larger in patients with BPD on mood-stabiliser treatment (37).

Prominent volumetric abnormalities of the anterior cingulate cortex have been reported in BPD, and chronic treatment with lithium has been associated with increased grey matter volumes in this region (30).

Hence, the existing data point to neurotrophic and neuroprotective actions of lithium in multiple areas of the limbic and/or prefrontal network by increasing cellular resiliency, enhancing synaptic plasticity and modulating neuronal morphology.

Inhibition of GSK-3β contributes to lithium-induced neural cell proliferation (34). An in vivo study showed that lithium increased survival of newborn cells in the hippocampus (5, 46). These results suggest that chronic lithium treatment may not only exert robust neuroprotective effects (as has been demonstrated in a variety of preclinical paradigms) but may also have neurotrophic effects in humans.

**Conclusions**

Despite intensive research, the crucial question of how lithium is able to alter mind and mood remains a mystery (44). It is also unclear how the action of lithium on ubiquitously expressed molecules that
are mostly involved in the regulation of cell signalling and not on specific neurotransmitter systems can explain its relative selectivity as a therapeutic agent in psychiatry (12).

It has become evident that the research strategy of trying to find one molecular target of lithium therapeutic efficacy does not provide any satisfactory explanation (44). Rather than looking for a single site of action, many actions of lithium must, and can, be integrated to obtain a cohesive picture of how neuronal function is modulated by long-term exposure to lithium. Simultaneous multiple actions of lithium (some of which are bimodal), must be considered to be critical for the therapeutic response. These complex effects support neural plasticity and stabilise neurotransmitter balances, signalling activities, and gene expression, each of which may make a necessary, but individually insufficient, contribution to the therapeutic effects of lithium. The critical property of lithium appears to be that it is able to act at multiple sites to adjust the balance, and dampen the magnitudes of fluctuations, of positive and negative inputs to neuronal function. This allows lithium to normalise the complex components of mood disorders and to have multiple therapeutic effects (19).

Lithium alters intracellular and intercellular signalling in critical brain regions in a unique way. New insights of the diverse and complex actions of lithium open up an entirely new field of research. They carry profound implications in the neurobiology of bipolar disorder, implicating the inflammatory response, neuronal atrophy and death (41). Moreover, they throw light on new therapeutic approaches to presently untreatable neurodegenerative diseases (16).

**GP Comment**

*What have I learned from this paper?*

This fascinating article described the multiple biochemical and molecular effects of this medicinal metal which has huge therapeutic potential in 'mood-stabilisation' and was first used by Aretaeus of Cappadocia (AD 81-139)!

Bipolar disorder affects 1.3% of both sexes globally and is a debilitating neuropsychiatric disorder. Each episode increases the risk of a future recurrence and results in decreased cognitive ability and social functioning.

The exact mode of action of lithium is unclear. Rather than an effect at a single target site, lithium causes an integrated complex of events which adjusts neuronal activity at multiple levels to achieve the neurochemical balance and neuroanatomical stability. It enhances neuronal resilience and dampens neuronal fluctuation and deterioration.

The effect of lithium on long-term stabilisation of mood has huge therapeutic potential in not only bipolar disorder and schizophrenia but also in all mood disorders and stress-induced mental illness. In addition the neurotrophic and neuroprotective effects, chronic lithium therapy offers promising prospects for patients with brain damage, dementia and other neurodegenerative disorders.

This article emphasised to me how much we have yet to learn about the mind, mood, the interaction between mental and physical health and the aetiology and treatment of ill-health.

*Dr Anthea Robinson, GP, Bedfordshire.*
References


7. Chin PC, Majdzadeh N, D'Mello SR. Inhibition of GSK3beta is a common event in neuroprotection by different survival factors. Brain Res Mol Brain Res. 2005;137:193-201.


Neurocognitive impairment, psychosocial stress, and functional adjustment in bipolar disorder: Implications for disability policy

Boaz Levy and Emily Manove
University of Massachusetts, Boston

Abstract

New research in bipolar disorder (BPD) has uncovered various factors that may account for the enduring functional impairment observed in people who experience the disorder. Neuroimaging studies point to abnormal reductions in brain volume related to age and illness duration. Consistent with these findings, studies employing neuropsychological measures reveal that cognitive dysfunction in BPD increases with a more severe course of illness. For many people with BPD, cognitive deficits linger into periods of euthymia, and correlate with psychosocial impairment. These studies collectively support a neurodegenerative model in which repeated exposure to mood disturbance leads to neurological impairment, cognitive decline and functional difficulties. In this respect, they highlight the importance of preventive care for preserving functional adjustment in BPD. Effective prevention will probably involve significant reductions in psychosocial stress, which remains among the strongest predictors of symptom recurrence in BPD. This process may be leveraged by actively removing distressing social barriers to functioning, such as stigma and discrimination. This paper discusses implications for disability policy.

Key words: bipolar disorder, cognitive deficits, disability policy.

Introduction

Bipolar disorder (BPD) is one of the top ten most disabling disorders in the world (1). Even during euthymia, BPD is often accompanied by extensive psychosocial disability (2-4). Longitudinal investigations indicate that up to 50% of people with BPD who are hospitalized for an acute episode experience poor post-hospital adjustment (5), and rarely regain premorbid functioning after the resolution of mood symptoms (6). During euthymia, many people with BPD report severe reductions on various measures of quality of life (7, 8), reflecting major struggles to meet the demands of daily tasks (9), fulfil expected family or community roles (10-12), and maintain occupational status commensurate with professional ability and education (13-17).

These findings, along with qualitative research, indicate that treatments targeting syndromal recovery are insufficient for restoring psychological well-being in many people who have BPD (18, 19). In addition, it is becoming increasingly clear that the acute presence of mood disturbance, albeit a significant contributing factor (20, 21), is not the only cause of functional impairment in BPD (13, 22-25).

Cognitive dysfunction and psychosocial impairment

Cognitive impairment appears to be one of the strongest predictors of psychosocial dysfunction in BPD, especially during euthymia (26, 27). Studies indicate that cognitive dysfunction exacerbates with acute symptoms (28); however, deficits in attention (29), memory (30), and executive functioning (31) linger into euthymia in many people, even in the absence of residual symptoms (32). Multiple studies have linked chronic cognitive impairment in BPD to functional difficulties, as indicated by diminished employment (33), pursuit of disability support (34, 35), challenges in completing tasks of daily living (36), inconsistent medication management (37), poor adherence to treatment (38), and marginalized social role (12, 39). There is also longitudinal evidence that cognitive deficits predict psychosocial adjustment one, two and even fifteen years after hospital discharge (39-42), suggesting that the
aetiology and course of functional impairment in BPD is related in part to cognitive dysfunction.

Brain abnormalities

Cognitive impairment in BPD is deemed to originate in abnormal brain structures. Several meta-analytic reviews of structural imaging studies document the presence of consistent structural anomalies in the brains of people with BPD (43-45). Genetic risk alone has been linked to neurobiological trait abnormalities in multiple studies, using various forms of examination (46-48). At illness onset, people with BPD show some enlargement of the lateral ventricles, associated with volume reductions in whole brain and total white matter (49). Volume reductions measured during the first manic episode appear to be more pronounced in white than in gray matter (50). Across various stages of the illness, gray matter reductions centre around paralimbic areas (i.e., the anterior cingulate and insula), which are involved in emotional processing (51). Additional studies documented an abnormally high presence of hyperintensities in the deep white matter and subcortical gray matter, potentially representing ischemic damage related to illness progression (52). Consistent with these observations, studies further indicate that reductions in whole brain and prefrontal lobe volumes relate to age and illness duration (45). In the absence of clear evidence of significant cognitive impairment before BPD onset (53, 54), these findings are consistent with a neurodegenerative hypothesis, which accounts for the accelerated cognitive decline observed in studies of people with a more severe course of illness (55, 56).

A small number of studies to date have attempted to relate morphological brain abnormalities directly to cognitive impairment in BPD (57-59). However, one of the studies in this category deserves particular attention due to its exceptionally rigorous methodology. In a four-year longitudinal study, Moorhead et al. (59) followed a group of people with BPD and a control group of people without psychiatric diagnoses with repeated imaging measurements, cognitive assessments, and clinical evaluations. Analyses indicated brain density reductions only in people with BPD, which were specific to gray matter in the cerebellar, fusiform, and hippocampal areas. The observed volume reductions in the temporal lobe related to both the number of acute mood episodes and changes in cognitive functioning that were recorded over the course of the study. The results of this study agree with the repeated observation that cognitive impairment occurs more frequently in people with BPD who suffer from a more severe course of illness (60). In this respect, this study provides some of the strongest support to date for an illness-related neurodegenerative process in BPD.

Evidence from functional neuroimaging studies generally indicates limbic hyperactivity and frontal hypo-activity during emotional and cognitive tasks in people with BPD (61). Other analyses confirm this abnormal frontal-limbic activation, indicating attenuated activation of the ventrolateral prefrontal cortex, and enhanced limbic activation (43). However, although euthymic patients exhibited hyperactivity in the limbic system, they did not show the hypo-frontal pattern during cognitive tasks (61). Thus, these studies may account for mood disturbance in BPD but they do not elucidate the neurological source of cognitive impairment in asymptomatic patients.

Genetics and psychosocial stress

Although no one gene has been identified as predictive of BPD with more than a small effect size (62), a large volume of studies point to a heritability rate for BPD ranging from 60 to 89% (63-66). Studies also indicate that genetics influence the age of onset and illness severity in BPD (67). At the same time, multiple studies support a diathesis-stress model of BPD, in which illness severity and progression are predicted by the interaction of genetics and stress (56, 68, 69). In this view, BPD emerges as a genetic condition with a psychiatric phenotype that is highly sensitive to environmental stress.

Several studies have documented the specific effects of psychosocial stress on symptom severity and recurrence in BPD (70, 71). Within the model of social rhythm disruption, studies show that stressful life events and a change in routine can predict higher frequency of mood episodes and delays in functional recovery (6, 71-74). There is also evidence that interpersonal stress, perception
of diminished social support, and failure to attain psychosocial goals are psychiatrically destabilizing for people with BPD (22, 74, 75). These studies highlight the importance of diminishing psychosocial stress in the interest of symptom prevention. Conventional pharmacological and psychotherapeutic treatments of BPD may be limited in their ability to decrease psychosocial stress. While psychiatric treatment facilitates changes within the individual, it carries little impact on the person's greater social environment. In many cases, an unsupportive psychosocial environment can substantially undermine the gains of treatment (23, 25, 34, 35, 76).

**Synthesis**

A synthesis of new findings across several research domains suggests that BPD develops from a genetic component that is highly sensitive to environmental stress (56, 68). In particular, psychosocial stress exacerbates the psychiatric syndrome, intensifies the ill effects of symptoms, and reduces quality of life (6, 70, 77). Repeated exposure to symptoms may then lead to neurodegeneration and cognitive decline over the course of the illness (55, 56). This process accounts for worsening psychosocial impairment in people with BPD that often persists in the absence of mood symptoms in the form of long-term disability (11, 12). As genetic factors remain largely unaffected by available interventions, preventive efforts need to focus on reducing psychosocial stress, particularly during early and vulnerable phases of the illness.

Current treatments that strive to reduce psychosocial stress, such as interpersonal and social rhythm therapy, attempt to improve functioning by engendering cognitive and behavioural changes within the individual (78, 79). While these therapies are effective in many cases, interventions aimed at altering the larger psychosocial environment of people with BPD might be as critical as internal treatments to their wellbeing, given that psychosocial disability is partly ‘psyche’ and partly ‘social’ in nature. Stated differently, the functional disability observed in people with BPD is not encapsulated within the individual, but rather is defined by the interaction between the individual’s characteristics and the social environment (34, 35). Broader environmental changes conducive to stress reduction on a larger social scale – such as reduced public stigma and increased employment supports – may therefore substantially increase lifetime functional adjustment in BPD, as several studies have found (23, 25, 80).

**Implications**

The new research findings regarding the important role of psychosocial stress in the aetiology of BPD, and its associated functional impairment, may inform the development of policies that can bring about changes to social structures larger than individuals’ immediate support networks. This process may begin with examining policies regarding disability support for BPD. The following discussion examines potential reforms to the current disability policies in the United States. Although disability policies vary across countries, the example of the U.S. Social Security Administration (SSA) may be useful in the present context for illustrating larger principles with global implications.

To provide a brief context for the discussion, the SSA provides cash benefits and public health insurance to people with disabilities in the United States through two programs: the Social Security Disability Insurance (SSDI) and the Supplemental Security Income (SSI) programs. SSDI, as its name reflects, was created to insure U.S. workers against disability. Thus, the SSDI program, in its original conception, aimed to provide long-term financial support to tax-paying U.S. workers over age fifty, who had developed severe physical impairments that precluded employment and from which they were not expected to recover (16). Current regulations governing SSDI eligibility are in large part unchanged since the program’s inception, although the list of qualifying impairments has broadened greatly. Specifically, the list now includes psychiatric disorders such as BPD (81). Otherwise, the three primary eligibility criteria – evidence of having paid sufficient recent FICA taxes as SSDI “premiums,” medical documentation of a qualifying impairment, and very limited earnings from employment for at least 12 continuous months (under $1,010 gross per month in 2012, totalling a limit of $12,120 gross per year) – remain the same (82).

The population of beneficiaries, however, has changed dramatically since the beginning of the
programme. People with psychological diagnoses are currently the biggest subset of SSDI and SSI benefit recipients, and their numbers are increasing (16). Unlike the more permanent and total disabilities acquired by older workers that were originally envisioned by SSDI policymakers, BPD, like many other psychiatric disorders, often presents early in life, and is typically long-lasting, fluctuating and highly treatable, with many people experiencing substantially improved functioning over time (16, 83). Prognoses for people with BPD are enhanced when interventions begin as close to initial symptom presentation as possible (84). In line with the history of the SSDI, however, to have BPD qualify as a disabling impairment, claimants are required to produce medical evidence of mood symptoms that have persisted over a significant period of time and either currently greatly limit their functioning, or did so at length in the past, such that even if presently asymptomatic, they are at high risk for future decompensation (85).

In this respect, SSA disability policy may be a poor fit with the needs of many individuals with BPD. People with BPD could likely benefit from financial, health insurance and employment supports early on in the course of their illness, with an eye towards relieving stress while preserving their functioning in mainstream settings to the greatest extent possible (16, 86-88). Further, the SSA requirement of evidence of prolonged mood disturbance ignores the detrimental effects that severe symptom exposure may have on the brain, cognition and prospective functional adjustment (59, 89, 90). Thus, the functioning of many people with BPD would probably be more greatly preserved if they were offered disability supports prior to experiencing prolonged psychiatric instability.

In addition, the SSA current disability policy does not consider that debilitating cognitive deficits can be present in BPD even in the absence of mood symptoms, and during early recovery from a severe episode of mood disturbance in particular (89, 90). The point of discharge from the first hospitalization is especially critical for intervention. For many people with BPD, the transition out of inpatient care may be accompanied by significant cognitive impairment in the context of residual mood symptoms. At this time, individuals with BPD are also vulnerable to the adverse effects of new medications, and the frightening confusion that follows the onset of a severe psychiatric disorder. Without proper support, they may be pressured into resuming functioning in a mainstream environment with demands that exceed their cognitive limitations and coping ability. This predicament is fraught with chronic stress that emanates from the constant threat of failure at work, school or other important social functions. The combination of a fragile emotional state, cognitive impairment, and chronic stress may exacerbate mood symptoms to the point of decompensation. Hospital readmission typically results in aggressive titration of sedative psychopharmacological medications (91), which may carry adverse effects that further impede recovery toward functional adjustment (56, 92). In this vicious cycle, inpatient treatment of BPD may unwittingly medicate the effects of psychosocial stress. An imbalanced reliance on pharmacological treatment may in fact add to functional challenges that could otherwise be diminished with policies that offer larger psychosocial supports.

The recognition that some people with BPD may not be able to compete for and successfully maintain employment right after leaving a first hospitalization may justify the provision of immediate financial and occupational support at discharge. Although many individuals with BPD eventually receive similar disability benefits in later stages of the illness, the long-needed support comes when their functioning is much more substantially curtailed – at a point in which their potential for psychosocial recovery has already been diminished by alterations in their developmental trajectory. In this regard, the early onset of BPD, most frequently calculated at an average of 25 years (93, 94), compounds the impact of this psychiatric illness on development. In fact, from a developmental perspective, in the absence of appropriate support, the passage of time alone may deepen functional impairments. For this reason, policies that emphasize early support may carry important preventive effects for BPD.

In addition, new studies in BPD can inform policy reform by pointing to gradations in functional adjustment. On one end of the spectrum are people fully dependent on external support due to unrelenting mood disturbance. On the other end, euthymic individuals face milder psychosocial challenges that emerge in mainstream professional, education and other settings. An effective disability policy needs to create conditions that allow for functional recovery in mainstream settings during the early stages of the illness instead of restricting the supportive effort to those who have
already reached a highly-dependent and socially-marginalized state (16, 88). The current policy of SSA leaves euthymic patients with mild to moderate cognitive dysfunctions at risk for further deterioration. Therefore, the chronicity of mood symptoms should not be the primary aspect of the illness that determines eligibility for support services, especially in younger age groups.

Supporting functional adjustment instead of disability

Under current SSA policies, a potential concern around providing early support for individuals with BPD - in an effort to help them resume or maintain mainstream functioning - might be that early support could incentivize reliance on disability benefits rather than on the exertion of compensated work. Indeed, most people who receive disability benefits for BPD do not return to full-time employment (95). However, this undesirable outcome may be partly due to a lack of program support for beneficiary employment, in keeping with the historical insurance mission of the SSDI program.

Many substantial disincentives to work embedded in SSA regulations have long been identified as impediments to beneficiaries (including specifically those with BPD) returning to mainstream functioning (16, 83). These disincentives include beneficiaries potentially losing the entirety of their cash benefits and putting their public health insurance eligibility at risk if they gross over $1,010 in any one month after a brief trial work period (82). Qualitative and quantitative research shows that, even when euthymic, beneficiaries with BPD view risking total loss of their benefits as overly risky, particularly given the occupational challenges and stigma they expect to face in the pursuit of new employment (83, 96). Fortunately, research aimed at replacing these barriers to work with employment incentives - including shifting to a more gradual reduction in benefits proportional to earned income – is ongoing and has found positive effects on participant beneficiaries' total income and other occupational outcomes (97, 98). Rapid implementation of these reforms is urgently needed, however, to improve occupational outcomes in BPD.

Furthermore, many people with BPD who experience milder forms of dysfunction may wish temporarily to rely on benefits at illness onset, without abandoning the natural pursuit of psychosocial growth. In other words, those who can continue to function in mainstream settings may not consider the financial benefits of disability as sufficient compensation for having to limit their income and employment, nor for having to experience the stigma, isolation, and other losses that come from adopting a formal status of disability (99). The pursuit of disability status by some individuals with BPD may therefore reflect their belief that fitting back into mainstream society is not currently possible for them. A shift in policies may help to change this view for many such people, especially during the earlier phases of their illness. Specifically, people with BPD may be more likely to pursue employment if they could rely on disability funds during periods of unemployment and recovery from debilitating mood episodes, without the need to endure recurrent, lengthy and complicated application processes.

A policy that supports full-time employment for people with BPD carries multi-faceted gains. From a purely financial perspective, the sheer monetary loss to the U.S. economy due to lost productivity of individuals with BPD and their caregivers was estimated at $38 billion in 1991 by the National Institutes of Health [NIH; 100]. Financial considerations aside, consistent employment represents one of the strongest predictors of psychiatric stability in people with BPD and plays an important role in their recovery process (101, 102). In this regard, early supported employment interventions have been found to correlate with improved future employment outcomes in adolescents and adults diagnosed with affective disorders (86-88). Thus, although a more severe course of illness clearly increases the probability of unemployment, a reverse direction of causality might also be true: unemployment can exacerbate illness severity (102-105). In some respects, there is no reason to assume that the effects of unemployment on those who are diagnosed with BPD and people without a psychiatric illness are widely different. In both cases, extended periods of unemployment, especially in young adulthood, are exceptionally detrimental to mental health and functional adjustment across multiple psychosocial domains (104-106). In the case of BPD, however, the stress, stigma and loss of income associated with unemployment can inflame symptoms and lead to decompensation.
Effective changes in disability policies may be further informed by studies that examined factors related to successful employment in BPD. A large-sample study from New Zealand found that, beyond clinical factors, the goodness-of-fit between the individual, their job and the level of social support they experienced at work played an important role in long-term employment outcomes (107, 108). An increasing number of studies have substantiated key elements of a supported employment (SE) model – known as Individual Placement and Support (IPS) - that has been found to result in better clinical outcomes, as well as improved global, social and occupational functioning for people with psychiatric disorders including BPD (109-111). Key evidence-based components of the IPS model of SE include open enrollment for all people with psychiatric disorders who are interested in working; an aim to obtain competitive employment for them, as opposed to volunteer or “stepping-stone” work; the integration of clinical and vocational services; the provision of counseling around working while receiving government benefits; the prioritization of clients’ employment preferences; rapid job placement; and the provision of long-term “follow-along” on-the-job support (109, 112). This last element, long-term on-the-job support from SE program case-workers (known as “employment specialists”) may be particularly helpful in empowering people with BPD to cope successfully with occupational challenges, including with cognitive impairment at work and with negotiations with their employers around the accommodations necessary to maximize their productivity (109). Indeed, recent studies have found that the more frequent the contact between these “employment specialists” and employees with psychiatric disorders such as BPD, the longer the employment lasts (112, 113). In addition, several studies have found that adding the option of supported education services, along with cognitive remediation and social skills training to SE programs, further improves outcomes for people with psychiatric disabilities (114-116). Finally, programs through which people with psychiatric disorders can obtain the support of peers facing similar challenges are showing effects in improving social and occupational outcomes (117). SE programs may also carry especially powerful impacts for young adults with BPD (86, 87). In summary, a growing number of studies have highlighted the effectiveness of long-term coordination between clinical services, vocational and peer support services, and employers in enhancing work performance and retention for people with BPD (109, 118, 119).

Supported employment programs currently exist and are offered in some cases to disability beneficiaries, yet access to them is limited and their quality varies widely (16, 120). Despite research bolstering the effectiveness of specific elements of SE programs, many such services are not fully evidence-based and are often not a central piece of disability support. A commitment by the SSA and other government agencies to focusing on supporting adjustment and person-centered recovery rather than disability in BPD may require a greater diversion of resources to develop, implement, monitor and evaluate widespread evidence-based SE programs. Increased competitive employment is likely to improve a wide range of outcomes for, and decrease public stigma and discrimination against, individuals who are negotiating BPD (121, 122).

Removing social barriers to employment

In BPD, mood disturbance may be one in an array of impediments to full-time employment (35). Therefore, a policy that works to remove additional barriers to employment may result in gains both to individuals with BPD and society at large. One of the most challenging barriers to overcome involves discrimination against people with BPD in the hiring of them into employment and, even more pronounced, in their retention (123, 124). This discrimination is probably based in part on the belief that hiring or retaining people with BPD is not cost effective (125-127). Employers have specifically emphasized concerns regarding inconsistent attendance, inability to cope with stress, poor performance, disruptive reactions of co-workers and the negative effects of emotional instability on the work environment (125, 128). This view is consistent with data indicating that people with BPD exhibit substantially higher degrees of workplace absenteeism, presenteeism and other occupational impairment compared to the general population (125, 129, 130). According to some estimates, people with BPD miss an average of up to 65.5 workdays a year when time lost due to illness-related absenteeism and presenteeism is combined (131). Thus, based on data and possibly their own experience, employers may feel that they have legitimate concerns regarding the employment of people with BPD (125). Disability and supported employment programs must therefore work with
employers to offset the cost of the potential accommodations for people with BPD, including those required by law under the Americans with Disabilities Act (99, 132).

While federal and most state governments already offer employer tax incentives and deductions for hiring people with disabilities, employers still currently bear the brunt of the cost of disability accommodations (132). More extensive governmental support of employers, such as through education, advising and additional funding is probably needed to increase hiring and retention rates in BPD. In addition, discussions between disabled employees and employers regarding which accommodations would most improve their functioning and productivity are currently optional and left largely to the initiative of the disabled employee (132). Disabled employees may fear stigma and discrimination, were they to begin such a discussion, however, and the need to do so may peak at a time when these employees are under high levels of stress. Once employees have identified themselves as disabled to their employer, employer-employee interaction around accommodation should be legally required and facilitated by governmental disability support programs (132). Thus, aside from providing financial support, programs may inform employers about effective accommodations that have been shown to reduce occupational impairments and improve productivity in BPD, and thus may result in savings that outweigh their cost.

Discrimination against employing people with BPD is also due in part to stigmatization (17, 99, 123, 133). Multiple recent studies in different countries documented intense public stigma against people with mood disorders, reflecting serious doubts about their ability to hold responsible jobs (127, 133, 134). Several authors have maintained that stigma may be a stronger barrier to employment than any limitations imposed by the psychiatric illness itself (17, 18, 135-137). Indeed, despite substantial therapeutic advances, levels of public stigmatization, social and occupational functional impairment, including unemployment and underemployment, of people with BPD have all significantly increased since the 1990s (14, 138), the 1970s (15) and even since the 1950s (139). People with psychiatric diagnoses such as BPD are, in fact, substantially more likely to experience discrimination in employment than people with other disabilities (140), despite that the average education level in BPD is higher than that of the general population (141). For instance, a study that controlled for gender, functional limitations and non-wage incomes still found a 21% unexplained difference in employment rates between people with mood disorders and people without psychiatric diagnoses (134). Notably, however, employers’ prior experience with employees with psychiatric difficulties increased their willingness to hire people who face similar challenges (142). Thus, substantial evidence indicates that high unemployment rates in BPD are not due entirely to functional impairment but also to the simple fact that employers refuse to hire or retain people with this diagnosis (125, 127, 133, 134).

While discrimination directly prevents employment opportunities, perceived stigma leads to work impairment and avoidance because of the stress associated with the inhospitable environment it creates. This notion emerges from studies showing that people with BPD experience high interpersonal stress at work surrounding their psychiatric illness (19, 101, 143). Surveys demonstrate that almost 90% of respondents diagnosed with BPD reported difficulty getting along with employers due to illness-related issues (143, 144). In both qualitative and quantitative studies, most respondents attribute employment difficulties in large part to stigma and discrimination, and highlight intense feelings of embarrassment and shame in the workplace (14, 19, 145). Further frustration comes from being offered poorly paid, entry-level or unskilled placements that are not commensurate with education level, professional skill, and the desire for pursuing meaningful work (137). These difficulties can lead to occupational avoidance that is related to expectations of rejection and social stress more than professional incompetence (19, 124, 143).

Low employment rates in BPD may therefore emanate from factors beyond those directly related to mood disturbance, including rejection by employers and avoidance of stressful environments that may contribute to psychiatric instability. In the current social climate, psychiatric treatment struggles to gain momentum, as it faces the challenge of caring for severe mental illness that is compounded by the devastating effects of extreme social marginalization. Discrimination has no pharmacological remedy. It can only be addressed by shifts in social climate and government policies. These may hold the promise of reducing stigma and discrimination, and consequently decreasing psychosocial stress, the severity of symptoms, excessive use of psychotropic medications, reliance on disability funds, and medical expenses.
Conclusions

New research in BPD reveals that poor functional adjustment persists beyond the resolution of mood symptoms. Studies indicate reductions in brain volume and cognitive decline over the course of the illness, especially in individuals with a more severe psychiatric syndrome. These findings advanced the neurodegenerative hypothesis in BPD, which highlights the detrimental effects of mood symptoms on the brain and cognition, and the consequent impairment in functional adjustment. The neurodegenerative account emphasizes the importance of preventive care, and the need to identify factors that exacerbate illness severity in BPD. Studies in this area indicate that the inflammation of mood symptoms in BPD is rooted in the interaction between genetic risk and psychosocial stress. As genetic factors are not subject to therapeutic change, preventive efforts should focus on the reduction of psychosocial stress.

These conclusions carry implications for public policies concerning disability benefits. In the case of BPD, current eligibility criteria emphasize the presence of chronic affective symptoms and the absence of significant employment. As a result, support is restricted to covering the basic needs of individuals who are debilitated by severe mood disturbance. Furthermore, efforts by disability benefit beneficiaries to return to full-time employment is discouraged by limited access to effective SE programs and the lack of a sufficient transition period in which beneficiaries can work and retain benefits. Providing supports during earlier stages of the illness may allow people with BPD to retain mainstream employment and other social roles at higher rates, in a manner that alters the course of their illness. Beyond financial supports that incentivize work over unemployed disability, policies need to create structures that actively reduce psychosocial stress for people with BPD. Supportive services need to address tensions between cognitive impairments and functional demands that arise at work. In addition, they need to accommodate and guide employers who hire people with BPD. This may be accomplished through various forms of external measures, including agents who actively seek to monitor and improve the goodness of fit between employees with BPD and their work environment. In this respect, taking case-specific steps to reduce stigma and discrimination against BPD in the workplace may be central to the effort of keeping people with BPD effectively employed in the long term.

In summary, new research may guide the development of effective disability policies for BPD. Specifically, informed policies may create supportive work environments and opportunities for employment commensurate with education level and professional competency. The combination of meaningful work, effective accommodations for illness-specific limitations, and social support, may bring significant improvement to the quality of life and mental stability of people with BPD. In many respects, it may reduce the stress that aggravates the illness and creates excessive reliance on psychiatric care. More broadly, research-informed polices may even hold the promise of shifting the psychosocial trajectory of BPD from disability to growth.

GP Comment

What have I learned from this paper?

This article considers how the neurodegenerative model highlights the importance of effective preventative care in order to preserve functional adjustment for those with bipolar disorder through reduction of psychosocial stress in addition to therapy and medication. The authors go on to discuss the important implications of this for disability policy.

For the front-line clinician and the commissioner there are clear messages with regard to considering support into beneficial employment, developing the understanding of employers, reducing psychosocial stresses in the work environment, reducing the significant employment stigma faced by those with bipolar disorder and reducing the psychosocial stresses in the individual's wider social environment.

The need to create conditions that allow functional recovery in mainstream settings for GPs means that medical reports need to reflect the challenges and the benefits of the work environment. Fit
notes need to be used effectively to communicate ways in which psychosocial stress can be reduced for the individual in a particular work environment. This paper contains a great deal of useful information to support these processes and highlights the need for long-term close liaison between clinical services, vocational and peer support services and employers. There is also useful information regarding heritability of disease and disease severity, questions often brought to the GP by family members.

Discussion of the importance of therapy, medication AND interventions which reduce stress in the wider social environment - all as close to initial symptom presentation as possible and the critical period of discharge from first hospitalization - are valuable for both the front-line clinician and commissioner.

Dr Jane Leigh, GP.

References

16. Drake RE, Skinner JS, Bond GR, Goldman HH. Social security and mental illness: reducing disability


85. U.S. Social Security Administration. http://www.ssa.gov/disability/professionals/bluebook/12.00-


122. Tsang HWH, Fong MWM, Fung KMT, Corrigan PW. Reducing employers’ stigma by supported employment. Vocational Rehabilitation and Mental Health 2010:51-64.


133. DBSA. Support or Stigma? Bipolar in the Workplace. 2008

134. Baldwin ML, Marcus SC. Stigma, discrimination, and employment outcomes among persons with mental health disabilities. In: (Eds.) IZSaESR, editor. Work Accommodation and Retention in


The Bipolar Spectrum and Psychoneuroimmunology: Implications for Diagnosis and Treatment

Moritz Muehlbacher1 and Aye-Mu Myint2

1 Moritz Muehlbacher, MD
University Hospital for Psychiatry and Psychotherapy
Bipolar Outpatient Clinic
Paracelsus Medical University
Christian Doppler Clinic
Ignaz Harrer Strasse 79
5020 Salzburg, Austria
m.muehlbacher@salk.at

2 Dr. Aye Mu Myint
M.B.,B.S.; M.Med.Sc.; PhD.
Laboratory for Psychoneuroimmunology
Psychiatric Hospital, LMU
Nussbaumstrasse 7
D-80336 Munich

Abstract

The potential contribution of chronic inflammation to the development of neuropsychiatric disorders such as bipolar spectrum disorders has received increasing attention during the last years. Elevated biomarkers of inflammation have been found in bipolar patients during acute phases and throughout the course of the disease. Inflammatory cytokines can interact with multiple pathways known to be involved in the development of psychiatric disorders, including monoamine metabolism, neuroendocrine function, circadian rhythms, synaptic plasticity, and neurocircuits relevant to mood regulation. In addition, a number of typical comorbidities seem to share an inflammation-related background and might have mutually aggravating effects. Awareness of these relationships should lead to greater diagnostic vigilance and thorough diagnostic assessment.

Key words: bipolar disorder, inflammation, biomarker, cytokine

Introduction

Bipolar spectrum disorders are severe psychiatric conditions with high prevalence and enormous economic and social burden (1;2). There is enough data presently to advocate a genetic immunological predisposition and a role of various environmental factors with an adverse impact on the immune system as part of the pathophysiological background of bipolar disorders and, possibly, associated comorbidities. Pro-inflammatory alterations of the immune system are closely interrelated with clinical symptoms and may prove to be useful diagnostic or therapeutic markers. Moreover, some inflammatory conditions or (auto-) immune disorders may elicit or worsen symptoms of depression, mania and associated comorbidities. A thorough and diligent investigation of the history and present condition of the patient with regard to possible immunological/inflammatory alterations should therefore always be included in the diagnostic work-up. In addition, new drugs targeting aberrant immunological mechanisms might become a welcome addition to the customary treatment in the future. In the current article, we aim to provide a short overview of the present state of knowledge relating to the immunological background and implications for diagnosis and treatment.
Epidemiological and genetic findings

Bipolar disorders are typical multifactorial disorders with a plethora of known associated genetic and environmental contributors, lacking, however, a readily identifiable single cause. A genetic domain of particular interest implicated in bipolar disorders on chromosome 6p22.1 contains several immunity-related genes (3). Other associated genetic regions include genes for inflammatory cytokines (4). Interestingly, pro-inflammatory and anti-inflammatory cytokines are known to play an important physiological role as regulators of the prenatal development of the central nervous system with substantial influence on neurogenesis and gliogenesis, cell differentiation, migration and synaptogenesis (5). Factors known to be associated with pro-inflammatory changes, like infection during pregnancy and early childhood, birth complications and early childhood traumata, amplify the risk to develop various psychiatric disorders in later life. (6-8). A positive family history of autoimmune disorders also augments the risk and patients who are newly diagnosed with certain autoimmune disorders are prone subsequently to develop bipolar spectrum disorders or psychosis (9). Notably, chronic inflammatory disorders are associated with a high rate of comorbid depression and pro-inflammatory cytokines are known to cause “sickness behaviour” with symptoms resembling those of major depression (10;11). Taken together, these findings corroborate the hypothesis of a bidirectional relationship between immunological/inflammatory processes and a variety of psychiatric disorders, including the bipolar spectrum.

Immunological changes during the course of bipolar disorders

Early Stages

Bipolar disorders and psychotic disorders often present with an initial prodrome of non-specific and variable symptoms, typically during teenage years or in adolescence. An up-regulation of the expression of genes with immunological functions - a “pro-inflammatory signature” – has been found in monocytes during these first stages, even before the development of clear-cut clinical symptoms (12). Twin studies suggest that the better part of these changes is not due to a genetic background but to environmental factors yet unidentified (13). At the same time, there is evidence for an up-regulation of regulatory T-Cell networks, suggestive of an activation of the immune system involving both pro-inflammatory and anti-inflammatory forces in early stages (14). Interestingly, in spite of some overlap, the exact pattern of aberrant gene activation in monocytes seems to show subtle differences between patients who are later diagnosed with schizophrenia, bipolar disorder or recurrent unipolar depression and might be a trait marker (15).

Acute phases

Abnormal cytokine levels, independent of other inflammatory processes, have been found during acute psychotic, depressive and manic episodes. In first episode and acutely relapsed psychotic patients, levels of macrophage-derived cytokines (Interleukin-1β, Interleukin-6, and Tumour necrosis factor α) and TH1-derived cytokines (Interferon-γ, Interleukin-12) are elevated. There is also evidence for an initial counter-regulatory elevation of anti-inflammatory cytokines like Tumour growth factor β and Interleukin-1 Receptor antagonist (16). In major depression, a recent meta-analysis reaffirmed previous findings of an activation of the inflammatory response system, reflected by elevated levels of tumour necrosis factor α and Interleukin-6 (17). Analogous changes with raised levels of pro-inflammatory cytokines were seen both during manic and depressive episodes in bipolar patients (18).

Remission and progression

Several studies report that the levels of pro-inflammatory markers like soluble Interleukin-2 receptor and Interleukin 6 drop to lower or normal levels with remission of the acute phase, while other pro-inflammatory markers (e.g. tumour necrosis factor α) seem to lack this association (19). Although the “pro-inflammatory signature” in monocytes of bipolar patients appears to be retained throughout the course of disease, a counteroffensive T-cell response- often present in younger patients- may be
lost in some subjects, leading to a less favourable outcome with a higher rate of complications (20). Few studies have reported findings regarding inflammation during euthymia or long-term remission. The results were inconsistent. One study comparing early-stage versus late-stage bipolar patients suggests that an initial counter-regulatory reaction with raised levels of the anti-inflammatory Interleukin-10 could be lost throughout the course of the disorder and the level of pro-inflammatory cytokines may rise along with increasing duration of the disorder in later stages. These findings may indicate a deterioration of the inflammatory status as a possible stage marker (21).

Impact of inflammation on bipolar disorders and possible causal connections

Inflammation during acute phases and throughout the course of disease can influence a variety of functions in the central nervous and endocrine system. These mechanisms may, in part, explain clinical symptoms of the disorder and its associated comorbidities.

Tryptophan Metabolism

Tryptophan is an essential amino acid and a precursor molecule of serotonin. Some aspects of its metabolism highlight interesting points to bridge the gap of knowledge about the interrelation between neurotransmission and immunology (22). Pro-inflammatory cytokines, like those seen elevated in acute phases of bipolar disorder, can induce enzymes involved in tryptophan metabolism, causing a shift away from the production of serotonin. The alternative pathway leads to kynurenine and a variety of subsequent neuroactive tryptophan catabolites with multiple functions. Under physiological conditions, some catabolites are used for the production of adenosine triphosphate and nicotinamide adenine dinucleotide, a pathway which is important for glycan storage/glycolysis and mitochondrial functioning. An excess of another catabolite, quinolinic acid, can cause excitotoxicity through an agonistic effect at glutamatergic NMDA-receptors, whereas kynurenic acid is an antagonist at the same target. By means of this dichotomy, tryptophan catabolism is closely intertwined with immunological, monoaminergic and glutamatergic functioning. In addition, kynurenic acid also antagonizes $\mathrm{N}^\text{M}-\text{nicotinic acetylcholine receptors which play a role in cognitive processes. Lastly, 3-hydroxykynurenine can induce neuronal apoptosis. In summary, inflammatory alterations of the immune system can lead to an imbalance between tryptophan catabolites and may therefore interfere with monoaminergic and glutamatergic transmission, cause cognitive impairment and contribute to cell damage. In agreement with this, disproportionate production of tryptophan catabolites has been shown in psychotic, manic and depressed patients in different patterns. (23-26). As yet, directly targeting these imbalances with pharmacological compounds remains a mere theoretical possibility. However, anti-inflammatory or immunomodulatory drugs with indirect effect on tryptophan catabolism have already been tested and demonstrated some beneficial effects.

Circadian rhythm and synaptic function

Circadian rhythms are endogenous oscillations of biological processes, including not only the sleep-wake cycle but also a variety of other bodily functions. These reiterative patterns are encoded on a genetic level by “clockwork genes”. A recognized core feature of bipolar disorders is the desynchronisation of circadian rhythms, which may partly be explained by genetic predisposition. However, the relationship between circadian rhythms, clockwork genes and the immune system is unquestionably bidirectional. On the one hand, the immune response is governed by superordinate regulatory clockwork genes and follows a chronobiological pattern. On the other hand, inflammatory cytokines exert an impact on the activity of clockwork genes and may inflict a loss of proper chronobiological functioning (27). In the light of these findings, it seems reasonable to suggest that the inflammatory alterations documented in bipolar disorders contribute to the typical clinical symptoms of disturbed circadian rhythms. In similar ways, proper functioning of monoaminergic synapses - like synaptic plasticity and synaptic scaling which both regulate synaptic activity in the central nervous system - and inflammatory signals have a reciprocal relationship (28;29). Whenever the balance between pro-inflammatory and anti-inflammatory signals is lost, the stability of synaptic transmission may be endangered (30).
Autoimmune Diseases

A family history of pernicious anaemia is known to be a risk factor for bipolar disorders, and patients with a history of Guillain-Barré syndrome, Crohn’s disease and autoimmune hepatitis have a heightened risk of developing bipolar disorders (9). Possibly the most important and most frequent autoimmune disease associated with bipolar disorders is Hashimoto’s thyroiditis (31). It seems to be linked to an unfavourable outcome, higher frequency of episodes and rapid cycling. Women are affected more frequently than men. Although lithium treatment may often lead to thyroid hypofunction, it is currently not thought to be the sole and exclusive cause. An early diagnosis and treatment of comorbid Hashimoto’s thyroiditis is crucial to a good outcome of patients with bipolar disorders. Some other autoimmune disorders are not clearly associated with bipolar disorders per se but may mimic symptoms of mania, depression and psychosis. These include autoimmune connective tissue diseases (32), multiple sclerosis (33), antiphospholipid syndrome (34), Behcet’s syndrome (35) and others.

Inflammation-related Comorbidities

A number of somatic diseases known to be frequent comorbidities of bipolar disorders are associated with chronic inflammation (18). For over a quarter of a century, studies have shown increased mortality due to cardiovascular disease in bipolar disorder (36;37). Inflammation is an antecedent of cardiovascular disease and may individually predict mortality. Measurement of inflammatory markers in cardiovascular disorders has become a regular medical procedure in cardiology and reducing inflammation may lead to a better outcome (38). Moreover, epidemiological data suggest a mutually increased prevalence of bipolar disorder, obesity and insulin resistance, even after controlling for psychotropic medication with possible metabolic adverse effects (39;40). Similar findings have emerged from studies on migraine (41;42), cigarette smoking (43), heavy alcohol abuse (44) and impaired sleep efficiency (45;46), which are all frequent among bipolar patients, even during phases of remission. All of these disorders share a pathophysiological background hallmarked by chronic inflammation. There is hope that targeting inflammation as a common denominator both of bipolar disorders and these comorbidities may help to achieve a better overall therapeutic outcome.

Febrile infections

A possible positive impact of febrile infections on the course of affective and psychotic disorders has been acknowledged for over two centuries (47). While, in some cases, bipolar patients may actually recover from an acute episode along with an infection, it should be noted that complex effects of febrile states on drug metabolism for medicated patients may also be expected. Barring non-specific effects on fluid homeostasis, electrolytes and excretion, pro-inflammatory cytokines can directly impair hepatic detoxification pathways and thereby alter pharmacokinetics of various psychotropic drugs (48). The importance of diligent clinical monitoring of bipolar patients and regular laboratory tests of drug plasma levels under febrile conditions is therefore strongly emphasised.

Immunosuppressive drugs with possible negative effects

A variety of psychiatric symptoms, including depression, psychosis and suicidal ideation, are possible adverse effects of immunosuppressive therapy with interferon-α; a history of psychiatric disorders is one of the known risk factors for these adverse events (49). Similarly, systemic high-dose cortisol therapy can be accompanied by psychiatric symptoms. However, in this case, a history of psychiatric disorders does not seem to a particular risk factor (50). While it does not seem justified to deny psychiatric patients the possible benefits of these therapies when needed for severe medical conditions, close monitoring for adverse psychiatric events and regular consultation with specialists are strongly recommended.
Possible future anti-inflammatory and immunomodulatory treatment approaches

At present the main focus of research interest and drug development for mood disorders has predominantly relied on targeting the monoaminergic system. Almost all of the currently available, effective and approved compounds interfere with one or more of the monoamine systems. New drugs targeting aberrant immunological mechanisms might prove to become a welcome addition to customary treatment. Celecoxib is a cyclooxygenase-2 inhibitor licensed for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and for the management of acute pain in adults. Benefits of celecoxib add-on therapy have repeatedly been shown in patients with schizophrenia, major depression and bipolar disorder (51-55). In addition to a reduction of overall symptom severity, celecoxib may also accelerate treatment response and have a positive effect on cognition (56). Future studies are needed to identify predictors of response, like cytokine and tryptophan catabolite levels or inflammation-related genotypes, in order to maximise the risk-benefit ratio of celecoxib treatment. Acetylsalicyc acid (ASA) is available worldwide on a generic basis. Findings from large epidemiological studies as well as controlled clinical trials point towards a favourable influence of low-dose ASA in both unipolar depressive and bipolar patients (57-59). Recently, the tetracycline antibiotic minocycline has gained increasing attention, since it attenuates the inflammatory response of T cells and microglia (60). In psychotic disorders, minocycline shows favourable effects on negative symptoms and executive function and was well tolerated up to 6 months of treatment (61). On a cautionary note, antagonists of pro-inflammatory cytokines have lately also been proposed as possible treatment options (62,63). However, these compounds are potent immunosuppressive agents and their safety and efficacy has not been assessed in psychiatric populations in controlled trials yet.

Discussion

A growing body of evidence points towards a multifaceted interrelationship between bipolar spectrum disorders, the immune system and inflammation. While many findings suggest a certain genetic background, additional environmental factors seem to be of considerable importance. No single environmental cause has been identified unequivocally yet, conceding the possibility that different environmental causes with an impact on the immune system might be responsible in different cases. As inflammatory signals can not only influence a variety of brain functions which are directly connected with mood regulation or psychosis but chronic inflammation is also related to a number of typical comorbidities, knowledge about this shared cause may become crucial for good medical practice.

Potential implications are clear:

• A thorough and diligent investigation of a bipolar patient’s history and present condition with regard to possible immunological/inflammatory alterations should always to be included in the diagnostic work-up.

• Auto-immune disorders mimicking bipolar symptoms have to be ruled out as a possible differential diagnosis

• Other frequent comorbid auto-immune disorders with negative impact on the course of the disorder (e.g. Hashimoto’s thyroiditis) should always be considered and referred to a consulting specialist. Early treatment may be crucial for a good outcome.

• Bipolar patients in need of immunomodulatory treatment for other serious medical conditions may be at risk of adverse psychiatric events. While it does not seem ethical or necessary to refuse such treatments to bipolar patients, regular clinical and psychiatric monitoring are necessary.

• Many typical comorbidities of bipolar disorders (e.g. cardiovascular disease, obesity, and diabetes) seem to share a common cause: chronic inflammation. Bipolar patients should be treated as “high...
risk” patients for these disorders. Some typical “lifestyle” modifications have a direct positive impact on chronic inflammation. These include smoking cessation, reduction of alcohol consumption and establishing a regular sleep/wake pattern.

• In the future, inflammatory or immunological markers may serve as state, trait or staging markers or as predictors for treatment response. Some anti-inflammatory compounds, e.g. celecoxib, have already been tested in bipolar disorders and merit further investigation.

**GP Comment**

**What have I learned from this paper?**

I learned of the fascinating links between measurable inflammatory biomarkers and bipolar disorder, with a definite signature in early, acute and remitted disease. It is thus important to rule out an inflammatory differential diagnosis, and especially to watch out for and treat Hashimoto’s thyroiditis, as this leads to a poorer outcome unless treated aggressively. Bipolar patients needing immune-modularity treatments need careful monitoring, due to the risk of deterioration. Lifestyle interventions such as smoking cessation, alcohol reduction, and establishing a regular sleep/ wake cycle have an impact on chronic inflammation, and can also reduce co- morbidities; they are important from diagnosis, and should be emphasised in routine care.

**Dr John Hague, GP, Suffolk.**

**References**


43. Gan WQ, Man SF, Sin DD. The interactions between cigarette smoking and reduced lung function on systemic inflammation. Chest 2005 Feb;127 (2):558-64.


Mood Instability, Bipolar Disorder and Disadvantages of Antidepressants

Rudy Bowen MDCM FRCP (C)
Professor of Psychiatry
University of Saskatchewan

Verinder Sharma MD FRCP (C)
Professor of Psychiatry
University of Western Ontario

Correspondence to:
R.C. Bowen
Department of Psychiatry
103 Hospital Drive
Saskatoon, SK. Canada.
S7N 0W8.

Abstract

Objective. To emphasize the clinical importance of mood instability (MI) in the treatment of patients with depression and anxiety, bipolar and substance abuse disorders.

Content. We summarize data to show that MI is common in patients with "neurotic" conditions; in fact, MI may be the central feature of neuroticism. We discuss the association of MI with irritability and suicidal thoughts. We also discuss the assessment of MI in family practice. MI and bipolarity are not well treated by antidepressants, which might actually aggravate the tendency to unstable moods and cycling. Suggestions are made about treatment but firm recommendations about medication are currently outside treatment guidelines.

Conclusion. MI is an important concern in the treatment of anxiety and mood disorders and more research is needed.

Key words: mood instability, bipolar disorder, antidepressants, anxiety.

Introduction

Unstable moods are a common concern of patients with anxiety, depression and bipolar disorders. Unfortunately, when mood (affective) instability is prominent, we have been instructed to think narrowly of borderline personality disorder. Here we describe the relationship of mood instability to mood disorders in general and the consequence for prognosis and treatment.

Definition of Mood Instability (MI)

The APA DSM-IV criteria for major depression require that symptoms be present “most of the day, nearly every day, for at least 2 consecutive weeks”). However, when patients with mood and anxiety problems rate their symptoms prospectively, most will report prominent fluctuations in mood within a day or days (2) (3). We refer to these as Mood Instability (MI) defined as “severe and frequent fluctuations of mood over time” (4).

Unstable moods in depression

Patients with anxiety and depression who rate their symptoms prospectively consistently score higher (Mean 3.072, SD 2.203) than controls (Mean 1.571, SD 1.50) on depressed MI (t 7.99, df 362, p<0.001) (2) (3). In these studies, patients rated depressed mood twice a day for 7 consecutive days on visual
analogue scales (10 cm lines). From the successive ratings, we calculated the Mean Square Successive Difference Statistic (MSSD), which is a better measure of point-to-point instability than the standard deviation (5). This gives a precise measure of MI for research but is too cumbersome for everyday clinical use. We have recorded unstable depressed, anxious, irritable and high moods.

Patients might not report these fluctuations spontaneously for several reasons. First, because they are usually not asked; second, there is a negative cognitive bias in depression that can overshadow fluctuations in mood (6), and finally people are often afraid of being labelled “bipolar”.

Correlates of MI

MI has been associated with low self-esteem (7), suicidal thoughts (8), borderline personality traits (9), anxiety (3), depression and alcohol abuse (10). We have also shown higher MI in women with premenstrual tension (11) and in pregnant and postpartum women (Bowen et al. submitted for publication) Interestingly, the absence of MI, in other words mood stability, is the best predictor of a sense of well-being (12).

Most psychiatric classifications and textbooks barely mention MI, and when they do, it is relegated to the category of borderline personality disorder (1). The definition of this syndrome rests on instability of relationships and self-image that could both be related to instability of mood as the primary characteristic (9). Anger is another characteristic of the borderline personality disorder, but fluctuating irritability is common in patients with depression and unstable moods (13).

How to inquire about MI clinically

We have used the question: “Do your moods often go up and down?” to elicit reports of mood instability from patients (14) (8). Another question is: “Do you have mood swings?” but patients often interpret this question as an inquiry about irritability; however, irritability is related to mood fluctuations and the bipolar spectrum (13). More recently we have used the short form of the Affective Lability scale to measure MI (15). This is an 18-item questionnaire with questions about mood shifts that correlates well with the MSSD statistic for depressed mood and the question about “moods often going up and down” (8).

Factor analysis of the Eysenck Neuroticism Scale (16) yields a reliable MI factor that is anchored by the same question about “moods often going up and down”. This factor predicted suicidal thoughts in a cross-sectional study (8) and also predicted general psychological wellbeing after 7 years in the British Health and Lifestyle study (Bowen et al. submitted for publication). This suggests that MI is the core feature of neuroticism.

Treatment

Not necessarily antidepressants

Depression, even subsyndromal depression, is a highly recurrent condition (17) (55% over 5 years) (18). The SSRI antidepressants alleviate some symptoms of depression over the short term but the evidence for remission of symptoms is not particularly strong (27.5% in the STAR*D trial (19, 20). This is true even when dosing is pushed to the maximum (60 mg citalopram) (20). There is even less evidence that these drugs are effective at preventing the recurrence of depression over the long term (21) (22). The longest studies are about 18 months in duration and by the end of the study, the attrition rate is so high that it is difficult to reach firm conclusions. Recently, it has been suggested that chronic use of antidepressants may induce a form of chronic dysphoria (23).
Bipolarity

We now know that at least half of depressed patients who present for treatment have a bipolar diathesis (13) (24). Chronic exposure to antidepressants is associated with worsening of the long-term course of bipolar disorder due to frequent changes in polarity, mixed symptoms and treatment refractoriness. (25) (26) (27). From the patient’s point of view, the typical presentation of hypsosomnic, retarded depression can turn into an agitated, anxious mood state with accompanying insomnia and racing thoughts. Consequently, depressed patients should be routinely screened for sub-threshold manic symptoms before the initiation of antidepressants. It may be that the SSRI antidepressants are more useful for symptoms of anxiety that often accompany MI, including mild symptoms of worrying, social anxiety, and obsessionality (28).

Indications of Bipolarity

When the right questions are asked, MI is found to be common among individuals on the bipolar spectrum (24,25,26,27). Therefore, patients presenting with MI or any history of activation should be screened for bipolar disorder. Clues to the bipolar nature of a mood disorder include early age of onset of depression, recurrent episodes, fast onset and brief depressive episodes, atypical depressive symptoms, postpartum depression, concomitant psychotic features, poor antidepressant response or loss of response, antidepressant-induced (hypo)mania, and family history of bipolar disorder in a first-degree relative (29) (30). Unfortunately, there are no studies on the prevalence of MI in bipolar disorder.

Pilot treatment studies

The main reason for inquiring about MI is to improve the mental health of patients, particularly those with anxiety, mood and substance-abuse problems. Patients with anxiety and depression treated with antidepressants tend to have partial improvement on symptom scales after 6 months of treatment, as might be expected (31). Depressed MI does not improve consistently, however; a few patients become better but others become worse. We are currently conducting an open study with lamotrigine and the early results seem promising for improvement of MI. Preliminary results from other studies suggest that lamotrigine is an effective drug for mood instability in borderline personality disorder (32). It is worth noting that a combination of medications may be necessary.

Why consider alternatives to antidepressants?

It is sobering that depression as a cause of disability days lost is now first or second in importance in developed countries. An equally urgent concern is that suicide continues to be a prominent cause of death, particularly among young people (33). About 50% of young people with suicidal thoughts do not fulfill the criteria for major depression and have not come to the attention of mental health services (34), although most of these have psychiatric symptoms (35). This is a reminder that subthreshold symptoms including MI are important. A relevant question is: “If simple effective treatments are available in the form of antidepressants, why is the outlook for depression not brighter?” In response to this, the emphasis has shifted to enhancing primary care (36) (37). Repackaging and disseminating current treatments will hopefully improve the outlook but does not address the issue that the treatments are not particularly effective. Increased awareness that one-half of depressed patients who present for treatment have a bipolar spectrum disorder will probably also help. Apart from medication, alternative ways of helping to manage MI, such as adequate physical activity, show promise (Bowen et al. in preparation). Because MI is related to neuroticism that is a relatively enduring (but modifiable) trait, it is not likely that it will spontaneously remit over the short term in a particular patient.
The association between MI and Depression

We are not suggesting that MI should replace the concept of “depression” as a general measure of sadness or lack of pleasure. Pooled data from many studies shows that depression correlates consistently but only moderately with MI (N = 161, r = 0.481, p<0.001). (38) This suggests that depression and depressed MI are related concepts but that MI is not redundant (38). Depression might be considered to be a vague term, akin to shortness of breath, and antidepressants are not necessarily the “first-line” treatment for all patients (39) (40). MI is a more specific term but whether it is more clinically useful only more research will reveal.

MI and formal psychiatric diagnoses

Many patients report high subjective distress but do not appear to be severely depressed. This is consistent with the observation that subjective rating scale scores are often higher than observer-rated scales (41). This difference in scores is predicted by “neuroticism” that we have related to MI (41) (8). This means that the patient may be better at assessing his or her own subjective distress than an external observer armed with a diagnostic inventory. In this sense, MI may be a true trans-diagnostic concept that is seen in patients with bipolar, depressive, anxiety, substance abuse and some personality disorders.

Conclusion

Depression is a very general concept but even the diagnosis of major depression lacks the precision necessary for assessing and treating patients effectively. Awareness that one-half of depressed patients have a bipolar disorder will undoubtedly help. Increasingly, evidence suggests that MI is a distressing trait that may affect the long-term outcome of patients with anxiety and mood disorders. The relationship of MI to the bipolar spectrum needs to be determined. Neither bipolar disorder nor MI is well treated by antidepressants alone. A comprehensive program of mood management that includes several medications and lifestyle changes may be necessary. More research on the assessment and treatment of MI and bipolar disorder is needed.

GP Comment

What have I learned from this paper?

Currently within the NHS England QOF indicators ask for a bio-psycho-social assessment at the time of diagnosis. A GP would use PHQ-9 (Patient Health Questionnaire) and GAD-7 (Generalised Anxiety Disorder) at the time of initiation of medication. These questions are repeated during medication reviews and can provide a way of monitoring improvement.

These are helpful tools in assessing the patient objectively at the time and could potentially identify mood instability or deterioration with the commencement of an SSRI.

As a GP I would check the BNF, which does not state an indication or license for lamotrigine. I would therefore rely on consultant psychiatric colleague to consider lamotrigine, as a pharmaceutical option.

Dr Vishal Naidoo, GP.

References


17. Patten SB, Williams JV, Lavorato DH et al. Depressive episode characteristics and subsequent recurrence risk. Journal of Affective Disorders 2012; Epub ahead.


Genetics of Bipolar Disorder: an Overview

Stefano Porcelli, Raffaele Salfi, Alessandro Serretti
Institute of Psychiatry, University of Bologna, Bologna, Italy

Running title: Genetics of bipolar disorder

Address correspondence to:
Alessandro Serretti, MD, Ph.D.
Institute of Psychiatry
University of Bologna
Viale Carlo Pepoli 5, 40123 Bologna, Italy
Tel.: +39 051 6584233
Fax: +39 051 521030
E-mail: alessandro.serretti@unibo.it

Abstract

Bipolar disorder (BPD) is a mood disorder caused by the interaction among a large number of genes and the environment. Recently, with the improvement of genome analysis techniques and the introduction of Genome Wide Association Studies (GWAS), the investigation of the genetic causes of BPD has moved several steps forward, allowing the confirmation of previous results and the identification of new genes involved in the pathogenesis of the disorder. Furthermore, in the last few years, several studies focused on the investigation of rare genetic variants, copy number variants (CNV) and epigenetic modifications, leading to a more complete knowledge of the picture. The aim of the present review is to give to the reader a comprehensive view of the current knowledge about the genetics of BPD, focusing on the most investigated genes and their biological function in the context of the more accepted theories about the pathogenesis of the disorder.

Most confirmed liability genes are involved in the serotoninergic, glutamatergic, GABAergic and circadian systems. In particular, a large amount of evidence was found for glutamatergic NMDA and Kainate receptors and some genes of the glutamate cycle, which are thought to be involved in a possible neurotoxic effect on neurotransmission. Other relevant genes are CLOCK, ARNTL and PER3 which may increase the risk of disease by altering circadian rhythms, through the modulation of the serotonin system.

In conclusion, it is still not possible to determine the exact genetic basis of BPD, because several genes are likely to be involved in the pathogenesis of the disorder, as well as environmental factors. Nonetheless, thanks to recent technological advantages, several steps forward have been made, allowing the identification of the main systems involved in the genesis of BPD. Through further technological improvement and the use of specific endophenotypes, more related to genetic and epigenetic variants compared to BPD itself, in the next few years the identification of the exact genetic basis of BPD might be an achievable aim for psychiatric research.

Key words: bipolar disorder, genetics, epigenetics, endophenotypes

Introduction

Bipolar disorder (BPD), previously called manic-depressive illness, is a chronic mood disorder characterized by the lifetime presence of both episodes of elevated mood (mania or hypomania), and episodes of depression, separated by periods of euthymia (“normal” mood). In some patients mania and depression may rapidly alternate in a form of disorder known as cyclothymia. BPD has a lifetime prevalence of about 1% (1) with no significant difference in worldwide or sex distribution (2). The median age of onset is in the range of 18 and 22 years (1). From the clinical point of view, mania, or hypomania, is a state of elevated mood, physical activity, talkativeness, flow of thoughts, decreased
need of sleep, distractibility; hypomania is an episode less severe than mania. The condition of depression is a state characterized by sadness, guilt, fatigue, apathy or indifference, loss of interest, disturbances in sleep and appetite. Sometimes manic and depressive symptoms may be present at the same time in the so called “mixed state”. Both manic and depressive symptoms may lead to an impairment in social and occupational functions (3). BPD is often associated with an increased risk of suicide, as well as with impulse-control and substance use disorders. Furthermore, and of particular interest for general practitioners, there are several medical co-morbidities associated with BPD, such as migraine, heart disease, thyroid disease, and type 2 diabetes (4). Another problem of great interest for the GP concerning BPD patients is their poor compliance with any treatment (including the ones for general medical conditions) that these patients have during both depressive and manic episodes. Taking into account all these aspects of the disorder, the great impact on national health systems is clear. Indeed, the cost of the disorder is estimated as a loss of $14.1 billion salary-equivalent in USA (1). Costs are both direct, consistent with hospitalization and treatment, and also for co-morbidities, and indirect related with the loss of workdays, work performance and through delayed diagnosis (5). Despite the relatively low frequency of BPD in the general population, its heritability is high: the concordance in monozygotic twins is more than 40% (up to 70%) compared with 10% in dizygotic twins. Moreover, adoption studies show that biological parents of bipolar adoptees have a higher risk of being affected by a mood disorder than their adoptive parents (6). Finally, there is strong evidence for a genetic overlap between schizophrenia and BPD (7). All these data provide not only the evidence of the indisputable role of genetics in susceptibility for BPD, but also the proof of an influence of other factors such as environment factors or epigenetic modification in the genesis of the disorder (8, 9). As BPD is a multifactorial and very complex disease where many systems take part in the development and determination of phenotypical traits, the use of the modern technique of genome-wide association study (GWAS) seems to be suitable to reach more consistent results, compared to the candidate gene approach. Indeed, this technique does not require any a priori hypothesis (as opposed to candidate gene studies) and is able to take into consideration about a million SNPs, or copy number variants (CNVs), and duplication or deletion of DNA segments of diverse size. Nonetheless, we have to keep in mind that the picture is even more complicated considering that epigenetic modifications may also alter gene expression; implying that this aspect should also be investigated in order to dissect the exact basis of the disorder. Taking into account all these considerations, the aim of the present paper is to give to the reader a comprehensive view of the current knowledge about the genetics and epigenetics of BPD, focusing on the most investigated genes and their biological function in the context of the more accepted theories about the pathogenesis of the disorder.

Methods

We reviewed all studies published on GWAS, epigenetics, linkage and association studies in BPD in the period comprised from January 2008 and June 2012, updating our previous paper on this issue, which makes an exhaustive review of genetic studies on BPD from 1990 to 2007 (10). For our research we employed both the Medline (http://www.ncbi.nlm.nih.gov/) and PsycINFO® (http://www.apa.org/pubs/databases/psycinfo/) databases, entering the following key words: bipolar disorder, mood disorder, gene, genetics, genome, genome wide association study, GWAS, association, linkage, chromosome. We considered only papers written in English, defining BPD according to DSM (3) or ICD-10 (11) criteria and clearly indicating modifications of genetic or epigenetic expression in patients. No other exclusion criteria were applied. This research was made by two different researchers (R.S. and S.P.) who then compared their results in order to diminish the possibility of rejection of some papers. From a total of 7624 papers, 1056 papers were discarded because they were reviews; the remaining 6568 were screened by reading abstracts and chosen following the criteria specified above: 700 studies were considered for the next step. We read full texts of all 700 papers, but 330 were rejected since they described only particular endophenotypes of BPD or they focused on only pharmacogenetics or neuroimaging aspects. Finally only 370 studies were considered for the present review (data available on request). For each article screened we marked every gene and every SNP investigated. All SNPs not unequivocally associated to a gene were searched in the “SNPper” database (http://snpper.chip.org/bio/snpper-enter-snp). Finally, every gene was put into a specific biological pathway through the “KEGG” database (http://www.genome.jp/kegg/pathway.html).
Since our intent is to summarize the current data in the literature on BPD genetics, the results are discussed in a concise way in order to underline consistent evidence about specific biological pathways.

**Results**

To provide a background to understand how the biological alterations reported could be implicated in the pathogenesis of BPD, here we briefly synthesize the main pathogenetic hypothesis of BPD (for comprehensive reviews see (12) and (13)). Briefly, although the exact pathogenic mechanism of BPD remains unknown, classical theories have identified main alterations in monoaminergic and chronobiological equilibrium (12), as well as in synaptic plasticity (13). Classical monoaminergic theory postulated that a dysregulation of the serotonin, norepinephrine or dopamine systems could explain the oscillation in mood. Subsequently, with the improvement of neuroimaging studies (14), the role of other neurotransmitters have been hypothesized, such as glutamate and GABA (13, 15), which may be involved in a neurotoxic/neuroprotective mechanisms. Finally, the clinical observation of the sleep-wake rhythm disruption and REM alterations in mood disorder and the efficacy of light therapy in major depressive disorder led us to consider as crucial the sleep disturbances in BPD and, therefore, to hypothesize a role for the genes involved in the modulation of the circadian system (16). In our previous review (10), we identified several genome areas and many genes associated with BPD. Now, with the introduction of GWAS, the study of CNVs, and the examination of large samples, we can extend our previous results. In particular, a large amount of evidence suggested the implication of specific neuronal pathways such as serotoninergic, GABAergic, glutamatergic systems, as well as genes implicated in the regulation of circadian rhythms and genes implicated in signalling transduction or cell maintenance in the pathogenesis of BPD.

**Serotonin-related genes**

The serotonin (5-HT) system has both inhibitory and facilitatory functions in the brain, where it is possible to find a great density of 5-HT receptors in the thalamus, hypothalamus and dorsal raphe nuclei. 5-HT is an important regulator of circadian rhythms, appetite, pain control and libido. It was an accidental discovery that drugs inhibiting monoamino-oxidase, historically used as anti-tubercular drugs, might lead to a hypomania like condition by increasing serotonin, dopamine and norepinephrine levels. Due to this empirical evidence and to the growing body of evidence of the role of these genes in major depressive disorder (17), in recent years many studies have investigated the possible implication of serotonin genes in the aetiology of BPD (18). Some positive associations were found for HTR1A (19) and HTR5A (20), which have an inhibitory role on neuronal excitability in favour of synaptic plasticity in the serotoninergic synapses. Moreover, in BPD the promoter of HTR1A is found to be hypermethylated, with the consequence of a diminution of gene expression and a decline of receptor function. There is also strong evidence of hypermethylation of the HTR2A (21) promoter region and hypomethylation of its first exon. This receptor, in contrast to HTR1A and HTR5A receptors, is coupled to stimulating G-protein, which activates the transcription of other genes and synaptic plasticity. Consequently, an inhibitory feedback in the presynaptic membrane and its epigenetic alteration may lead to a disruption in serotoninergic biological modulation, particularly in chronic stress conditions.
Table 1. Association studies for serotoninergic system genes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Name</th>
<th>N° of association studies (+ positive, - negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC6A4</td>
<td>solute carrier family 6 (neurotransmitter transporter, serotonin), member 4</td>
<td>+++-------</td>
</tr>
<tr>
<td>TPH1</td>
<td>tryptophan hydroxylase 1</td>
<td>++-------</td>
</tr>
<tr>
<td>TPH2</td>
<td>tryptophan hydroxylase 2</td>
<td>+++-------</td>
</tr>
<tr>
<td>HTR1A</td>
<td>5-hydroxytryptamine (serotonin) receptor 1A, G protein-coupled</td>
<td>+++-------</td>
</tr>
<tr>
<td>HTR1B</td>
<td>5-hydroxytryptamine (serotonin) receptor 1B, G protein-coupled</td>
<td>-</td>
</tr>
<tr>
<td>HTR2A</td>
<td>5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled</td>
<td>+++-------</td>
</tr>
<tr>
<td>HTR2C</td>
<td>5-hydroxytryptamine (serotonin) receptor 2C, G protein-coupled</td>
<td>+++-------</td>
</tr>
<tr>
<td>HTR5A</td>
<td>5-hydroxytryptamine (serotonin) receptor 5A, G protein-coupled</td>
<td>+</td>
</tr>
<tr>
<td>MAOA</td>
<td>monoamine oxidase A</td>
<td>+++-------</td>
</tr>
</tbody>
</table>

GABA-related genes

GABA is one of the most important inhibitory neurotransmitters, particularly in the mesocortical and mesolimbic pathways, and its receptors are the target of benzodiazepines, as well as of some mood stabilizers. An alteration in its receptors had been implicated in schizophrenia (22), while only marginal associations have been found in BPD. Our research confirms a minor role of the GABAergic system in the pathogenesis of BPD. Indeed among the GABA receptor genes investigated, no metabotropic receptors appear to have any SNP or epigenetic modification of particular interest. On the other hand there are a few positive results for an SNP in the GABRAS (22) and GABRB2 (23) genes, two subunits of the ionotropic receptor GABAA. This receptor has the function of hyperpolarizing and so decreasing global neuronal excitability, if activated by other neural systems such as the 5-HT or endocannabinoid pathways. Moreover, the biosynthesis of GABA itself has been associated with BPD as well. Particularly, a CNV in GAD1 (24), the enzyme responsible for catalyzing the production of GABA from L-glutamic acid, was associated with the disorder. This CNV leads to a decrease of enzyme activity and consequently to a reduction of GABA level in the synaptic cleft, i.e. a reduction of the main brain inhibitor. All these data suggest a possible role of disequilibrium in GABA inhibiting control in the central nervous system in BPD.
Table 2. Association studies for GABAergic system genes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Name</th>
<th>N° of association studies (+ positive, - negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABRA1</td>
<td>gamma-aminobutyric acid (GABA) A receptor, alpha 1</td>
<td>+</td>
</tr>
<tr>
<td>GABRA3</td>
<td>gamma-aminobutyric acid (GABA) A receptor, alpha 3</td>
<td>+</td>
</tr>
<tr>
<td>GABRA4</td>
<td>gamma-aminobutyric acid (GABA) A receptor, alpha 4</td>
<td>-</td>
</tr>
<tr>
<td>GABRA5</td>
<td>gamma-aminobutyric acid (GABA) A receptor, alpha 5</td>
<td>++</td>
</tr>
<tr>
<td>GABRB1</td>
<td>gamma-aminobutyric acid (GABA) A receptor, beta 1</td>
<td>-</td>
</tr>
<tr>
<td>GABRB2</td>
<td>gamma-aminobutyric acid (GABA) A receptor, beta 2</td>
<td>+</td>
</tr>
<tr>
<td>GABRB3</td>
<td>gamma-aminobutyric acid (GABA) A receptor, beta 3</td>
<td>-</td>
</tr>
<tr>
<td>GABRB3</td>
<td>gamma-aminobutyric acid (GABA) A receptor, beta 3</td>
<td>-</td>
</tr>
<tr>
<td>GABRR3</td>
<td>gamma-aminobutyric acid (GABA) A receptor, rho 3</td>
<td>-</td>
</tr>
<tr>
<td>GAD1</td>
<td>glutamate decarboxylase 1</td>
<td>+++</td>
</tr>
<tr>
<td>GAD2</td>
<td>glutamate decarboxylase 2</td>
<td>-</td>
</tr>
</tbody>
</table>

Glutamate-related genes

Glutamate is the main excitatory neurotransmitter in the central nervous system and this system has been recently associated with psychosis and schizophrenia (25). When in excess it can exert neurotoxic effects and, in conjunction with high cortisol levels, it has been hypothesized to mediate the deleterious effects of chronic stress on cognition. Consistently, the hippocampus and amygdala, which have a high concentration of glutamate ionotropic receptors, were found to be decreased in volume in BPD (26). Among ionotropic receptors, the mRNA levels of GRIN1 and GRIN3A (27), which encode for NMDA receptors, are increased in BPD post-mortem studies. Moreover, some alterations of DAOA gene products, which degrades an activator of NMDA receptors, has been strongly correlated with BPD (28). Consistently, genetic association studies also found positive associations among both SNPs and CNVs for GRIK4 (29), GRIK5 (30), GRIK2 (24), which encode for kainate receptors, and BPD. Interestingly, NMDA receptors seem to mediate an excitatory activation and neuronal plasticity in postsynaptic cells and preclinical studies provided evidence about the antidepressant-like action of their antagonists (31). On the other hand, kainate receptors have an inhibitory function and loss of their action may be related to manic behaviour. Among metabotropic receptors, a rare CNV was associated with BPD in the GRM7 gene (32), which encodes for a receptor activating other neuroprotection systems. Therefore, its depletion may lead to disease through losing the functionality of these neuroprotective systems. Finally, in BPD a significantly decreased expression of glutamate transporter SLC1A2 and SLC1A1 (33) and of vesicular glutamate transporter, SLC17A7 (VGLUT1), has been found (34). These alterations lead to a diminished re-uptake and recycling of the neurotransmitter at the presynaptic level, with an easier achievement of toxic neurotransmitter levels. Finally, not only receptors, but also the glutamatergic signal transduction pathway was found to be altered in BPD; particularly, the mRNA expression of the PPP1R1B gene (35), normally associated with synaptic modification due to NMDA stimulation, seems to be modified in BPD patients.
Table 3. Association studies for glutamatergic system genes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Name</th>
<th>Nº of association studies (+ positive, - negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAOA</td>
<td>D-amino acid oxidase activator</td>
<td>++</td>
</tr>
<tr>
<td>GRIN1</td>
<td>glutamate receptor, ionotropic, N-methyl D-aspartate 1</td>
<td>++</td>
</tr>
<tr>
<td>GRIN2A</td>
<td>glutamate receptor, ionotropic, N-methyl D-aspartate 2A</td>
<td>---</td>
</tr>
<tr>
<td>GRIN2B</td>
<td>glutamate receptor, ionotropic, N-methyl D-aspartate 2B</td>
<td>+</td>
</tr>
<tr>
<td>GRIN2C</td>
<td>glutamate receptor, ionotropic, N-methyl D-aspartate 2C</td>
<td>-</td>
</tr>
<tr>
<td>GRIN2D</td>
<td>glutamate receptor, ionotropic, N-methyl D-aspartate 2D</td>
<td>-</td>
</tr>
<tr>
<td>GRIN3A</td>
<td>glutamate receptor, ionotropic, N-methyl D-aspartate 3A</td>
<td>+</td>
</tr>
<tr>
<td>GRIA1</td>
<td>glutamate receptor, ionotropic, AMPA 1</td>
<td>+</td>
</tr>
<tr>
<td>GRIA2</td>
<td>glutamate receptor, ionotropic, AMPA 2</td>
<td>++</td>
</tr>
<tr>
<td>GRIA3</td>
<td>glutamate receptor, ionotropic, AMPA 3</td>
<td>-</td>
</tr>
<tr>
<td>GRIA4</td>
<td>glutamate receptor, ionotropic, AMPA 4</td>
<td>++</td>
</tr>
<tr>
<td>GRIK1</td>
<td>glutamate receptor, ionotropic, kainate 1</td>
<td>-</td>
</tr>
<tr>
<td>GRIK2</td>
<td>glutamate receptor, ionotropic, kainate 2</td>
<td>++</td>
</tr>
<tr>
<td>GRIK3</td>
<td>glutamate receptor, ionotropic, kainate 3</td>
<td>-</td>
</tr>
<tr>
<td>GRIK4</td>
<td>glutamate receptor, ionotropic, kainate 4</td>
<td>++</td>
</tr>
<tr>
<td>GRIK5</td>
<td>glutamate receptor, ionotropic, kainate 5</td>
<td>-</td>
</tr>
<tr>
<td>GRM2</td>
<td>glutamate receptor, metabotropic 2</td>
<td>-</td>
</tr>
<tr>
<td>GRM3</td>
<td>glutamate receptor, metabotropic 3</td>
<td>-</td>
</tr>
<tr>
<td>GRM7</td>
<td>glutamate receptor, metabotropic 7</td>
<td>++</td>
</tr>
<tr>
<td>SLC1A3</td>
<td>solute carrier family 1 (glial high affinity glutamate transporter), member 3</td>
<td>+</td>
</tr>
<tr>
<td>SLC1A2</td>
<td>solute carrier family 1 (glial high affinity glutamate transporter), member 2</td>
<td>+</td>
</tr>
<tr>
<td>SLC1A1</td>
<td>solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1</td>
<td>-</td>
</tr>
<tr>
<td>SLC1A6</td>
<td>solute carrier family 1 (high affinity aspartate/glutamate transporter), member 6</td>
<td>-</td>
</tr>
<tr>
<td>SLC17A7</td>
<td>solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 7</td>
<td>+</td>
</tr>
<tr>
<td>SLC17A6</td>
<td>solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 6</td>
<td>-</td>
</tr>
<tr>
<td>SLC17A8</td>
<td>solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 8</td>
<td>-</td>
</tr>
<tr>
<td>PPP1R1B</td>
<td>protein phosphatase 1, regulatory (inhibitor) subunit 1B</td>
<td>++</td>
</tr>
</tbody>
</table>

CLOCK-related genes

Body temperature, hypothalamic-pituitary-adrenocortical axis function and sleep-wake cycles are examples of circadian rhythms regulated by a primary circadian pacemaker located in hypothalamus, whose zeitgeber is the light which regulates biosynthesis and secretion levels of melatonin by the pineal gland (36). The interest in clock-related genes came from the clinical observation of the disruption of the sleep-wake rhythm in affective disorders. Indeed, in major depressive disorder there is can be insomnia or hypersomnia and early awakening, while in bipolar patients, sleep deprivation may be conducive to a state of hyperactivation. The detail of the specific function of single genes which take part in the modulation of circadian cycles is still not known. Nonetheless, the knowledge about this fundamental system has greatly increased in the last decade. For example, the role of the
CLOCK and ARNTL genes, which are highly correlated with BPD (37), has begun to be clarified. They encode for proteins which form a heterodimer, enhancing the transcription of PER and CRY genes. PER3 and CRY2 genes (37), together with CSNK1D gene (37), are able to activate other pathways involved in preference of diurnal hours for daily activity and sleep hygiene; the aberrant transcription of all these three genes was associated not only with BPD but also with common co-morbidities of BPD, such as alcohol abuse and anxiety disorders (38).

Table 4. Association studies for circadian rhythm genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Name</th>
<th>No. of association studies (+ positive, - negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AANAT</td>
<td>aralkylamine N-acetyltransferase</td>
<td>--</td>
</tr>
<tr>
<td>ARNTL</td>
<td>aryl hydrocarbon receptor nuclear translocator-like</td>
<td>+++</td>
</tr>
<tr>
<td>CLOCK</td>
<td>clock homolog (mouse)</td>
<td>+++</td>
</tr>
<tr>
<td>CRY2</td>
<td>cryptochrome 2 (photolyase-like)</td>
<td>+</td>
</tr>
<tr>
<td>MTNR1A</td>
<td>melatonin receptor 1A</td>
<td>-</td>
</tr>
<tr>
<td>NR1D1</td>
<td>nuclear receptor subfamily 1, group D, member 1</td>
<td>+</td>
</tr>
<tr>
<td>PER3</td>
<td>period homolog 3 (Drosophila)</td>
<td>+++</td>
</tr>
<tr>
<td>PROK2</td>
<td>prokineticin 2</td>
<td>-</td>
</tr>
<tr>
<td>CSNK1D</td>
<td>casein kinase 1, delta</td>
<td>+</td>
</tr>
<tr>
<td>TIMELESS</td>
<td>timeless homolog (Drosophila)</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations
Other Genes

Among other genes investigated in BPD, genes which encode for proteins involved in signal transduction seem to play a relevant role in the pathogenesis of the disorder. Consistently, the gold
standard of mood stabilizers, lithium, seems to act through the stabilization of the signal transduction cascade, although the exact mechanism of action of this drug is still unknown (39). Main activators of the signal transduction cascade associated with BPD are the CACNA1C (40, 41) and DGKH (42) genes. The first encode for an L-type calcium channel mediating a variety of calcium-dependent processes in neurons. Its variants have also been associated with a severe prolongation of the QT interval in the electrocardiogram, cognitive abnormalities and autism spectrum features. It is involved in serotonergic, GABAergic and glutamatergic transmission and, together with DGKH, in the modulation of MAPK pathway, which is involved in neural plasticity, proliferation and differentiation. Similar is the action of ANK3 product (41), the function of which is to stabilize the cytoskeleton, to maintain the membrane Na+/K+ channels and to mediate signal in response to cell adhesion. Genes implicated neurodevelopment may also play a role in BDP and alterations in these genes may lead to a disequilibrium in neurotransmission. Among these, are the ODZ4 gene (43), which is involved in transcriptional control of other genes during neurogenesis, the DISC1 gene (28), primarily associated with schizophrenia, which acts by guiding the migration of the cortical interneurons, the NGR1 gene (44), the task of which is to manage myelination, both central and peripheral, by influencing the proliferation of oligodendrocytes and Schwann cells. Finally, also the expression of miRNAs may be modified in BPD during neurodevelopment. Particularly, in BPD these RNA particles, which control gene expression by a post-transcriptional mechanism, are found to be under-expressed (45) and some genes, normally silenced or acting with attenuated transcription by this mechanism, lose their physiological control.

Discussion

BPD is a worldwide public health problem, characterized by fluctuations in mood alternating with periods of normal mood. It is a life-lasting diagnosis which affects patients with both direct symptoms and several co-morbidities, with the consequence of important impairment in both social and economic life. We have endeavoured to provide a comprehensive view of current evidence on the genetic background of BPD, updating our previous paper on this issue (10).

We found an increasing body of evidence supporting the role of multiple neurotransmission and neurodevelopment pathways, which interact differently in the various regions of the central nervous system. The main genetic factors involved in the pathogenesis of BPD seem to be the glutamatergic and the CLOCK-related genes systems, which appear to be the final common effectors of the pathogenetic mechanism, and the GABA and 5-HT systems, which seem to have a modulation role. In particular, the 5-HT system regulates the expression of CLOCK genes in response to light stimuli in the suprachiasmatic nucleus (46) and modulates, in different central nervous system areas, glutamatergic transmission, enhancing or suppressing its transmission directly or through GABA interneurons (47).

Despite this evidence, it is still impossible to detect the specific genetic alterations underlying this disorder. The main problems in achieving this aim are related to the great phenotypical heterogeneity of BPD itself, as well as to the complexity of the genetics of BPD, which is likely to involve several genes and several interactions among them. Finally, epigenetic modifications and environmental effects are also likely to play relevant roles in the pathogenesis of BPD. The improvement of analysis techniques and the analysis of endophenotypes (48) more related to genetic variants, could lead to substantial improvement in the understanding of the basis of this important psychiatric disorder in the next few years. In the future, the exact biological causes of BPD could be revealed, with clear advantages both for determining the prognosis and choosing the correct treatment for this debilitating disorder.

GP Comment

What have I learned from this paper?

Whilst complex genetics are unlikely to be discussed in a primary care consultation, awareness of these issues, and of the neurotransmitter and circadian rhythm consequences, are important as they may explain some of the symptoms (e.g. irritability, insomnia, hypersomnia). Other research may
bring clarity to this area and may have important ramifications for predicting treatment response and perhaps even heritability. A key message is that bipolar disorder has a significant genetic component and a positive (or suggestive) family history should alert the GP to a possible diagnosis of this condition.

Dr Daniel Dietch, Lonsdale Medical Centre

References


40. WTCCC. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447 (7145):661-78. Epub 2007/06/08.


Epigenetics of bipolar disorder

Peter Pregelj1,2

1. University Psychiatric Hospital Ljubljana, Studenec 48, SI-1260 Ljubljana Polje, Slovenia.
2. University of Ljubljana. Faculty of Medicine. Department of Psychiatry, Vrazov trg 2, SI-1000 Ljubljana, Slovenia.

Abstract

Bipolar disorder is a common, chronic, and recurring mental disorder with a poorly understood and complex genetic basis. Epigenetic mechanisms refer to the regulation of DNA transcription without alteration of the nucleotide sequence. Epigenetic mechanisms are: DNA methylation, histone modifications and non-coding micro RNAs. Epigenetic information is not stored in the DNA nucleotide sequence; nevertheless it can be transmitted through generations. Recent studies have indicated that epigenetic mechanisms are involved in the pathophysiology of bipolar disorder and also in the mechanisms of action of current medications used for the treatment of bipolar disorder.

Key words: bipolar disorder, epigenetics, DNA methylation, histone modulation, micro RNAs, mood stabilizers.

Introduction

Bipolar disorder is a common, chronic, and recurring mental disorder with a rather poorly understood pathophysiology on the neurobiological level. Family, twin, and adoption studies indicate that bipolar disorder has a genetic basis. However, the genetic basis of bipolar disorder is complex, involving the interplay between genetic as well as environmental factors.1 Several studies have tried to find specific genetic mutations and polymorphisms in association with bipolar disorder; however no genetic mutation or polymorphism underlying this disorder has been definitively identified.1,2 It seems that aberrant nucleotide sequence per se could not be directly linked to the pathophysiology of the bipolar disorder. However, the interplay of different genes and their regulation by environmental factors could better explain the complexity of the bipolar disorder phenomenology and also its unstable course. Beside other mechanisms involved in gene regulation, epigenetic mechanisms by their reversibility, could explain the changing, episodic course of bipolar disorder.

Epigenetic mechanisms

Epigenetic information is defined as information-carrying molecular processes that are inherited through mitosis or meiosis, influencing gene expression independently of the DNA sequence.3 Environmental factors could, via specific intracellular signalling pathways, control neuronal differentiation at multiple levels, such as neuronal precursor cell-cycle control, migration, synaptogenesis, neuronal survival and neurotransmitter phenotype (for review see3). One specific regulation on the cellular level, the induction of timely coordinated cascades of gene expression, controlled by specific and ubiquitous transcription factors, is further regulated by epigenetic mechanisms (Figure 1). Transcription factors, in turn, induce either the expression of structural genes required for specific functions of a given neuronal lineage and/or the expression of non-coding RNAs that play an important further regulatory role.3 However, binding of the transcription factors to the specific regions of the DNA is influenced by different mechanisms such as DNA sequence, especially in the promoter regions on one hand, and epigenetic mechanisms such as histone modulation or methylation of DNA molecule, on the other (Figure 2).4
Histone modification

In association with the DNA molecule, nuclear protein histones are the basic building units of nucleosomes. The DNA molecule is wrapped around a histone protein octamer made of histones. Each histone has a “tail” protruding out of the nucleosome, which can be modified in different ways such as phosphorylation, ubiquitination, sumoylation, acetylation, and methylation. For example, histones are deacetylated by a group of enzymes known as histone deacetylases (HDACs). When deacetylated the affinity of histones for the DNA molecule is increased. Gene expression is influenced by the chromatin structure via histone modification and chromatin remodelling complexes (remodelers). The chromatin structure could switch from a closed or transcriptionally repressive state, to an open or transcriptionally permissive state. It could be summarised that this histone modification influences gene transcription in a specific region by changing the affinity between histones and the DNA molecule. Not only histone tail modification but also other processes such as histone post-translational modifications and also different histone variants could influence the packaging of chromosomal DNA and suppress gene expression in a specific DNA region.

DNA methylation

DNA methylation is a stable but reversible covalent modification of the DNA molecule not influencing nucleotide sequence. When the promoter region of the DNA is methylated, the affinity for activators of DNA transcription is, in most cases, decreased, resulting in reduced mRNA production. The methylation occurs at the 5’ position of the pyrimidine ring of the cytosine in the CpG dinucleotide and is facilitated by different types of DNA methyltransferases (DNMTs). However, cytosines in the CpG dinucleotide are the preferred, but not the exclusive, targets for DNA methylation. An interesting observation has been reported for one of the DNMTs, a DNMT1. This DNMT is the main enzyme responsible for the maintenance of DNA methylation. It has also been observed that DNMT1 methylates hemimethylated DNA more rapidly than unmethylated DNA indicating the possibility that methylation profiles could be inherited from mother to daughter cell and from one generation to the next. The establishment and maintenance of CpG site methylation is essential during central nervous system differentiation. DNA methylation has been implicated in synaptic plasticity, learning, and memory. Not all CpG dinucleotides are methylated. There is a cell-specific pattern of distribution of methylated CpG dinucleotides carrying the epigenetic information in the methylation sequence itself. In contrast to the information stored in the nucleotide sequence, the DNA methylation is not only heritable but also reversible. Furthermore, it has been shown that both described epigenetic mechanisms, histone modulation and DNA methylation, are interconnected. It has been reported that methylated cytosines attract methyl-CpG–binding protein, which recruits chromatin-remodelling proteins to influence the histone structure. All these mechanisms could work together to induce transcriptional silencing.

MicroRNAs

The third known epigenetic mechanisms are micro ribonucleic acids (abbreviated miRNA). MiRNA is a short RNA molecule, on average of 22 nucleotides, found in eukaryotic cells. These molecules are involved in post-transcriptional regulation and bind complementary sequences on target messenger RNA transcripts (mRNAs), usually resulting in translational repression or target degradation and gene silencing. The human genome may encode over 1000 different miRNAs, which may regulate numerous genes. During the process of translational repression, miRNA bind to specific proteins, such as proteins from the Argonaute family.

Bipolar disorder and abnormalities in epigenetic regulation

Aberrant epigenetic regulation (epimutations) could have a similar effect to DNA mutations because an epimutation could lead to the abnormal expression of a gene by enhancing or silencing that gene. Differences in epigenetic regulation of gene expression have been found in patients with bipolar disorder in comparison to controls. However, it is not clear whether some of these differences are the cause or the effect of the disease process in bipolar disorder. Although the understanding
of the role of miRNAs and histone modulation in bipolar disorder is in its very early stages. Several studies have addressed the role of epigenetic mechanisms in this mental disorder.

**Epigenetic dysfunction of GABAergic and glutamatergic systems**

The main systems for suppressing and activating the activity of the central nervous system are GABAergic and glutamatergic systems respectively. Numerous genes are involved in the regulation of those two systems. However, only recently, differences in epigenetic regulation of specific genes involved in the regulation of these two systems have been reported. For example, it has been reported that the promoter of the GAD1 gene has been found to be hypermethylated in post-mortem samples of the prefrontal cortex in patients with bipolar disorder due to over-expression of the enzyme DNA methyltransferase 1 (DNMT1), resulting in decreased expression of GAD67. GAD67 is one of two isoforms of glutamic acid decarboxylase, the enzyme that catalyses the conversion of the excitatory neurotransmitter glutamic acid to the inhibitory neurotransmitter gamma-amino butyric acid (GABA), influencing the activity of GABAergic and glutamatergic systems. Furthermore, in a genome-wide profiling of DNA methylation in patients with bipolar disorder it was found that beside other genes abnormalities in the methylation, a gene for RNA binding protein was involved in the synthesis of functional GABA-B receptors.

**Epigenetic dysfunction of dopaminergic and adrenergic systems**

Abnormalities in neurotransmission in the dopaminergic and adrenergic systems have been reported to be involved in the pathogenesis of bipolar disorder. Although GABAergic, glutamatergic, dopaminergic and adrenergic systems are interconnected and dysfunction of one system could affect the others, epigenetic deregulations of genes involved mainly in the regulation of dopaminergic and adrenergic systems have been reported. It has been shown that hypomethylation of membrane bound catechol-O-methyltransferase (MB-COMT) promoter is a major risk factor for bipolar disorder. MB-COMT is one of the two isoforms of the COMT enzyme which is involved in the degradation of the neurotransmitters dopamine and noradrenaline. It could be speculated that hypomethylation of MB-COMT promoter could lead to increased expression of the MB-COMT gene and consequently to decreased levels of dopamine and adrenaline.

**Neuroplasticity and epigenetic regulation in bipolar disorder**

At the cellular level, it has been suggested that abnormal brain derived growth factor (BDNF) gene activity is a leading etiological hypothesis by which early-life adverse experiences persistently modify brain and behavioural plasticity (for review see). In the genome-wide profiling of DNA methylation in patients with bipolar disorder, abnormalities in the methylation of the BDNF gene have also been found. Recently, in a study investigating the degree of DNA methylation at the promoter region of the BDNF gene in peripheral blood mononuclear cells isolated from patients with bipolar type I and type II and healthy controls, a significant BDNF gene expression downregulation in bipolar II patients but not in bipolar I patients in comparison with controls was found. Consistently, a hypermethylation of the BDNF promoter region was specifically found in bipolar II patients. Another study reported changes in DNA of patients with bipolar disorder associated with hypomethylation and hypermethylation of CpG islands in cyclooxygenase-2 and BDNF promoter regions, respectively.

**Treatment and epigenetic influences**

Many psychotropic drugs that are currently in use for the treatment of bipolar disorder have been shown to influence epigenetic mechanisms in addition to other mechanisms of action. Specific epigenetic drugs with their primary mechanism of action influencing directly epigenetic regulation of gene expression are under development.

**Mood stabilizers**
Valproic acid has mood-stabilizing effects in patients with bipolar disorder. Valproic acid has diverse mechanisms of action. It prolongs the inactive state of sodium channels after depolarization; it potentiates the action of GABA at GABAergic synapses, and it blocks T-type calcium channels in thalamic neurons. In addition to the mechanisms of action as an antiepileptic drug, which could contribute to the mood stabilization, it is thought to influence epigenetic mechanisms by inhibiting HDACs and also by causing demethylation of DNA. It has been speculated that beneficial effect of valproic acid may be due to activation of DNA demethylation, leading to reversal of a repressed nuclear epigenetic state in cortical neurons. Recently, a study investigating the degree of DNA methylation at the promoter region of the BDNF gene in peripheral blood mononuclear cells isolated from patients with bipolar I and II found higher levels of DNA methylation in patients with bipolar disorder receiving pharmacological treatment with mood stabilizers plus antidepressants in comparison to those exclusively treated with mood-stabilizing agents. Moreover, among the different pharmacological therapies, lithium and valproate were reported to be associated with a significant reduction of DNA methylation in comparison to other medications. A study using animal models reported that rat hippocampal miRNA changes following chronic administration of valproic acid and lithium.

Antidepressants

The primary mechanism of action of the tricyclic antidepressant imipramine is inhibition of the reuptake of noradrenaline and serotonin into the presynaptic neurons but it has also been found to influence chromatin remodelling in animal models of five BDNF splice variant mRNAs (I–V) and their promoters in the hippocampus. Chronic imipramine administration reversed BDNF transcripts III and IV downregulation induced by stress and increased histone acetylation at the corresponding promoters. It was further explained that the observed histone hyperacetylation associated with imipramine administration was also associated with a selective downregulation of histone deacetylase 5. Selective serotonin reuptake inhibitors (SSRIs) seem to have similar effects to those of tricyclic antidepressants. Fluoxetine has also been shown to induce expression of the methyl-CpG-binding proteins in adult rat brain after chronic administration.

Antipsychotics

A preclinical study showed that two atypical antipsychotics, clozapine and sulpiride, but not the typical antipsychotic haloperidol or the atypical antipsychotic olanzapine, administered in mice alone or in association with valproate, in clinically relevant doses for 3 days, down-regulated reelin and GAD67 promoter methylation in the frontal cortex and striatum. The authors speculated that these results suggested that clozapine or sulpiride associated with valproate, by increasing DNA demethylation via an unknown mechanism, causes chromatin remodelling that brings about a beneficial change in the epigenetic GABAergic dysfunction typical of patients with bipolar disorder.

Future specific epigenetic medications

Regarding mechanisms of action, there are three types of epigenetic medications that are being investigated for the treatment of bipolar disorder: compounds inhibiting HDACs, compounds targeting DNA methylation, and compounds targeting miRNAs. Trials of epigenetic medications for the treatment of bipolar disorder are presently at preclinical stages and include compounds such as SAHA (vorinostat), benzamide MS-275 and phenylbutyrate. For example, it was reported that the benzamide MS-275 is much more potent than valproic acid, as a long-lasting and brain-region-selective HDAC inhibitor. It was also reported that the infusion of HDAC inhibitors into the nucleus accumbens exerted antidepressant-like effects in the social defeat stress model as well as other behavioural tests in mice. On the level of miRNA manipulation, it has been suggested that there are two possible methods that can be used to target miRNAs: inhibiting miRNAs using small molecules, or using smart technologies such as liposomes, nanoparticles, and specific nucleotide delivery systems through the cell membrane to administer double-stranded synthetic RNA which mimics or antagonises the miRNA in the cell.

Conclusions
Recent research indicates that epigenetic mechanisms are involved in pathophysiology of bipolar disorder and that existing treatments could influence the same mechanisms. Furthermore, data on possible mechanisms of action of medications used in the treatment of bipolar disorder indicate that BDNF regulation might be a crucial target for their effects. Current psychopharmacological drugs, including antidepressants, antipsychotics and mood stabilizers, may exert some of their effects through epigenetic mechanisms. It could be concluded that reversibility of epigenetic changes opens the possibility of evolving new specific treatments for patients with bipolar disorder, from pharmacological approaches to psychotherapy.

**GP Comment**

**What have I learned from this paper?**

This is a fascinating area, especially with the advent of personalised medicine, with increasing numbers of patients bringing printouts of their DNA, from commercial companies, to their GP for interpretation - which can be challenging! Although epigenetics is complex, knowing that these mechanisms could account for both environmental and pharmacological effects on the course of bipolar disorder is important. Moreover, pharmacogenomics is a developing area and the GP consultation of the future may include discussions around these themes.

**Dr Daniel Dietch, Lonsdale Medical Centre, London.**

**References**


Figure 1. Transcription and translation of the DNA molecule. Activators are bound to promoter
region of the DNA molecule inducing the transcription of DNA resulting in mRNA production. mRNA is further translated into the protein. Different mechanisms are involved in the regulation of gene expression. The activation of this mechanisms resolve in gene silencing in most cases (Riccio 2010).

Figure 2. Epigenetic mechanisms involved in the regulation of gene expression. Binding of the transcription factors to the promoter regions of the DNA is influenced by different mechanisms including epigenetic mechanisms such as histone modulation and methylation of DNA molecule. The DNA molecule is wrapped around a deacetylated histone proteins resulting in gene silencing. DNA methylation is a stable covalent modification of the DNA molecule. When the promoter region of the DNA is methylated the affinity for activators of DNA transcription is decreased resolving in reduced mRNA production. On the post-transcriptional level miRNA molecules are involved in regulation of gene expression. MiRNAs bind complementary sequences on target mRNA transcripts, usually resulting in translational repression or target degradation and gene silencing.
Neurotransmitter and Intracellular Mechanisms of Bipolar Disorder; an Explanation of Kato’s Theory of Mood-Stabilising Neurons

James Edmonds, Cambridge University School of Clinical Medicine, Christ’s College Cambridge. Dr Mark Agius South Essex Partnership Foundation Trust; Department of Psychiatry, University of Cambridge; Clare College Cambridge.

Abstract

Investigations into the neurobiology of bipolar disorder have produced evidence of abnormalities within many processes and chemicals in the brain. There are differences between bipolar disorder patients and controls in terms of the functioning of neurotransmitters such as dopamine, intracellular messengers such as GSK-3b, protein kinase C and calcium, and organelles such as mitochondria and the endoplasmic reticulum. A large number of genes have been identified as increasing the risk of bipolar disorder. This article reviews this evidence and examines the hypothesis that these observed abnormalities are contributing towards, or resulting from, a fundamental neurodegenerative process which affects neurons which ordinarily have a ‘mood stabilising’ effect.

Key words: bipolar disorder, neurobiology, dopamine, calcium, mood stabilisers, neurodegeneration.

Introduction

Bipolar disorder is a disease for which a wide variety of biological markers can be identified which show differences from control groups. Differences can be found at the genetic level, within intracellular messenger and gene expression systems, in neurotransmitter levels, and even on imaging, but none of these appear to be entirely necessary or sufficient to account for the disease. It seems likely that many of these markers we observe to be altered in bipolar disorder are contributing towards, or resulting from, a single main pathological process which is ultimately responsible for the symptomatology of the disorder, and which ties together all the diverse abnormalities that have been identified. Kato has proposed a theory of mood-stabilising neurons, which become dysfunctional in bipolar disorder, and this seems an intriguing candidate for such a ‘common pathway’. In this paper, we shall discuss the various observations in the neuropathology of bipolar disorder, including abnormal function of Ca2+ channels, GSK-3b, mitochondria, and the ER stress response (1), and explain how these might fit with the theory of mood-stabilising neurons.

The Neurotransmitter and synaptic cleft level; Dopamine as a neurotransmitter in bipolar disorder

The classical view of bipolar disorder has been of a disorder primarily of neurotransmitter function. Three neurotransmitters, each with their own system of neurons and receptors, play an important role in mood disorders. These are serotonin, noradrenaline and dopamine. Reuptake transporters specific for each of these neurotransmitters regulate their concentration within the synaptic cleft by promoting reuptake of the transmitters into the presynaptic neuron. Hence SSRIs exert their action by blocking the serotonin transporter and venlafaxine blocks both the noradrenaline and serotonin transporters. It is the conventional wisdom that SSRIs and venlafaxine exert their effects in this way, and that the binding of serotonin (and in a similar way noradrenaline) to its receptor causes a second messenger cascade within the postsynaptic neuron, which in turn increases brain derived neurotrophic factor (BDNF) within the cell, which promotes neurogenesis in unipolar depression, thus alleviating the condition.

It appears that there is much evidence for dopamine being an important neurotransmitter in mania and depression. Antipsychotics effective against mania block dopamine neurotransmission, while
psychostimulants, such as amphetamine, by increasing dopamine neurotransmission, cause mania. In the context of bipolar disorder, tricyclic antidepressants can precipitate a rapid ‘switch’ from depression into mania, but the SSRIs do not tend to cause this (2). Tricyclic antidepressants block the noradrenaline and serotonin transporters, but have negligible effect on the dopamine transporter. However, in the prefrontal cortex, dopamine transport uses the noradrenaline transporter, such that tricyclics are able to increase the concentration of dopamine within prefrontal cortex synapses, while SSRIs do not (3).

In dopamine-deficient transgenic mice, lower locomotor activity and hypophagia is observed (4, 5). Ventral tegmental area dopamine neuron degeneration is known to cause depression (6). The cerebrospinal fluid concentration of the dopamine metabolite homovanillic acid is seen to alter in a state-dependent manner (7). Thus, dopamine neurotransmission appears to alter with mood state. Serotonin systems, on the other hand, can be seen to alter in a manner that is not dependent on overall mood state. Reduced serotonin activity, as measured by neuroendocrine challenge (8) and decreased cerebrospinal fluid concentrations of HIAA (a serotonin metabolite), were reported in both depressive and manic states (7). Putting this more simply, there is evidence that dopamine in particular is an important neurotransmitter in bipolar disorder. This indicates an important difference in terms of neurotransmitters between bipolar and unipolar depression. It is important to remember, however, that neurotransmitter levels are merely the product of the neurons that produce them, and that these abnormalities might be the result of a number of more fundamental cellular changes in bipolar disorder, most likely effecting the neurogenesis and degeneration of neurons which then, in turn, affect levels of transmitters such as dopamine.

The Role of Calcium Channels

In the platelets of patients with bipolar disorder, it is found that basal levels of calcium, and the degree of calcium influx provoked by agonists such as thrombin, serotonin, and platelet activating factor, are enhanced, regardless of which agonist is used (9, 10). The ER calcium pump can be inhibited using thapsigargin, which results in Ca2+ depletion from the ER stores, and a secondary Ca2+ influx via the SOCC on the plasma membrane, leading to increased cytoplasmic Ca2+ concentrations. Peripheral blood cells taken from patients with bipolar disorder have an enhanced response to thapsigargin (11, 12), and SOCC disruption appears to be contributing towards the Ca2+ signalling changes seen in bipolar disorder (10). Within neurons, Ca2+ signalling could also be disrupted by altered function of the NMDA receptor, Ca2+ permeable AMPA/kainate receptor, and voltage-gated Ca2+ channel. Studies of post-mortem brains from patients with bipolar disorder have shown changes in the genes for these receptors.

The Phosphoinositide pathway

Intracellular calcium levels are also affected by the phosphatidylinositol pathway, the likely target of lithium. Phosphatidylinositol bisphosphate hydrolysis yields diacylglycerol (DAG) and inositol triphosphate (IP3), which in turn causes ER Ca2+ stores to be released. Lymphoblastoid and lymphocyte cell lines from patients with bipolar disorder show lower levels of inositol (13), reduced inositol monophosphatase 2 mRNA (14, 15), and reduced IMPase activity (16). Protein kinase C, which is activated by DAG and Ca2+, is found to be active, bound to membranes, and translocates to the membrane in response to serotonin stimuli, in higher levels in drug-free patients, and this dysregulation is reduced following lithium or valproate treatment (17, 18, 19). As well as acting on the phosphatidylinositol pathway, mood stabilisers also seem to inhibit glycogen synthase kinase 3b (GSK-3b) (20, 21), and thus the GSK-3b pathway may also have a role in the neurobiology of bipolar disorder. GSK-3b is controlled via intracellular Ca2+ signalling, and has a role in the neurotrophin and Wnt signalling pathways. There is evidence to suggest that GSK-3b overactivity in bipolar disorder may be responsible for a shortening of the circadian rhythm period, and that lithium is able to affect circadian rhythm by GSK-3b inhibition (22).
Mitochondrial dysfunction

Studies using magnetic resonance spectroscopy (MRS) have indicated that differences in energy metabolism are present in patients with bipolar disorder, including reductions in phosphocreatine (23) and creatine (26, 27, 28), a decreased intracellular pH (24), and increased lactate (25). These are similar findings to those seen in mitochondrial diseases like chronic external ophthalmoplegia (CPEO), caused by mitochondrial DNA (mtDNA) deletions and primarily affecting muscle cells. mtDNA deletions were reported to be numerous in the brain of a patient with CPEO who presented primarily with severe retarded depression (29). Thus, it has been suggested that mtDNA deletions in the brain might be a cause for depression. In some mitochondrial cytopathies, convincing associations have been shown with depression (54% of 36 patients with mitochondrial disease,) and bipolar disorder (17%) (30, 31).

These abnormalities of mtDNA, known to be accumulated in the brains of some bipolar disorder patients (33), are likely to effect the pathology of bipolar disorder through mitochondrial Ca2+ dysregulation (32). Mitochondrial-related nuclear gene expression also appears to be decreased in bipolar disorder, for instance in the hippocampus (34). The lymphocytes of bipolar disorder patients appear to down-regulate mitochondria-related nuclear genes in response to glucose deprivation stress, whilst healthy control subjects respond by upregulating these genes (35), suggesting that a cellular stress response impairment may be of importance in bipolar disorder. Transgenic mice have been studied, which show mutations of mtDNA polymerase gamma (POLG), modelling one of the causes of CPOE (36). These mice have accumulations of mtDNA deletions within neurons, and show bipolar disorder-like phenotypes. This included changes to the circadian rhythm, which were exacerbated by tricyclic antidepressants but improved by lithium (37) or electroconvulsive therapy (38). Mitochondria from the brains of these transgenic mice were found to sequester calcium more rapidly (39). Mitochondrial dysfunction in bipolar disorder is also likely to cause oxidative stress, and markers for this, such as thiobarbituric acid reactive substances, are found to be raised in patients with bipolar disorder (40).

Endoplasmic reticulum stress dysfunction

The leucine zipper transcription factor gene X-box-binding protein 1 (XBP1) has been linked with ER stress dysfunction, and may have a role in bipolar disorder. XBP1 response to ER stress within lymphoblastic cells is shown to be weaker in patients with bipolar disorder (41, 42). This weakened response is not dependent on the XBP1 genotype in these patients (42). Within neurons, XBP1 mRNA is spliced as a result of ER stress, induced locally by BDNF as it raises protein synthesis. Neurons with XBP1 knockout show an impairment in the growth and extension of neurites which would be the normal response to BDNF (43). This impaired extension response might be mediated by an impairment in the differentiation of GABAergic interneurons normally induced by BDNF (44). A mutation in Caenorhabditis elegans which prevents XBP1 splicing causes an abnormality in AMPA glutamate receptor transport from the ER (45). Thus, a diminished XBP1 response in the neurons of bipolar disorder patients could cause impaired neurite extension in response to BDNF, impaired GABA interneuron differentiation, and impaired AMPA receptor trafficking.

The endoplasmic reticulum function of protein folding appears to be influenced by a protein with a peptidylprolyl isomerase (PPI) domain, encoded by the peptidylprolyl cis-trans isomerase E like (PPIEL) gene. This is found to be significantly hypomethylated in bipolar II disorder patients and this resulted in raised mRNA expression in lymphoblastoid cells. PPIEL mRNA is expressed throughout the brain, particularly within the substantia nigra and pituitary gland, possibly suggesting a role in dopaminergic neurons (46).

Vulnerability of neurons

The most established neuroimaging finding in bipolar disorder is that of increased numbers of subcortical hyperintensity (SCH) lesions in T2-weighted MRI (47). This increased SCH lesion frequency
in bipolar disorder is thought to be a consequence of increased vulnerability to cellular stress within
the neurons or oligodendrocytes. The neuroprotective effect of mood-stabilising drugs supports this
idea that bipolar disorder may be associated with some neuronal vulnerability or impaired resilience
(48). If this were the case, bipolar disorder would be expected to be associated with neuronal loss.
Indeed this is the case, with the anterior cingulate (49, 50, 51), prefrontal cortex (52, 53), hippocampal
corpus ammonius (CA2) (54), ventromedial thalamic nucleus (55), hypothalamic paraventricular
nucleus (56), and the dorsal raphe ventrolateral subnucleus all showing reduced neuronal density
or numbers in patients with bipolar disorder. It is of interest that primarily, the findings of reduced
neuronal numbers in these areas are accounted for by reductions in interneurons as opposed to
pyramidal neurons (49, 51, 54, 55). Furthermore, of all these areas found to have reduced neurons in
bipolar disorder, only the hypothalamic periventricular nucleus also shows gliosis (56). This neuronal
vulnerability in bipolar disorder patients appears to be related to altered neurotrophin signalling,
impaired calcium signalling, mitochondrial dysfunction, and endoplasmic reticulum (ER) stress
response dysfunction. These pathways are closely linked, with neurotrophin regulation vital for
correct calcium signalling, and mitochondria and ER important for regulating store-operated calcium
channels (SOCC) used in intracellular calcium signalling.

**Mechanism of clinical action of mood stabilisers**

The mechanism of action of mood stabilisers, particularly lithium and valproate, give useful indications
of the important intracellular pathways which affect bipolar disorder. It is known that both lithium
and valproate are neuroprotective, and that they act in this way by affecting inositol metabolism,
and thus neurogenesis, especially GABAergic neurogenesis (58), (59). The trophic factors BDNF, BAG1
and bcl-2, are important in this process of enhancing neurogenesis. Lithium most probably acts by
inhibiting inositol-monophosphatase (IMPase), thus depleting intracellular inositol (57). Both lithium
and valproate act to enlarge growth cones (60), and enhance adult neurogenesis (61, 62), particularly
of GABA neurones (62).

The mechanisms by which the mood stabilisers cause these neurogenesis effects include inositol
depletion (62), bcl-2 upregulation on the outer membrane of mitochondria (22), glycogen
synthase kinase 3b (GSK-3b) inhibition (63, 64), BDNF-ERK pathway enhancement, glutamate
receptor trafficking effects (65), upregulating the glucocorticoid receptor co-chaperone BAG-1
(66), glucocorticoid receptor functioning inhibition (67), glutathione S-transferase upregulation
(68), Notch signalling activation (69), and, in the case of valproate, histone deacetylase inhibition
(70). Furthermore, the glutamatergic agents lamotrigine, ketamine and riluzole, which are currently
showing some promise as mood-stabilising drugs, all appear to upregulate AMPA receptors, increasing
AMPA/NMDA stimulation, and thus may induce neuroproliferation through enhancement of BDNF and
other intracellular signalling cascades (71).

**Mood-stabilising neuron hypothesis**

The progression of bipolar disorder tends to be characterised by a shortening of the interval between
episodes and a higher vulnerability to stress. If progression leads to rapid cycling, the effectiveness of
lithium is reduced.

This tendency for the disease to progress is usually put down to a ‘kindling’ theory of repeated
external stressors which may precipitate symptoms requiring progressively lower stimulus levels to
trigger a response (72). However, a progressive degeneration of neurons with a mood-stabilising
role is an alternative explanation. This theory is intriguing as it could tie together much of the known
cellular pathology and neurobiology of bipolar disorder discussed above. The inhibitory GABAergic
interneurons, which are reported to be reduced in bipolar disorder patients, could fill this role.
Impaired ER stress response of bipolar disorder, as discussed above, may result in impairments of
differentiation of GABAergic neurons. Cortical inhibition was seen to be decreased in bipolar disorder
in a study using transcortical magnetic stimulation (73). In the hippocampal CA2 region, interneurons
(74) are found to be reduced and, in particular, the GABAergic marker GAD67 and transcription factors
needed for GABAergic interneurons like LHX2 and PAX5 are found to be reduced in the striatum oriens
of the CA2/3 region (75).

Neurons regulating the circadian rhythm, in the retino-hypothalamic pathway, have also been posited as ‘mood-stabilising’ neurons. Bipolar disorder patients have been reported to show disruptions in the melatonin response to light (76), and social rhythm therapy is effective in preventing relapses in bipolar disorder, by aiming to regularise the social rhythm of patients (77).

Concluding Remarks

It is now quite clear that, although abnormalities are readily detected at the neurotransmitter level in bipolar disorder, the more fundamental intracellular signalling pathologies responsible for these abnormalities must be understood in order to elucidate the neurobiology of the disorder fully. It seems that a diverse number of different genetic, epigenetic and environmental risk factors can have a detrimental effect on the function of key pathways, such as the ER stress response, mitochondrial function, Ca2+ channels, and GSK-3b, and that the ultimate effect of dysregulation of these pathways may be progressive damage to the neurons normally responsible for stabilising mood.

GP Comment

What have I learned from this paper?

Although, on the face of it, a very ‘technical’ article, this is a useful and comprehensive review of current understanding with regard to the neurobiological variations in neurotransmitter, intracellular messenger and organelle functioning associated with bipolar disease.

It provides a valuable knowledge base to add to the symptomatology, progression and current treatment of bipolar disorder which can underpin information sharing and collaborative work in frontline clinical practice with those who suffer from the disease. This article will also support the clinician to explain and understand the mechanisms by which medication can help.

In addition the article explores the potential relationship between these changes causing progressive damage to the neurons which normally stabilise mood and the observed progression of the disease as characterised by a shortening of the interval between episodes and higher vulnerability to stress, rather than the tendency for repeated external stressors to reduce the level of stimulus required to produce symptoms. It will be interesting to see the future potential of this debate to improve understanding and treatment of the disease.

Jane Leigh, GP.

References


fMRI comparison between bipolar I and bipolar II disorders

Melissa Ng  
School of Clinical Medicine, University of Cambridge  
Clare College, University of Cambridge

Abstract

Bipolar disorders are mood disorders characterised by manic (bipolar I disorder,) or hypomanic episodes and major depressive episodes (bipolar II disorder). These have been reworked into the model of “bipolar spectrum disorder”, where manic symptom load increases from unipolar depression to bipolar II to bipolar I. In this article we consider the fMRI findings for bipolar I, bipolar II and major depressive disorder (MDD) and conclude that bipolar disorder and MDD do not share the same pattern of neural disturbance. The distinction between bipolar I and bipolar II is less clear, as the data is still preliminary in nature, but the two disorders appear to share a similar pattern of brain activity. This fMRI data suggests that the bipolar spectrum model still requires refining, but provides a useful framework upon which to base future research into affective disorders.

Key words: bipolar disorder, mood disorders, bipolar spectrum, fMRI, neuroimaging

Introduction

Bipolar disorders are a group of affective disorders characterised by the occurrence of manic episodes in the lifetime of the patient. It is a serious condition that can cause significant distress, social and occupational impairment and suicidal tendencies. DSM-IV-TR divides bipolar disorders into subtypes including bipolar I disorder and bipolar II disorder. Bipolar I is defined by one or more manic or mixed episodes. Bipolar II is characterised by at least one hypomanic episode and one or more major depressive episodes. Bipolar disorder has been conceptualised as “bipolar spectrum disorder”, with increasing load of manic symptoms from depression to bipolar II to bipolar I (1,2). In this paper we review what functional neuroimaging has contributed to the understanding of the neural differences between these disorders.

Functional magnetic resonance imaging (fMRI) has become increasingly popular in psychiatry. Grossly simplified, it is an MRI technique that measures brain activity by detecting changes in magnetic properties which accompany changes in cerebral blood flow. It uses the principle that changes in blood flow to an area are related to the neuronal activity of that area. The main difference between functional and structural studies is that fMRI can measure changes in brain activity between a control state and an experimental psychological state. The control measurements are subtracted to identify areas sensitive to the processes involved. fMRI is therefore able to identify state and trait disturbances by comparing across mood states and examining at-risk individuals.

The current model of the neural network responsible for emotional processing involves early processing of the emotional stimulus by a limbic-subcortical network, which allocates attention and processes sensory information, followed by regulation of the emotional response by a cortical network, which reappraises the stimulus and inhibits irrelevant information (3). It is thought that disturbances in this network give rise to the abnormal processing seen in affective disorders.

The limbic system

Studies and meta-analyses have consistently shown that in bipolar disorder, the limbic and subcortical structures, specifically the amygdala and parahippocampal gyrus, are overactive (4-7), particularly on the left (5). Although this finding has been widely replicated, some studies have either failed to show hyper-responsiveness of the limbic structures (8-11) or found decreased responsiveness (12,13). The amygdala has been found to be overactive in mixed bipolar I and bipolar II groups in elevation (14)
and euthymia (15) and in bipolar II depression (16). However, Ladouceur et al. (17) found an increase in amygdala activity in bipolar I but not in bipolar disorder not otherwise specified youth, suggesting a different neural basis.

Limbic hyperactivity, especially in the amygdala, is also seen in MDD (18). Lawrence et al. (19), comparing bipolar disorder and MDD, found greater limbic activation in bipolar disorder, which is supported by meta-analysis (6).

The striatum and cortico-basal ganglia network

The striatum and cortico-basal ganglia network has generally been found to be overactive in bipolar disorder (20). Meta-analysis revealed increased activation of the striatum and globus pallidus in response to emotional tasks and decreased activation in response to cognitive tasks (4). Individual studies variably showed increased activity in the striatum (21,22), global pallidus (21) and thalamus (22) in mania. Hyperactivity of these areas has also been found in bipolar I depression (22,23). Studies showed that striatal activity was increased in mixed bipolar I/bipolar II populations (14,23,24) and in bipolar II depression, correlating with depression severity in the latter (25). Increased activation in the left thalamus was also found in bipolar II depression (25).

Striatal underactivity is well described in MDD (20), although overactivity has also been reported (19). Meta-analysis showed striatal hypo-responsiveness, specifically in the left caudate and right putamen (6).

The anterior cingulate cortex (ACC)

A number of studies have suggested that subgenual ACC activity in bipolar disorder depression is characterized by decreased activity on the left and increased activity on the right (3,27,28) and vice versa in mania (29). Other studies have shown a state-related decrease in dorsal ACC activity bilaterally (14,30). However, increased ACC activity has also been reported (28). Meta-analysis revealed decreased left dorsal ACC activity to fearful faces and decreased right dorsal ACC activity to happy faces (6). Increased right dorsal ACC activity has been shown in bipolar II depression (16).

Subgenual ACC activity that was decreased on the left and increased on the right was also seen in MDD (3). Hyperactivity in the right subgenual ACC, also shown on meta-analysis, was particularly increased during acute depressive episodes and normalised with treatment (31). Meta-analysis suggests that the right-sided hyperactivity was more prominent in bipolar disorder, but left-sided pregenual ACC activity was more prominent in MDD (6). One study directly compared MDD and bipolar disorder depression in women and showed increased dorsal ACC activity in MDD (32).

Other cortical areas

Decreased activity in the inferior frontal gyrus, specifically the ventrolateral prefrontal cortex (VLPFC) and part of the orbitofrontal cortex (OFC), has been demonstrated consistently in bipolar disorder (4-7). This was more marked on the right (5) and has been shown in bipolar depression (9), mania (33) and euthymia (34). Meta-analysis also shows decreased activity in the lingual gyrus (4,6). Disturbances in other cortical areas have been implicated, such as overactivity in the ventromedial prefrontal cortex (VMPFC) in mania (33) and in the dorsomedial prefrontal cortex (DMPFC) in euthymia (15), but these changes were not robustly revealed on meta-analysis (4). Studies examining dorsolateral prefrontal cortex (DLPFC) activity have produced inconsistent findings (4,5). Frontal hypo-responsiveness, especially in the ventral areas, has been shown in mixed bipolar I/bipolar II depression (23) and bipolar II depression (35), while increased OFC activity has also been demonstrated in bipolar II depression (16).

In contrast with bipolar disorder, VLPFC activity may be increased in MDD (36), although the two disorders appear to have increased VMPFC and DMPFC activity in common (37). DLPFC activity also
seems to be reduced in MDD (3), though these prefrontal disturbances receive limited support from meta-analysis (6).

Conclusion

To summarise the current findings, limbic overactivity has been well demonstrated in both bipolar disorder and MDD, and it is also a possible finding in bipolar II. Striatal activity is also increased in bipolar disorder and possibly bipolar II, but it has been shown consistently to be decreased in MDD. Data examining cortical areas are more preliminary in nature, although at present it seems that the subgenual ACC is underactive on the left and overactive on the right in both bipolar disorder and MDD. VLPFC is thought to be underactive in bipolar disorder but potentially overactive in MDD, while activity in the medial PFC appears to be overactive in both bipolar disorder and MDD. Neuroimaging data in bipolar II is limited, but appears to follow a similar pattern to bipolar I. On the other hand, while MDD shares some common features with bipolar disorder in terms of regional disturbances, there are also some well-documented differences in activity.

There are a number of problems which arise when interpreting these findings. First, it may be premature to form conclusions when there are still many disparities in the data, which is especially preliminary when it comes to BD-II. Second, it is important to consider the limitations of functional neuroimaging. When interpreting fMRI data, we assume that emotional processing can be meaningfully mapped onto brain structures, that it can be manipulated in isolation, that the neural basis can be localised, that the patient groups are controlled for all other factors apart from the diagnosis, and that the same psychological process can be compared across all groups. In view of these assumptions, it is important to not to interpret neuroimaging data in isolation. It would also be instructive to consider the connectivity between structures and how changes in neural activity translate into phenotypes.

Finally, and perhaps most important, the bipolar spectrum model still requires further clarification and validation in terms of the different gradations. The current conceptualisation of the spectrum model is that it describes overlapping clinical manifestations, which are not necessarily products of the same genetic or neural changes. Some studies describe a diagnostic change from unipolar to bipolar depression over time (1), highlighting either the difficulties in nosology and diagnosis or the possibility of a physiological progression from one disorder to the other. The latter would have profound implications for research into impeding the neural changes from unipolar to bipolar depression. Regardless of the implications, it is clear that the bipolar spectrum model needs refining, but it has proven useful as a framework for classifying mood disorders.

GP Comment

What have I learned from this paper?

This article explains that a number of functional neuroimaging changes have been demonstrated in bipolar affective disorder which seem to distinguish it from unipolar depression. Some of these differences raise fundamental questions about the classification of mood disorders. Additional information from functional neuroimaging may help to improve our understanding of the spectrum of bipolar disorder and its relationship to unipolar depression.

Dr Jenny Hopwood, GP Trainee.

References

3. Savitz J, Drevets WC. Bipolar and major depressive disorder: neuroimaging the developmental-


Part 3. Pharmacology of the Bipolar Disorder

Neuroprotective and Neurotrophic Effects of Lithium on Bipolar Disorder

Cristian Vargas 1-2, Eduard Vieta 2, Carlos López-Jaramillo 1
1Department of Psychiatry, School of Medicine, University of Antioquia, Medellín, Colombia
2Bipolar Disorders Program, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain.

Abstract

Despite the development of other medications with mood-stabilising properties, such as atypical antipsychotics and antiepileptic drugs, lithium still remains the first-line treatment for bipolar disorder (BPD), and there is increasing evidence for the hypothesis of its neuroprotective and neurotrophic effects as key factors for its clinical effects. Methods: A literature research was conducted using the PubMed database without chronological or language limits to August 2012. The following MESH terms were used: Bipolar Disorder and Lithium combined with: Neuroprotective, Neurotrophic, Neurocognitive effects, GSK-3b, bcl-2, BDNF, hippocampal. Original studies and reviews were selected (in vitro, in vivo and clinical studies). Results: We found evidence in basic studies of neuroprotective and neurotrophic molecular pathways like GSK-3b, Bcl-2, BDNF, glutamate excitotoxicity, AP-1, mitochondrial dysfunction and neurosteroids. Several clinical studies in BPD show increased brain areas, reduced neuronal loss, reduced risk of dementia and one study showed improvement in neurocognitive function (verbal memory) associated with increased hippocampal size in lithium-treated groups versus controls, and other medications. The main areas were hippocampus (HC), anterior cingulate and prefrontal cortex (PFC). Functional Studies with N-Acetyl-aspartate (NAA) also support this hypothesis. Conclusions: Despite basic, structural and functional evidence that shows neurotrophic and neuroprotective effect of lithium, longitudinal studies are needed to clarify the clinical relevance of these findings and their correlation with cognitive performance, which seems to be directly related with functional outcome.

Key words: bipolar disorder, lithium, neuroprotective, neurotrophic, neurocognitive effects, GSK-3b, bcl-2, BDNF, hippocampal.

Introduction

Despite the development of other medications with mood-stabilising properties, such as atypical antipsychotics and antiepileptic drugs, lithium still remains among the first-line treatments for bipolar disorder (BPD) (1;2). Studies continue to discuss mechanisms of action that go beyond the stabilising function; neuroprotective and neurotrophic effects remain targets of investigation (3-5). The results have sometimes been contradictory. The information is becoming more abundant and it is therefore appropriate to undertake an updated and critical review of the current literature, which allows basic studies to be correlated with clinical research.

In order to know whether or not lithium has the following features, the studies must show that its use enhances the growth of a subpopulation of neurons and protects against some kind of injury (oxidative stress, glutamate excitotoxicity, etc.) or the pathological process of disease, in this case the BPD (6;7). According to the available evidence it is difficult to separate the neuroprotective effects from the neurotrophic, or to know the importance of these findings in the BPD (8). Furthermore, the issue of progressive impairment and whether there is correlation between anatomical changes and cognitive deficits remains unclear (6). From this point of view there are also several reasons why a systematic review of the literature, of the effects of lithium on the brain and the clinical implications, is currently needed.
(i) The neuroprotective pathways are common in several treatments for BPD (6;8-10).
(ii) There is a decrease in size of brain areas of bipolar patients (11;12).
(iii) Lithium reverses anatomical changes, reduces apoptosis, favours neurogenesis and synaptogenesis (13-15).
(iv) There is cognitive impairment in BPD, which some authors relate to severity and duration of illness (16;17).
(v) Some studies show that lithium reduces the risk of dementia in BPD patients (18-20).
(vi) Lithium has neuroprotective effects in other neurological diseases (21-23).
(vii) Some results show improvement in memory deficit associated with increased hippocampal volume with lithium (24).

This article will review these areas, based on the main neuroprotective mechanisms and the evidence of in vitro, in vivo and in clinical studies. We shall discuss the role of lithium in neurogenesis and the relationship between cognitive deficits and structural changes as potential therapeutic targets for neuroprotection.

Methods

A literature search was conducted using the PubMed database without language or chronological limits through to August 2012. The following MESH terms were used: bipolar disorder and lithium combined with: neuroprotective, neurotrophic, neurocognitive effects, GSK-3b, bcl-2, BDNF, hippocampal. Nine MESH terms combinations were made, with 585 results. Duplicate papers were excluded and the searches were supplemented by cross-referencing of included studies and review articles. The papers were selected by assessing the abstract according to the following inclusion criteria: original studies and reviews about the hypothesis of the neuroprotective and neurotrophic effects of lithium on BPD. Papers on the effects of lithium in humans or animals were included. Many animal in vitro studies were found. The papers chosen discussed known pharmacological pathways of lithium. One Japanese review was not included by language limitation.

Results

Neuroprotective pathways

Lithium has a mechanism of action that goes beyond neurotransmitters or traditional receptors; it has effects on a series of second messengers (25), signaling pathways and transcription factors (8;25;26). The following is a summary of the most important pathways related to neuroprotection and neurotropism.

Inhibition of GSK3

GSK3 is a serine/ threonine kinase (27), which inhibits a number of antiapoptotic factors such as CREB (cAMP-response element binding protein), Beta Catein and HSF-1 (heat shock factor) (28). Lithium inhibits GSK-3b by phosphorylation of serine residues releases; the control of these factors promotes survival and neuroprotection (29). The effect of GSK3b inhibition has been studied in animal models of depression and mania. It is believed that inhibition of this kinase is associated not only with a stabilising effect but also with the neuroprotective effects (27).

Increased BCL-2

Chronic treatment with lithium can increase the cytoprotective protein BCL-2 in cell cultures of human neurons and in mice brains (30), specifically in the striatum, hippocampus (HC) and prefrontal cortex (PFC), even at subtherapeutic levels (31). The effect is like a “protector” in apoptotic pathways; the mechanisms include regulation of calcium homeostasis and decreasing free radical production, among others (32). In an animal model of ischemia lithium prevented memory impairment associated with low concentrations of P-53 (pro-apoptotic) and Bcl-2 increased in CA1 neurons of HC (33).
Protection against glutamate

Lithium also protects against glutamate, which is a powerful excitotoxin (33-35). Chronic exposure of lithium protects neuron cultures of HC, cerebral cortex and cerebellum against glutamate-induced toxicity (7). This effect cannot be identified in short treatments and is not explained by the down-regulation of receptors (36). Possible mechanisms include the decreased phosphorylation of tyrosine residues of the subunit NR2B of the NMDA receptor, thereby inhibiting the calcium influx required to activate the apoptotic pathways (34).

Brain-derived neurotrophic factor and other mechanisms

One of the pathways most involved in this topic is the Brain-derived neurotrophic factor (BDNF) (37). Lithium induces BDNF which, at the same time, activates the receptor tyrosine kinase B (TrkB) and the signaling pathways of phosphatidylinositol 3 kinase/Akt (PI3K/Akt) and the MEK/ERK (extracellular signal-related kinase) (38). In the last pathway, through the RSK kinase (ribosomal S6 kinase) CREB is activated, which is involved in learning and plasticity (38;39) and regulates the transcription of genes such as BDNF and nerve growth factor (38). These pathways have been studied in mouse cortical neurons and are associated with protection against glutamate (33-35). It is also proposed that lithium, through an inhibition of GSK-3b, is responsible for activating the promoter IV of BDNF (40).

A clinical study with patients in mania showed an increase in BDNF at 28 days of treatment with lithium. Others have found an inverse relationship between BDNF and lithium (41). It has been suggested that lithium responders show higher levels of BDNF (42), for example up to 87% after treatment of a manic episode (43). The responder patients with high BDNF levels showed better neuropsychological performance but more studies are needed to clarify confusing factors.

Lithium also has direct action on the transcription factors (44). There is a protein complex activator known as AP-1, which includes the proteins FOS and JUN, and joins the domain of DNA to regulate the expression of neurotrophins, proteins, membrane receptors, transcription factors, and enzymes involved in the process of neurotransmitters in PFC and HC (31;45). Lithium changes the binding process between AP-1 complex and DNA, thus modulating the transcription of several structural and functional molecules (44).

Lithium has been described as an antioxidant, with increased gene expression of NADH-ubiquinone reductase, which is known as a multi-enzyme complex of the respiratory chain (46;47). Moreover it increases hippocampal neurotrophin-3 (48) and active neurosteroids of PFC in animal models (49).

In vitro – in vivo studies

Based on the research in vitro and in vivo (50-53), neuroprotective mechanisms of lithium have been proposed. Clinical studies with lithium show structural (postmortem and MRI) and functional changes (levels of N-Acetyl-aspartate) (54;55) and many authors have extrapolated these results to molecular findings to defend the neuroprotective hypothesis. However, a direct correlation is unavailable and more studies are needed to clarify this debate (8;56).

Lithium has been studied in human and rodents cell lines as cortical, hippocampal and cerebellar neurons (9), PC12 and neuroblastoma cells (57). It has been shown to prevent cellular death to stressors such as high doses of anticonvulsants (58), quinolinic acid (52;53;58), potassium deprivation (26;53), beta-bungarotoxin (59), glutamate (34-36) and beta-amyloid peptide.

Cross sectional studies

Several studies have attempted to correlate the biochemical effects of lithium with clinical/cognitive findings. There are results in BPD patients using structural and functional methods. Spectroscopy studies show that lithium patients, in comparison with controls, have increased levels of cortical
N-acetyl-aspartate (NAA) (55), a marker of neuronal viability and function which is not found in glial cells (60). This increase has not been reported in patients treated with valproic acid (55). A recent study found in the prefrontal cortex of patients (without lithium) lower NAA levels than in the lithium group (p<0.001) or controls (p<0.05), with a negative correlation between levels and duration of illness (61). Another study reported a positive correlation between cortical NAA and brain lithium levels (62).

An increasing volume of literature has related structural findings with lithium treatment, with an increase in cerebral volumes through 4 weeks of 3% (24cm³) (54) and preventing loss of anterior cingulate volume in the lithium group compared with other medications (63). The increase of gray matter in the right anterior cingulate has been reproduced in other studies (64;65).

Lithium has also been associated with an increase of bilateral hippocampal volume, specifically the hippocampal head, in comparison to valproic acid and lamotrigine (24). The head of HC has the largest amount of CA1 projections to the medial PFC, which shows the role of HC in the fronto-limbic circuit and emotional regulation (66). A higher volume of the hippocampus compared with controls and relatives was recently demonstrated; it was suggested that thickening produced by lithium could be a protective factor against recurrence because this finding was also found in twins (67). An increase of right HC size in adolescents treated with lithium, compared with the controls and valproic acid (68) has also been reported, as has increased hippocampal nerve growth factor in treatment of models of mania (69). Patients without lithium had a lower hippocampal volume than controls (p<0.005) but the difference was not significant in the lithium group (p<0.1) (70).

Other regions of the hippocampusamygdalainsula complex, as well as the postcentral gyrus have also shown changes with lithium, related to the treatment duration (71). A meta-analysis with meta-regression techniques correlated lithium with overall increase of gray matter (12) and a meta-analysis showed that the increase was specifically in the HC and amygdala (11). The last meta-analysis found significantly smaller bilateral hippocampal volumes in patients who were not treated with lithium in comparison to healthy controls or patients treated with lithium (72).

Although it is difficult to talk about neurogenesis in BPD because it is a relatively new concept, over the past 15 years several studies have shown there is neurogenesis in the hippocampus (dentate gyrus) of humans and mammals (73;74) and in the neocortex of primates (75); according to some results lithium seems to play a possible role in this area. Bcl-2 protein induced by lithium has been associated with regeneration of axons in mammalian CNS (30;76) and with the increase of thymidine analogs of the cell division in the dentate gyrus within 2 to 3 weeks of therapy (31). Lithium also increased the synaptogenesis of hippocampal neurons, even four hours after administration, and cellular differentiation (14;15).

Longitudinal Clinical Studies

Three longitudinal studies with positive outcomes (24;77;78) showed an increase of hippocampal volume with lithium of 4% to 5% in a follow up from 2 to 4 years and one survey with a small sample size showed improved verbal memory cognitive performance with the California Verbal Learning Test (CVLT), which was not explained by improvement of affective symptoms (24). Four weeks of treatment have also been associated with a significant increase in prefrontal gray matter in responder patients to lithium (78) and according to some reports the effect has a peak at week 10 to 12 and persists after 4 months when it is compared with valproic acid (77). One study showed an increase in prefrontal gray matter volume in healthy volunteers following lithium administration with therapeutic doses during 4 weeks (79), but others had negative results (80).

Neuroprotective effects in several pathologies

A report from the Research Committee of The American Neuropsychiatric Association (21), which evaluated the preclinical and clinical evidence for neuroprotective therapies in neurodegenerative disorders, concluded that the most promising research (low and moderate preclinical evidence) included lithium, in diseases such as tauopathies, frontotemporal degeneration (81), Alzheimer-type
dementia (lithium plus paroxetine, lithium plus valproic acid) (21;82) and amyotrophic lateral sclerosis (83;84).

The effects on dementia have been described from the inhibition of GSK-3b, which decreases the production of beta amyloid from the precursor protein of amyloid (27), and the aggregation and phosphorylation of tau protein (86).

Studies with lithium have shown protection against ethanol toxicity (87), anti-inflammatory effects and an increased proliferation and survival of stem cells in models of ischemia and neonatal hypoxia (45). Some authors using models of cerebral ischemia in mice have linked the neuroprotective effect with the GSK-3b pathway (88). With respect to neurocognition in other disorders, several studies have shown a positive effect in HIV-associated cognitive deficit (89) and in the prevention of neuropsychological sequelae following cranial irradiation (90).

Neurocognition and lithium as a neuroprotective agent

Many studies have shown neurocognitive impairment in BPD including the euthymic phases (85;86). The magnitude of cognitive impairment averages between 0.2 and 1 standard deviation (87;88) and appears to be greater for executive function, attention and processing speed (89;90), although a meta-analysis also demonstrated impairment of verbal memory (91). The cognitive deficits in verbal memory, executive function, ideational fluency, attention and visual/motor processing are major variables related to functional performance (6;92;93). Despite the evidence of cognitive changes in BPD, to conclude that there is progressive impairment may be too preliminary because we need more longitudinal studies with good control of confounding variables (6).

The understanding of the relationship between lithium and neurocognitive effects has changed lately; several years ago the lithium was recognized as an agent causing cognitive impairment (94) but now research has shown a neutral effect (85) and some suggest a positive effect that could be correlated with the described neuroprotective mechanisms (24;66). There is even evidence that lithium significantly reduces the risk of dementia in patients with BPD (18-20).

Discussion

Lithium, within its mechanisms of action, acts on pathways associated with neuroprotection and neurotropism (6;7); there is evidence that lithium favors neuronal survival against multiple exotoxic factors and stimulates in-vitro and in-vivo synaptogenesis (50-53). Few studies can correlate these molecular findings with clinical outcomes but the available literature shows that lithium increases markers of neuronal function such as N-acetyl-aspartate (55;60), prevents the reduction of gray matter when compared with other mood stabilizers and increases the volume in brain areas, including the anterior cingulate, PFC and HC (63;78;95;96). A systemic review attempting to search for the neuroprotective and neurotoxic effect of lithium, found discrepancy between basic and clinical research, with level of evidence C “unclear and conflicting” for this topic. Few clinical studies were identified and some showed indirect evidence of neuroprotective effect (97).

There are structural and neuropsychological alterations in BPD (11;12;16;92;98), although it is unclear whether the cognitive impairment is static or progressive (6;8). Even though lithium is associated with an increase in brain volumes (63;64;67;71), further longitudinal studies are necessary to reproduce these findings and to demonstrate correlation with the neuropsychological and psychopathological features of patients. Such studies could resolve the doubts about the clinical relevance of the neuroprotective and neurotrophic effects. Only one study showed improvement in verbal memory with lithium related to the increased size of HC (24) and several authors demonstrated lower risks of dementia in older adults with BPD treated with lithium when compared with other medications (18;20). Many of the studies appear to show that the hippocampus is a region of strong neurogenesis (99). This brain area has strong connections with the PFC and an important role in verbal memory, which is altered in BPD according to several authors (100;101). Studies that seek to continue the
investigation into this hypothesis should ideally be longitudinal and must have as a primary goal the correlation between neuroanatomical changes, neurocognitive performance and functionality.

The findings of the neuroprotective and neurotrophic effects of lithium on other neurological disorders appear promising (21). Current research not only views lithium as being a mood stabilizer but also as a possible neuroprotective agent (29;36). Studies appear to indicate a strong association between cognitive deficit and functionality (16;92;98). A therapy that protects against the development of the cognitive deficits could be of great value in the treatment of psychiatric patients. On theoretical grounds, lithium has mechanisms that might play such a role but further studies are necessary since the findings are partial and preliminary.

Conclusion

Despite in-vitro and in-vivo studies that show neurotrophic and neuroprotective effects of lithium, structural and functional evidence for bipolar patients is indirect. Beyond the effects related to the prevention of relapses, longitudinal studies are needed to clarify the clinical relevance of these findings and their correlation with cognitive performance, which seems to be directly related with the functionality of the patients.

References

4. Manji HK, Moore GJ, Chen G. Lithium at 50: have the neuroprotective effects of this unique cation been overlooked? Biol Psychiatry 1999 Oct 1;46 (7):929-40.
59. Tseng WP, Lin-Shiau SY. Long-term lithium treatment prevents neurotoxic effects of beta-


62. Forester BP, Finn CT, Berlow YA, Wardrop M, Renshaw PF, Moore CM. Brain lithium, N-acetly aspartate and myo-inositol levels in older adults with bipolar disorder treated with lithium: a lithium-7 and proton magnetic resonance spectroscopy study. Bipolar Disord 2008 Sep;10 (6):691-700.


The Place of Antidepressant Medication in the treatment of Bipolar Affective Disorder

Gursharan Kashyap1, Clare Thakker2
1 South Essex University Partnership NHS Foundation Trust
2 School of Clinical Medicine (University of Cambridge-Clare College)

Abstract

In patients with bipolar disorder, the use of antidepressants without mood stabilisers has been thought to have the potential to induce mania, mixed affective states and rapid cycling bipolar disorder. Since both mixed states and rapid cycling are associated with an increased risk of suicide, the use of antidepressants in the treatment of bipolar disorder has been questioned. In this paper the evidence and the guidelines for the use of antidepressants in the management of depressive episodes in bipolar disorder are reviewed. The evidence suggests that the risk of mania is not significant with the use of certain antidepressants. However, there is emerging evidence that antidepressants have limited effectiveness in treating bipolar depression. We suggest antidepressants should not be the first choice of treatment for depressive episodes in bipolar disorder and if used should always be given in combination with mood stabilisers. Other compounds such as quetiapine and lamotrigine appear to be of more use in the treatment of bipolar depression.

Key words: antidepressants, bipolar disorder, mood stabilisers, quetiapine, lamotrigine.

Concerns have been raised about the consequences of using antidepressants to treat patients with bipolar disorder. Antidepressants have the potential to induce mania, mixed affective states and rapid cycling bipolar disorder in patients with bipolar disorder who are not concomitantly treated with mood stabilisers. Since both mixed states and rapid cycling bipolar disorder are related to an increased risk of suicide, this use of antidepressants in the treatment of bipolar has been challenged (1). Such theories also suggest potential hazards in the treatment unipolar depression with bipolar disorder has not been excluded. Moreover, Bipolar III disorder has been described as mania induced by the use of antidepressants in the treatment of a patient who had previously been considered to have unipolar depression (2). An important question is, therefore, whether antidepressants are effective in the treatment of bipolar depression and whether there is an alternative agent, such as a mood stabiliser, with greater efficacy. Second, it is important to consider whether antidepressants can be used for short-term treatment in bipolar depression without the induction of mania.

Several studies have considered the efficacy of antidepressants in the treatment of bipolar disorder. In 2004 Gijsman et al. (3) carried out a systematic review of randomised controlled trials (RCTs) on the use of antidepressants in bipolar depression; they concluded that antidepressants were more effective than placebo in the treatment of bipolar depression. In particular, Tohen et al. (4) found the olanzapine and fluoxetine combination (OFC) to be effective and this was licensed by the FDA for treatment of bipolar depression in America in 2003 (5). However, other studies have found that, when compared to the use of a mood stabiliser or an atypical antipsychotic, antidepressants have no additional benefit in bipolar disorder. In the STEP-BD study (Systematic Treatment Enhancement Program for Bipolar Disorder) (6) all participants commenced the study on an optimum dose of a mood stabiliser, i.e. lithium, valproate or carbamazepine, and were then randomised into groups receiving paroxetine, bupropion or placebo. Results demonstrated that the addition of an antidepressant to a mood stabiliser did not offer any additional benefit when compared to a mood stabiliser alone. The authors therefore suggested that a mood stabiliser should be the first-line treatment for acute bipolar depression in the outpatient setting. In the EMBOLDEN 2 study (7) acutely depressed bipolar patients were treated with paroxetine, quetiapine or placebo. Based on the Montgomery–Åsberg Depression Rating Scale (MADRS) score there was a significant improvement in the quetiapine-treated group compared to the placebo-treated group but not in the paroxetine-treated group, suggesting that...
atypical antipsychotics may be of more benefit than antidepressants.

More recently a meta-analysis by Sidor & McQueen (8), covering 2373 patients (including those from the STEP-BD and EMBOLDEN 2 studies), concluded that antidepressants did not provide statistically significant benefits when compared to placebo or other current standard treatments for bipolar depression. This conclusion is further supported by a meta-analysis of 68 studies by Amit & Weizman (9) which concluded that the majority of well-designed studies did not find a significant benefit from using any class of antidepressant in bipolar disorder of any subtype.

When considering whether the use of antidepressants in bipolar disorder increases the occurrence of a switch to mania/hypomania, the evidence suggests that there is no significantly increased risk with at least some types of antidepressants, such as the selective serotonin re-uptake inhibitors (SSRIs) or bupropion. Goldberg et al. (10) found that bipolar patients who have an earlier onset of illness and have a strong family history of bipolar illness are at a higher risk of developing antidepressant-induced manias. However, Gijsman et al. (3) found that antidepressants were not associated with an increased rate of mania when compared to placebo. Furthermore, the results of the STEP-BD study suggested that there is no increase in hypomanic or manic switch when paroxetine or bupropion are added to a mood stabilizer during a depressive phase (6). Sidor & McQueen (8) came to a similar conclusion in their meta-analysis, as did Amit & Weizman (9), who found that there was no significant increase in the rate of manic/hypomanic switch when patients were treated with antidepressants, especially if they were already taking a mood stabilizer. Taking these two aspects together, it appears that, although antidepressants do not increase the risk of a switch to mania/hypomania their clinical efficacy is doubtful. This is reflected in the available guidelines for the treatment of bipolar disorder, where agents other than antidepressants are generally preferred for the treatment of depression in bipolar disorder. The following recommendations for the treatment of bipolar depression are based on tables recently published in the Maudsley Guidelines (11), from which the information has been extracted.

1. Quetiapine should be the drug of choice in bipolar depression, with limited evidence for the use of valproate and lithium.

2. If antidepressants are needed, SSRIs are the preferred option. Alternatively, bupropion has been used in previous trials and is not associated with a switch to mania. Venlafaxine can also be used though it is associated with a higher risk of a switch to mania. Monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants should be avoided. None of the antidepressants is recommended for prophylactic use against depression.

3. Antidepressants as monotherapy should be avoided, especially in bipolar I disorder, due to inefficacy and potential risk of a switch to mania.

4. The combination of olanzapine and fluoxetine is more effective than either individually (or lamotrigine) and also offers a prophylactic effect.

5. Lamotrigine has been shown to be effective in acute bipolar depressive episodes and has a modest protective effect against future depressive episodes. Titration of the dose is necessary. However, it can be used to augment treatment in patients who are already on lithium or as an alternative to lithium in pregnancy.

The BAP (British Association for Psychopharmacology) guidelines (12) for managing acute depression in bipolar disorder divides its advice on the basis of whether patients are already on long-term therapy. In patients not already on long-term therapy, the guidelines suggest lamotrigine (with necessary slow titration of the dose to decrease the risk of skin rash) or quetiapine (if a rapid effect is required) as initial treatment, rather than antidepressants. According to the same guidelines, if a patient has a history of mania, antidepressants should only be used in combination with a mood stabiliser. An antipsychotic should be considered if psychotic symptoms are present. BAP also recommends electro-convulsive therapy (ECT) in acutely depressed patients with bipolar disorder if they present with a high risk of suicide, psychosis or when there is a risk to life due to severe bodily
and functional inhibition. ECT is also recommended for severe acute depression in pregnant women if they are not already on long-term treatment for bipolar disorder. In cases where symptoms are less severe, lithium or valproate may be considered. Psychological therapies such as IPT, CBT and family-focused therapies may help to reduce the duration of the acute episode.

For the treatment of an acute depressive episode in patients already on long-term therapy for bipolar disorder, the BAP guidelines (12) recommend optimisation of current medications, as well as ensuring that lithium levels are within the therapeutic range. Consideration should also be given to the prevention of a manic relapse with a mood stabiliser or antipsychotic. If the depression does not respond to treatment, augmentation or a change of treatment should be considered.

When considering the choice of antidepressant, the BAP guidelines (12) indicate that tricyclics and drugs such as venlafaxine and duloxetine carry a higher risk of manic switch than SSRIs. If there is a history of antidepressant-induced mood destabilisation then quetiapine or lamotrigine should be considered. Since the duration of acute depression in bipolar disorder is usually shorter than in unipolar disorder, antidepressants can often be discontinued after 12 weeks.

NICE Guidelines (13) and the Canadian network for mood and anxiety treatments (CANMAT) guidelines (14) have retained the use of an antidepressant as one of the options for treatment, stressing the concurrent use of a mood stabiliser.

In 2010, the Psychopharmacology Algorithm Project at Harvard South Shore program (PAP HSS) (15) bipolar depression algorithm presented a slightly different route for management but still did not favour antidepressants as a first-line treatment. It was suggested that the first action following diagnosis should be to assess whether ECT is required. If ECT is not necessary then a pharmacological route is suggested. If the patient has psychotic symptoms, an antipsychotic should be considered. The next level is either to initiate or optimise treatment with mood stabilisers (lithium is the preferred agent in these guidelines). It is noted that patients with rapid cycling mood disorder may need a combination of mood stabilisers. If this is ineffective, quetiapine or lamotrigine should then be considered. Only if all three fail and the risk of mood destabilisation is low, should the use of antidepressants be considered. PAP HSS acknowledged the possible risk of antidepressants causing manic switch and long-term mood destabilisation. The guidelines suggested that bupropion is associated with the lowest risk followed by sertraline, while venlafaxine is associated with the highest risk.

Finally, the World Federation of Societies of Biological Psychiatry (WFSBP) in its updated guidelines in 2010 (16) stated that quetiapine at 300 mg per day is an effective treatment for bipolar I and II depression but that the olanzapine/fluoxetine combination (OFC) is also effective. Fluoxetine, and other antidepressants to a lesser degree, were advised when used in combination with either a mood stabiliser or lamotrigine or as an addition to lithium in patients with a poor response.

Taken together, the various guidelines include antidepressants in their recommendations for the treatment of acute depression in bipolar disorder but generally this is not as a first-line treatment. Importantly, NICE guidelines suggest that the emergence of mixed agitated states, mood cycling and treatment-emergent affective switch due to antidepressants in bipolar disorder demands extreme caution in the use of antidepressants (17). Moreover, the American Psychiatric Association (APA) practice guidelines have stated that antidepressants in bipolar disorder carry the risk of mood destabilization and affective switching and as such they are contraindicated, especially in rapid cycling bipolar patients (18).

However, Grunze 2008 (19) suggests that much of the evidence surrounding the effects (both favourable and unfavourable) of antidepressants comes from small, poorly-designed studies and that, because of this, the risk of switch may have been overestimated. This is a view supported by the meta-analyses and systematic reviews cited earlier in this article which, in general, found no increased risk of switch with antidepressants. However, as these studies also call into question the efficacy of antidepressants in bipolar disorder, the guidelines on antidepressants may have to be reconsidered, not because of adverse effects but because of a lack of treatment benefit.
Some fundamental questions have arisen with regard to the management of bipolar depression. The first and most important question is whether antidepressants have any role to play in the treatment of bipolar depression. Second, if antidepressants do have a role, in what circumstances should they be used? Third, what are the risks of using antidepressants, especially in terms of affective switch to hypomania/mania and how might these risks be avoided or minimised?

Taken together, recent evidence does not favour the use of antidepressants in bipolar depression but rather encourages the use of mood stabilisers or antipsychotics as first-line treatment for an acute depressive episode. The majority of guidelines have suggested that the role of antidepressants is as an adjunct in the treatment of bipolar depression. There is conflicting evidence on whether antidepressants increase the rate of a switch to mania in bipolar disorder, with more recent evidence suggesting that they do not. However, when antidepressants are used, the concomitant use of mood stabilisers is advocated. As bipolar disorder is a remitting and relapsing disorder (with a high recurrence rate of more than 90%) (20), when an antidepressant is prescribed it is of the utmost importance to consider the response to antidepressants in any previous depressive episodes. In particular, it is important to identify whether there has been the emergence of manic or hypomanic symptoms in the past, in order to minimise the risks, on an individual basis, of using antidepressants.

**GP Comment**

**What have I learned from this paper?**

I found this paper extremely helpful because it emphasised to me, as a future GP, the importance of managing patients with depression as part of bipolar disorder differently from those patients with unipolar depression. We are much less familiar with the management of this group and it was interesting to find that first-line management is with quetiapine. This paper will change my practice in prescribing for patients with bipolar disorder affected by depression and reminded me of the importance of taking a careful history from patients with depression to elicit any previous manic or hypomanic episodes, to make sure they receive an accurate diagnosis and safe, effective treatment.

Abigail Davis, GP Trainee.

This article questions the evidence that antidepressants lead to a switch to mania or mixed state when used in bipolar disorder but argues that they should not be used alone due to lack of efficacy and potential risk. Guidelines advise anti-depressants as an adjunct to treatment, but advise mood stabilisers or antipsychotics as first-line treatment for an acute depressive episode. If an antidepressant is prescribed it is vital to consider the response to antidepressants in any previous depressive episodes and the previous emergence of any manic or hypomanic symptoms.

Dr J Hopwood, GP Trainee

**References**

5. U.S Department of Health & Human Services and U.S Food & Drug Administration. Symbyax Product Label #NDA21-520.
Antiepileptic drugs in the treatment of Bipolar Disorder

Mark Lyons1

David Taylor1,2

1. Senior Clinical Pharmacist
Pharmacy Department
South London and Maudsley NHS Foundation Trust
Pharmacy Department
Denmark Hill
London SE5 8AZ, UK

2. Director of Pharmacy and Pathology
Professor of Psychopharmacology
King’s College, London
Institute of Pharmaceutical Science
5th Floor, Franklin-Wilkins Building
150 Stamford Street
London SE1 9NH

*Author for correspondence
Email: David.Taylor@slam.nhs.uk
Telephone: + 44 20 3228 5040
Fax: + 44 20 3228 5279

Introduction

Antiepileptic drugs (AEDs) were first shown to be effective in mania nearly 40 years ago (1973 carbamazepine; 1975 valproate) (1;2). The discovery that carbamazepine and valproate are effective for mania encouraged interest in other antiepileptic agents as potential treatments. Although the exact mechanism of action of the AEDs in Bipolar Affective Disorder (BPD) is not fully understood, these drugs have provided a successful means of treating and managing a very complex illness. This review aims to summarise the effect of five of the most commonly used AEDs for acute mania, bipolar depression, prophylaxis of BPD, and rapid cycling BPD.

Valproate

Acute mania

Valproate has been fairly widely studied in the treatment of mania both as a single agent (3;4) and as an adjunct to lithium (5) or antipsychotic drugs (6). A selection of the randomised controlled trials (RCTs) of valproate in the acute treatment of mania were included in a recently published multiple treatment meta-analysis by Ciprani (7). This meta-analysis places valproate at 9th position out of 14 possible interventions for the treatment of acute mania when considering both efficacy and tolerability together (7). Valproate was found to be more effective than lamotrigine (10th), placebo (11th), topiramate (12th), and gabapentin (13th). Antipsychotics, lithium, and carbamazepine, however, were all considered more effective than valproate (7).

Bipolar Depression

Two meta-analyses containing 4 RCTs concluded that valproate is effective for the treatment of acute bipolar depression (8;9). The first meta-analysis reported a number needed to treat (NNT) of 5
(8) (response), while the second reported a NNT of 7 (9) (remission). These meta-analyses should be interpreted with caution because there were only 142 participants when all RCTs were combined. Larger trials are therefore needed to assess the true clinical effectiveness of valproate for the acute treatment of bipolar depression. Although there is evidence which supports the use of valproate for the treatment of bipolar depression, it is probably not a first-line agent. The Maudsley Prescribing Guidelines recommend using quetiapine as a first-line agent and valproate or lithium as a second-line agent (10).

Prophylaxis

Valproate is effective in the prophylaxis of BPD, but may be less effective than other treatments (5;11). Lithium monotherapy was compared with valproate monotherapy and combination treatment of valproate and lithium in a non-randomised cohort study. There was no statistical difference between combination treatment and lithium monotherapy. However, both were significantly better than valproate monotherapy for preventing an affective relapse (11). This confirmed a previous finding in the BALANCE study, which was conducted over 2 years and also showed that lithium monotherapy was equivalent to combination therapy and that both were superior to valproate monotherapy at preventing any mood episode (5). In contrast to these studies, a 47 week RCT comparing olanzapine with valproate found no difference in relapse rates between the two treatment arms (12). Valproate is therefore a suitable prophylactic agent for patients intolerant to or unwilling to use lithium, which is still considered the gold standard (5;11).

Rapid cycling

Combination therapy (13) with lithium and valproate is the first-line treatment choice for rapid cycling BPD (10;14). Despite no available trials that prove combination superiority, this has become the accepted standard in the treatment of this condition. In a 6-month double-blind maintenance study in patients with rapid cycling BPD and co-occurring substance abuse or dependence, there was no significant difference in time to relapse for any mood episode between lithium monotherapy or combination lithium and valproate therapy (15). Studies of monotherapy in rapid cycling BPD also show no difference in efficacy. In a 20-month maintenance trial of lithium versus valproate monotherapy (following previous acute mood stabilisation with lithium and valproate combination therapy) neither monotherapy agent differed in time to additional treatment for a mood episode (16). Patients with rapid cycling BPD usually spend more time in the depressive rather than manic phase (10). A 12-month open-label trial comparing valproate with quetiapine monotherapy found no significant difference in effectiveness (measured by study discontinuation) (17). There were some minor differences in outcomes for those on quetiapine. These patients showed fewer days with moderate to severe depressive symptoms (17). No difference was observed, however, between the treatments for mania (17). Rapid cycling patients have a worse prognosis for response to treatment compared with non-rapid cycling patients (18). The recommendation for combination treatment is based on expert opinion (10;13;14).

Lamotrigine

Acute mania

There are 3 RCTs of lamotrigine in Cipriani’s meta-analysis on the treatment of acute mania which all showed negative results (7). Lamotrigine was ranked behind placebo in 12th position for efficacy and tolerability (7). The slow titration requirements for lamotrigine render this treatment option inappropriate for the treatment of acute mania. It takes at least 6 weeks (19) to reach a suitable dose, during which time other treatments would have been more successfully started.
Bipolar Depression

There are 5 company-sponsored RCTs of lamotrigine which were included in a meta-analyses (20). Lamotrigine was significantly better than placebo for response to treatment as assessed by the Hamilton Rating Scale for Depression (HRSD) (21) and Montgomery-Asberg Depression Rating Scale (MADRS) (22) with NNT’s of 11 and 13 respectively depending on which assessment tool was used (20). There was no difference for response between BPD I or II patients for the acute treatment of bipolar depression. In a different meta-analysis, olanzapine and fluoxetine combination therapy was significantly better than lamotrigine monotherapy at treating acute bipolar depression (23). Predictably, time to 50% reduction in MADRS was significantly shorter for the combination group compared with lamotrigine monotherapy (23), most likely attributable again to the slow titration regimen required for lamotrigine. The Maudsley Prescribing Guidelines recommend lamotrigine as a 3rd line choice for the treatment of acute bipolar depression behind quetiapine, or valproate/lithium respectively (10).

Prophylaxis

There are 2 RCTs comparing lamotrigine, lithium, and placebo maintenance treatment over an 18 month period in BPD I patients (24;25). One study included recently depressed patients, while the other included recently manic patients. The results from both studies were consistent. Both lamotrigine and lithium monotherapy are significantly better at preventing any mood episode compared with placebo. When manic and depressive episodes were separated and analysed separately, lamotrigine but not lithium was significantly better than placebo at preventing a depressive episode, but not a manic episode. Conversely, lithium but not lamotrigine was significantly better than placebo at preventing a manic episode but not a depressive episode.

Rapid cycling

There are 2 RCTs investigating maintenance treatment with lamotrigine for rapid cycling BPD. Only one study is published (26). There was no significant difference compared with placebo for time to additional pharmacotherapy and subsequent study discontinuation (26). All-cause study discontinuation, however, was significantly greater for lamotrigine with a median time of 14 weeks compared with 8 weeks for placebo (26). In addition, there was a significant difference between BPD I and II subgroups favouring a longer survival rate for BPD II patients receiving lamotrigine compared with placebo (26). Overall this study suggests that lamotrigine is a useful treatment for rapid cycling BPD II patients for preventing a relapse. In contrast to this, an unpublished study failed to find a significant difference in BPD II patients (27) which highlights the need for further research in this area.

Carbamazepine

Acute mania

Carbamazepine is probably the most effective antiepileptic for the treatment of acute mania. RCTs with placebo and carbamazepine arms have shown that carbamazepine is superior. For example, the results of a 21 day RCT with 204 BPD I patients concluded carbamazepine is more effective than placebo, with significant decreases in Young Mania Rating Scale (YMRS) (28) at days 14 and 21 (29). Similarly in a 21 day RCT with 239 BPD I patients, carbamazepine was more effective than placebo, with significant decreases in YMRS as early as day 7 (30). Both of these RCTs showed response rates for carbamazepine were twice that of the placebo arms (10). There is no statistical difference between combination treatment of olanzapine and carbamazepine compared with carbamazepine monotherapy (31). RCTs comparing carbamazepine with lithium show no statistical difference between the treatment arms (32;33). It is therefore not surprising that Ciprani’s meta-analyses (7), placed carbamazepine 5th, falling just behind the main antipsychotics and ahead of all other antiepileptic agents and lithium (7). The troublesome drug interactions that carbamazepine pose make it unpopular amongst clinicians, despite its efficacy for the treatment of acute mania.
Bipolar Depression

Carbamazepine would not be a first-line treatment choice for the treatment of bipolar depression; other agents have a stronger evidence base (10). One of the largest open-label studies of carbamazepine in bipolar depression, which included 27 patients, showed that carbamazepine provided remission rates of 63% (34). Larger RCTs are required to assess the true effect of carbamazepine in bipolar depression and at present another agent, such as quetiapine, would be considered as the first-line choice (10).

Prophylaxis

Carbamazepine is generally considered an effective prophylactic agent in BPD. A meta-analysis which compared 4 RCTs to assess the effect of carbamazepine or lithium on the prophylaxis of BPD failed to show any significant difference between treatment groups both individually and from the meta-analysis (35). One RCT concluded that lithium was more effective for BPD II patients than for BPD I patients when the subgroups were separated (36). A different RCT suggested the opposite (35;37). Despite similar efficacy, lithium is considered superior to carbamazepine in reducing suicidal behaviour (10;38). Further to this, carbamazepine is also less well tolerated than lithium with numbers need to harm (NNH) of 13 (35).

Rapid cycling

Carbamazepine is not routinely recommended as a first-line treatment choice for rapid cycling BPD. The evidence base for its use is limited. One small open trial of carbamazepine suggested that it might be of use for some, but different treatments are generally required for the management of most rapid cycling patients (39). Data from a small 5-year retrospective chart and notes review failed to find any differences in outcome between lithium monotherapy and combination lithium and carbamazepine therapy (40). The data did suggest that improvement was noticed earlier with the combination group (40). As lithium and valproate combination therapy is widely accepted as the treatment of choice for rapid cycling BPD (10;14), carbamazepine might be worth considering for patients who are intolerant or nonresponsive to valproate and not receiving full therapeutic benefit from lithium monotherapy. Lamotrigine might also be considered but it does not protect against mania.

Gabapentin

Despite there being no RCTs for gabapentin in BPD, sales for gabapentin (Neurontin) increased rapidly during the late 1990’s. Although not licensed, the second most common use for gabapentin was for mental health indications (41). Multiple articles including case reports and reviews encouraged the prescribing of gabapentin until negative RCTs were eventually published in 2000 (41). The first negative trial was a placebo-controlled trial of adjunctive gabapentin to existing lithium or valproate therapy for the management of mania, hypomania, or mixed states (42). Significant differences in YMRS change scores favoured the placebo arm showing that gabapentin was inferior. A second negative RCT compared gabapentin, lamotrigine and placebo in refractory mood disorders. Lamotrigine was found to be superior to gabapentin and placebo as assessed by the Clinical Global Impression scale (43) that was modified for bipolar illness (44). Following these 2 negative findings the rapid growth in gabapentin prescribing ceased and prescriptions eventually reduced (45). Two further RCTs were published in 2002 and 2006 (46;47) which again found negative results. Gabapentin was recently found to be the least effective drug in Cipriani’s meta-analysis on the treatment of acute mania (7).

Topiramate

Topiramate is not effective for the treatment of acute mania (7;13;14), and is not recommended by the National Institute of Clinical Excellence (NICE) (14). There are no monotherapy RCTs that assess the efficacy of topiramate for the treatment of bipolar depression. A randomised, single-blinded study
offered weak evidence that topiramate is as effective as bupropion as an adjunct to either lithium or valproate for the treatment of bipolar depression (48). This finding has not been confirmed in a robust RCT and therefore topiramate is not recommended for bipolar depression. The prophylactic effect of adjunctive topiramate to risperidone treatment has been suggested in a long term (1 year) open, prospective observational study (49). However, prophylactic efficacy has not been confirmed in a RCT and is therefore not recommended. Topiramate has not been studied for the treatment of rapid cycling BPD and its use in this condition is therefore more experimental than evidence based.

Discussion

Although valproate is the only AED that holds a licence (50) for the use in mania, there is sufficient evidence to support the use of other AEDs. Nonetheless, acute mania is treated most efficiently with antipsychotics. When considering the AEDs, carbamazepine is perhaps the most effective, but valproate would be the first-line treatment choice because it is easier to use. Similarly with bipolar depression, antipsychotic treatment (quetiapine) would be the preferred option, followed by lithium (10). Valproate or lamotrigine would be the most suitable AED to use if quetiapine or lithium were ineffective or poorly tolerated. More than 60 years since the first report of the use of lithium in BPD (51) it remains the gold standard treatment for prophylaxis (5), but in its absence valproate would be the next best choice from the AEDs. Rapid cycling BPD is difficult to treat; 30 – 40% of cases are preceded by antidepressant exposure and worsened by treatment with antidepressants (13). NICE guidance for rapid cycling BPD is for first-line use of lithium and valproate combination treatment (14). The British Association for Psychopharmacology also recommends combination therapy (13). Valproate is the AED of choice in combination with lithium, but lamotrigine and carbamazepine also have evidence worth considering if the combination of valproate and lithium fail or are inappropriate. The role of gabapentin or topiramate in the treatment or management of BPD is limited by poor supporting data and discouraging clinical observations.

Table 1: Suggested sequence for BPD

<table>
<thead>
<tr>
<th>1st choice AED</th>
<th>Others with efficacy</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute mania</strong></td>
<td>Valproate</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td><strong>Bipolar depression</strong></td>
<td>Valproate, Lamotrigine</td>
<td>Carbamazepine, Topiramate?</td>
</tr>
<tr>
<td><strong>Prophylaxis</strong></td>
<td>Valproate, Carbamazepine</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td><strong>Rapid cycling</strong></td>
<td>Valproate or carbamazepine with lithium</td>
<td>Lamotrigine</td>
</tr>
</tbody>
</table>
What have I learned from this paper?

This is a very useful paper, giving clear guidance on the role of antiepileptic drugs in the treatment of bipolar disorder in its various manifestations.

As GPs we are rarely involved in the initiation of treatment for bipolar disorder with antiepileptic drugs, although of course it is helpful that we understand their use and monitoring when prescribing repeats or when we are asked about side effects.

Some antiepileptic drugs have a role both in the treatment and prophylaxis of bipolar disorder, although, generally speaking, antipsychotic drugs such as quetiapine are probably better for acute treatment and lithium remains the gold standard for prophylaxis.

Of the antiepileptic drugs, valproate is clearly the first choice for mania, although it would seem that lamotrigine might be of considerable value for treating the depressed phases of bipolar disorder. Both valproate and carbamazepine seem to have a role in prophylaxis, although lamotrigine might again be of value in preventing the depressed phases. There seems to be no good evidence for the use of gabapentin and topiramate in the treatment of bipolar disorder and these drugs should probably be avoided.

For me the most important section was in the summary where it reminded us that in BPD, particularly in rapid cycling BPD, the use of antidepressants (as opposed to antiepileptic or antipsychotic drugs) can make the situation worse. This is particularly important for GPs as this is often our fault because we prescribe before we may even have considered a diagnosis of BPD.

Dr Jenny Wilson, GP, Bedfordshire.

References

32. Okuma T. Effects of carbamazepine and lithium on affective disorders. Neuropsychobiology 1993;
27 (3):138-145.


The role of atypical antipsychotics in treatment of bipolar disorder

Jonathan Rogers 1,2
Rashid Zaman 3, 4

1: School of Clinical Medicine, University of Cambridge
2: Gonville and Caius College, Cambridge
3: SEPT: South Essex Partnership University NHS Foundation Trust
4: Department of Psychiatry, University of Cambridge

Correspondance:

Dr Rashid Zaman
BSc (Hons) MB BChir (Cantab) DGM MRCGP FRCPsych,
Consultant Psychiatrist (SEPT) & Director BCMHR-CU
Hon. Visiting Fellow, University of Cambridge
SEPT, Weller Wing, Bedford Hospital,
Kempston Rd, Bedford, MK42 9DJ
& Dept of Psychiatry, University of Cambridge
rz218@cam.ac.uk

Abstract

In the 1990s, a new group of antipsychotics emerged, also known as second-generation and described as atypicals because of the low incidence of extrapyramidal side-effects (EPSE). These drugs were considered to be a great step forward in the treatment of schizophrenia; the low incidence of EPSE allowed patients to avoid the stigma of the well-recognised movement problems caused by the typical antipsychotics. Almost a decade later, these atypical drugs began to be used widely in bipolar disorder. In this paper we review their pharmacology, neurobiology and uses in various forms of bipolar disorder.

Key words: bipolar disorder, atypical antipsychotics

Introduction

Antipsychotic drugs, also known as ‘neuroleptic’ drugs, were originally used to treat schizophrenia, first being demonstrated to act against psychosis in 1953 (1). The first generation of antipsychotics largely exerted their action through antagonism of the dopamine D2 receptor and included drugs such as chlorpromazine and haloperidol. These first-generation drugs are sometimes described as ‘typical’ due to their extrapyramidal side effects (EPSE).

In the 1990s a new generation of antipsychotics emerged possessing a higher affinity for 5-HT2A receptors than for D2 receptors (2). Initially marketed for the treatment of schizophrenia, these were termed ‘atypical’ antipsychotics because of the lower rates of associated EPSE and their different pharmacology. These atypical drugs include, risperidone, olanzepine, sertindole, quetiapine, asenepine, zotepine, aripiprazole and amilsulpride, although the mechanisms of action of aripiprazole and amilsulpride are somewhat different from the rest, aripiprazole being a partial dopamine agonist and amilsulpride being a selective D2/D3 antagonist (2). Clozapine, which is reserved for the treatment of resistant schizophrenia in the UK, is also considered to be among the atypical antipsychotic drugs (3). Although in recent years some have claimed that the distinction between typical and atypical antipsychotics is artificial and misleading (4,5), nevertheless, there is convincing evidence that typical and atypical antipsychotics exert different effects on neurosurvival and neurogenesis, the former promoting apoptosis, and the latter enhancing neurogenesis (6).
Over the last decade, atypical antipsychotics have often become the treatment of choice for bipolar disorder. There has been a surge in their popularity for the treatment of bipolar disorder (7). However, it should be noted that research has largely centred on bipolar-I disorder and consequently any implications for bipolar II disorder, mixed state or cyclothymia should be considered with caution. In the UK, NICE now recommends atypical antipsychotics as first-line for treatment of mania and preventative therapy, as well as second-line for treatment of bipolar depression (8). To explore the role of atypical antipsychotics in bipolar disorder, we shall examine the putative neurobiology that underlies their action. The ideal would be to have a single drug to treat mania, depression and mixed states in addition to providing long-term maintenance. However, the reality is that these entities constitute different indications and consequently each will be discussed separately. Because there are significant contraindications to the treatment of bipolar disorder with alternative drugs, notably lithium and antiepileptic drugs, treatment with atypical antipsychotics in particular groups will be discussed. A treatment algorithm will then be proposed.

Neurobiology

Receptor Specificities

Since olanzapine, quetiapine and risperidone have similar pharmacology and are all commonly used as mood stabilisers, the discussion will be focused on their properties. Atypicals have a variety of receptor activities, possessing serotonergic (5-HT1A and 5-HT2A), dopaminergic (D1 and D2), histaminergic (H1), adrenergic (α1 and α2) and cholinergic (M1) affinities (9). To discuss all of these would be beyond the scope of this paper. Some of the actions that have been less studied will be discussed.

Atypicals are partial agonists of the 5-HT1A receptor, which is a presynaptic receptor on serotonergic neurons. (9) That is, these drugs act to create a consistent level of inhibition of serotonin release. SSRIs similarly increase the stimulation of these autoreceptors by increasing the amount of 5-HT in the synapse. The partial agonist activity of atypicals could be perceived as mood-stabilising by avoiding extremes of serotonin discharge, according to the monoamine hypothesis. Since its conception, much of the research surrounding this monoamine hypothesis has focussed on serotonin and noradrenaline; increasingly, however, there is a growing awareness of the importance of dopaminergic signalling in bipolar disorder. Higher CSF levels of the dopamine metabolite homovanillic acid (HVA) are found in mania, while concentrations are reduced in depression. Moreover, DA levels in the mesocorticolimbic system, which are associated with motivation and reward, are found to be high in mania and low in depression. This finding has the helpful corollary of providing a putative explanation for the causal role of stress in the pathogenesis of depression, since glucocorticoids reduce DA levels in the prefrontal cortex, while long-term use of antidepressants is able to elevate it (3). Nonetheless, while the D2 antagonism of atypicals is considered an important aspect of their function, they have a much lower affinity than typical antipsychotics, so it is thought that this may underly their comparatively small dysphoric effect (9).

As well as directly antagonising dopaminergic function, atypicals also indirectly act on DA release by antagonising presynaptic 5-HT2A receptors on dopaminergic neurons. This has the result of enhancing DA release in the prefrontal cortex (9). Atypicals thus cause a rather paradoxical action on mesocorticolimbic dopamine, increasing levels but decreasing responsiveness; it is possible that the latter is counteracted by the former but it seems likely that the brief adherence of the drug molecule to the D2 receptor permits some response to the raised synaptic DA.

To summarise this evidence, it is not possible to delineate, with any great specificity, the exact mechanism of action of atypicals at the receptor level, but it does seem likely that mood stabilisation requires a balance between 5-HT and DA that is particular to different brain regions (9). It is possible that atypicals might raise mood through serotonin but prevent the mediation of mania by dopaminergic reward.
Distant Actions

As well as the direct actions of atypicals, their function on downstream processes has also been explored, notably in relation to neurogenesis, neurosurvival and neuroplasticity. These mechanisms will be explored briefly, through some examples.

In simple terms, olanzapine has been shown to up-regulate Bcl-2 (which protects against apoptosis), CREB (a transcription factor mediating the long-term effects of activation of the cAMP pathway) and BDNF (which promotes neurogenesis and facilitate neuroplasticity). (10) In addition, quetiapine has been shown to prevent the down-regulation of BDNF caused by stress. (3) Glycogen synthase kinase-3 (GSK-3) is known to alter neuronal function by several mechanisms, affecting gene expression and modifying survival and plasticity of neurons. Its activity is also found to be abnormal in affective disorders, so it seems a likely target for pharmacotherapy. It is inactivated by phosphorylation via the Akt (PKB) pathway, which can itself be modulated by the downstream targets of both dopamine and serotonin. Both antidepressants and quetiapine result in GSK-3 inhibition in mice, the effects potentiating each other in combination. (11)

Neuroplasticity is also thought to be defective in bipolar disorder and lithium is considered to have a role in enhancing neuroplastic processes. In a recent study on rats, olanzapine and lithium were shown to affect neuronal transmission in CA1 pyramidal cells of the hippocampus. However, while lithium acted to increase long-term potentiation without altering baseline synaptic transmission, olanzapine had no lasting effect on long-term potentiation but did create a steeper dose-response relationship than in controls. (10) Atypicals, thus appear to function differently to lithium, in this regard, at a fundamental level but with a potentially similar outcome.

Treatment of Mania

On conducting a systematic review, Bridle and colleagues found that quetiapine and olanzapine were both superior to placebo in treating acute mania (defined as lasting 10 weeks or less). These had a similar effectiveness to valproate but it is unclear, based on current research, whether there is a statistically significant difference from the effect of lithium (12). In practical clinical terms, in a medication-naïve patient, it is easier to treat acute mania with atypical antipsychotic medication, without the medical work-up and dose-loading that is necessary before reaching therapeutic lithium levels. In the light of the term ‘antipsychotic’, it is also worth pointing out that their use in mania is not merely confined to treating psychosis, as they have also been shown to be effective in non-psychotic mania (13); in fact, atypicals have been demonstrated to be particularly useful in treating the agitation and aggression that sometimes feature in manic episodes (14).

In terms of which particular atypical to use, olanzapine and quetiapine have been shown to have similar effectiveness (12); the best evidence exists for olanzapine (15), although this may merely be an artefact of its longevity. It should be noted that the evidence base for risperidone in the treatment of acute mania is weak, with trials either being small or only including those patients who had already responded to the drug (14). There is some evidence for the use of aripiprazole. Indeed, its better adverse-effect profile, particularly with regard to metabolic disturbance, (which is common with other atypicals) makes it an attractive option, but it has yet to be compared against other antipsychotics (16). More recently, a new atypical called asenapine has also been approved (28).

Clinicians should always be wary of polypharmacy, as adverse effects can be additive and sometimes even potentiate each other. However, where clinically indicated, there is sometimes a case for it in the treatment of bipolar disorder. Although polypharmacy, also described as combination therapy, can lead to additive adverse effects, when used cautiously, with knowledge of the pharmacology of each of the drugs and their potential interaction, it has an important role in effective management of bipolar disorder. In acute mania, a combination of either lithium or valproate with an atypical has been shown to have a 20% better response rate than either lithium or valproate monotherapy (17). There is also evidence from a small trial for superiority of a combination of quetiapine with lorazepam over lorazepam monotherapy (13).
Treatment of Bipolar Depression

Research into depression in the context of bipolar disorder has been somewhat inadequate for two reasons. First, although most patients with bipolar disorder spend a much greater period of time in a depressed mood state rather than in an elevated one, the majority of studies have focused on mania rather than depression (18). Second, authors have often avoided comparison with antidepressant monotherapy due to the justifiable fear of pushing patients towards a mixed state, even though there is thought to be less risk of this with modern SSRIs than there was with monoamine oxidase inhibitors and tricyclic antidepressants.

Olanzapine monotherapy has been shown, in randomised controlled trials, to be superior to a placebo in the treatment of depression, as measured by the change in MADRS score (19). Quetiapine monotherapy has also been shown to be effective (18), with an 8-week trial recently confirming its advantage over placebo (20). On the other hand, no statistically significant difference from placebo was found with aripiprazole treatment for bipolar depression (19).

As for combination therapy, adding fluoxetine to olanzapine has been found to yield better outcomes than olanzapine monotherapy (18).

Treatment of Mixed States

Mixed states, so called because they exhibit features of both manic and depressive episodes, occur in 40% of bipolar patients, but research into them has been somewhat limited (22) and where it has been conducted, a variety of definitions for a mixed state have been used (23). NICE considers treatment of mixed states to be identical to manic episodes (9). In general terms, a systematic review found that the manic component of mixed states responds more rapidly and more substantially to atypicals than the depressive component. In particular, olanzapine and aripiprazole improve both manic and depressive features, while risperidone has only been shown to act on manic symptoms (21,22). Evidence is lacking for the roles of risperidone and quetiapine in the treatment of depressive symptoms (21).

Regarding combination therapy, olanzapine plus either valproate or lithium has been shown to be superior to valproate or lithium monotherapy but a similar trial with risperidone did not show any advantage (21). Adding fluoxetine to olanzapine is not superior to olanzapine monotherapy and may even be inferior (21).

Recently a new atypical asenapine has also been approved for mixed states (28).

Prevention

Beynon and colleagues conducted a comprehensive systematic review and meta-analysis on prevention in bipolar, examining 34 trials. They found evidence for three drugs in monotherapy for reduction in mania (lithium, olanzapine and aripiprazole) and three for reduction of depression (valproate, lamotrigine and imipramine), when compared to a placebo, although tricyclic antidepressants are now seldom used in practice, because of concerns about mixed states. One trial even showed that treatment with olanzapine resulted in fewer manic episodes and total mood episodes than lithium therapy but depressive episodes were more common (23). In addition to the effects on mania and depression, atypicals have also been shown to have a role in lowering rates of mixed states and prolonging the time period before they recur (21).

In terms of individual antipsychotics, the atypical with the best evidence base for prevention is olanzapine (15). Quetiapine is often claimed to be effective, but the evidence for its use relies on a trial where only those patients who had already responded to quetiapine were included; the study is, nevertheless, useful, as it has some implications for trying patients on the medication, but it is very weak evidence on which to base recommendations for a first-line therapy.

On the basis of the absence of good evidence for a single antipsychotic drug preventing both mania and depression, combinations with other drugs have been suggested. However, Beynon and
colleagues have commented that there is still no strong evidence for combination therapy (23). Nonetheless, aripiprazole may also have a role in combination with lithium or valproate in preventing manic episodes (16). Moreover, quetiapine as an adjunct to lithium or valproate has been shown to be superior to monotherapy in preventing all mood episodes, including mixed states (21), in a combination which has been shown to be cost-effective in the UK and US health models (24).

Some issues to consider when using atypicals in bipolar disorder

Adverse Effects

The adverse effect profile (side effect profile) is often a significant reason for choosing one drug over another. Indeed it is an important factor in adherence. The traditional dichotomy holds that while typical antipsychotics have more extrapyramidal adverse effects, atypicals cause metabolic adverse effects. Some argue that the total side effect burden from the atypicals is no less severe (16). Aripiprazole is known to have a better adverse effect profile, with lower rates of hyperprolactinaemia, elongation of QT interval and metabolic complications (17). In terms of the neurocognitive burden, atypicals seem to compare favourably. Dias and colleagues recently examined this aspect of drugs used for bipolar disorder and found that, while lithium is detrimental for psychomotor speed and verbal memory and antiepileptic drugs seem to exert a negative effect on cognition, atypicals are associated with a small improvement in cognition, although this finding requires validation with further investigation (25).

Age

Unfortunately, there have been no trials of the atypicals in children and adolescents and lithium is currently the only licensed treatment for bipolar disorder in those under the age of 18. However, NICE guidelines suggest the off-license use of adult treatments where appropriate, albeit starting at lower doses (8).

Regarding the elderly, there have, in recent years, been concerns about prescribing antipsychotics for behavioural disturbances in dementia; it is natural that there have been similar apprehensions using them in the treatment of bipolar disorder. Bhalerao and colleagues examined data from the US Department of Veterans Affairs on individuals with bipolar disorder; they found marked differences between drugs. Mortality for patients taking risperidone was highest at 11.8 deaths per 100 person-years. The figures for other drugs were: olanzapine 10.3, quetiapine 5.3 and valproate 4.6 (comorbid antiepileptic medication being excluded from the results). The same pattern emerged from the data after multivariate and propensity-weighed analyses, but the mechanism for the increased mortality remains unclear, as death from all causes increased proportionately. Nonetheless, this is a serious caution against the use of risperidone and olanzapine in the elderly (26).

Formulation

In those patients for whom taking multiple tablets in a day is considered unacceptable, an extended-release form of quetiapine is now available and has been found to be equally effective to the immediate-release form (28).
Pregnancy

Table 1 suggests that atypicals could be used in the first half of pregnancy (of course, after having weighed up the gains and the possible negative effects on the foetus of the treatment in detailed discussion with the patient) and lithium for the second half, though this is by no means straightforward, as lithium dosing changes as pregnancy advances.

Hepatic and Renal Impairment

Table 2 suggests that lithium might be the first choice in hepatic impairment, while quetiapine and aripiprazole can be used in renal impairment. It should be noted that reduced doses may not result in reduced effectiveness, as organ dysfunction may prolong the half-life of the drug.

Conclusion

Table 3: Quick reference guide to use of atypicals in bipolar

Table 3 shows an outline of recommendations for the use of atypical antipsychotics, though this would not be complete without reference to some other mood stabilisers, which have been included for the sake of clinical utility. It should also be used in combination with tables 1 and 2 to ascertain the relevant contraindications. The distinction between 1st and 2nd choice therapy represents a preference for monotherapy over the increased side effects and risks of combinations, although these combinations have better success rates than the 1st choice drugs alone, so might be used first-line if clinically indicated.

Having summarised the information, a few salient points emerge. First, olanzapine monotherapy may be used as first-line for treatment of any acute state as well as for prevention of relapse. Second,
in addition to being associated with the highest mortality in the elderly, risperidone has only been demonstrated to act against mixed states, and only partially at that, so it should usually be avoided. Quetiapine has a few indications but the evidence is generally weaker than for olanzapine. Aripiprazole has a favourable adverse effect profile but again its uses are limited. Selective polypharmacy/combination therapy still seems to be beneficial in certain cases.

In terms of how to apply this information to clinical practice, the obvious problem with dividing up pharmacotherapy into the different indications in Table 3 is that very often a clinician will be trying to achieve two or more aims simultaneously; for instance, it may be desirable to treat a current mixed state but also to avoid the recurrence of a depressive episode from which the patient has recently emerged. Hence, the doctor must identify the particular priorities of treatment for each individual patient and tailor treatment appropriately. Moreover, most patients with bipolar disorder will not be medication-naïve and their clinician must weigh the risks and benefits of switching from an already established treatment rather than just altering the dose.

Finally, as mentioned initially, the vast majority of research has been conducted in bipolar-I, so our conclusions are much more cautiously applied to bipolar-II and cyclothymia.

**GP Comment**

What have I learned from this paper?

This paper highlights the use of atypical antipsychotics in the management of bipolar disorder, explaining their modes of action and side effect profiles. Antipsychotics are recommended by NICE as first-line in the management of acute mania and hypomania, quetiapine as an additional treatment in moderate or severe bipolar depression, and olanzapine in long-term management to prevent relapse.

Dr Jenny Hopwood, GP Trainee.

**References**


Part 4. Diagnosing Bipolar Disorder

Treatment and early Intervention in Psychosis Program (TIPP)

For correspondence:
Prof. Philippe Conus, MD
Service of General Psychiatry
Department of Psychiatry-CHUV
Lausanne University, Switzerland
Tel: +41 21 643 61 11
Fax: +41 21 643 64 69
Mail: philippe.conus@chuv.ch

Philippe Conus

Affiliations:
a. Treatment and early Intervention in Psychosis Program (TIPP), Service of General Psychiatry, Department of Psychiatry-CHUV, Lausanne University, Clinique de Cery, 1008 Prilly, Switzerland
b. Orygen Youth Health Research Centre, Centre for Youth Mental Health University of Melbourne, 35 Poplar Road, Parkville Victoria 3052, Melbourne, Australia

Running Title: Identification of initial mania prodrome

Abstract

While early intervention in psychotic disorders has received much attention over the last few years, early intervention in bipolar disorders is still in its infancy. Such developments are greatly needed in order to reduce the usually very long duration of untreated illness and perhaps to improve outcome that often remains rather poor. Besides promoting earlier diagnosis of first-episode mania and exploring ways to characterize bipolar depression, identification of patients during the prodromal phase to their first manic episode has emerged as a valid domain of investigation. The observation that symptoms developing during this phase are likely to be very non-specific has lead to the recent development of two strategies which may improve the situation. However, to date there is no valid way to identify patients in the prodromal phase to bipolar disorders and more research is warranted in this area.

Key words: early intervention, bipolar disorder, prodrome, mania, first episode.

Introduction

The elaboration of preventive strategies has become a priority in mental health. Early intervention programs for psychotic disorders are examples of such developments which have lead to the emergence of a vast domain of clinical and neuro-scientific research. However, until recently, most of the attention has been directed towards schizophrenia; affective disorders, including the bipolar disorders (BPD), have been neglected (1). Although Fava et al. (2) suggested, thirty years ago, the existence of a prodromal phase preceding the first full manic syndrome by weeks or months and the idea that the identification of such a prodrome would allow the development of earlier and probably more efficient interventions, this domain has received very limited attention. This is rather unfortunate, considering the many elements which suggest that early intervention strategies are needed in BPD. Accumulating data converge to show that outcome of BPD is poorer than formerly thought (3), already after the first manic episode (4,5), suggesting that available treatment strategies are inadequate. In addition, various studies have shown very clearly that a long delay usually occurs between the
onset of the disorder and introduction of adapted treatment, patients spending on average 6 to 10 years before mood-stabilising treatment is introduced (6,7). It is likely that such delays have similar negative consequences to those observed in psychotic disorders (8). Moreover, the high prevalence of co-morbidities observed in patients at first presentation of mania suggests that earlier intervention might prevent their development. Finally, it seems clear to clinicians that patients with first-episode mania have different needs from those who present with a first psychotic episode, suggesting that the development of specific strategies could be very useful for treatment. The identification of patients before the first manic episode, that is during the “initial prodromal phase” (as opposed to the relapse prodromal phase), would not only pave the way to the prevention of a first manic episode, which usually has highly stigmatizing consequences, but it might also allow the prevention of the deterioration occurring before the first manic episode, through the development of specific psychological interventions and the study of the utility of potentially neuroprotective treatments. In addition, a reduction of the delay between onset and appropriate treatment might result in a better treatment response and better engagement of patients.

Which targets for early intervention?

In a recent paper, Berk et al. (9) have retrospectively reconstructed the natural history of the development of the illness in a sample of 207 patients with BPD (see figure 1). On the basis of the various stages through which patients usually go, it is possible to identify various phases where early intervention strategies could be implemented. Indeed, considering the long delay between the time when patients reach treatment threshold and the time where mood-stabilising treatment is started, and based on the observation that more than 50% of patients begin bipolar disorder with a depressive episode, 3 main different targets can be identified for earlier intervention.

The most readily accessible would be to promote a better identification of a first manic episode. Due to frequent co-morbidities and often atypical presentation (high prevalence of psychotic symptoms, irritability and aggressiveness rather than euphoric mood), patients with a first episode of mania are often misdiagnosed and the introduction of proper treatment is therefore delayed (1). Such misdiagnosis can have many consequences, such as prescription of maladapted treatment (antipsychotic or antidepressants), as well as rejection, when mania is misdiagnosed as antisocial behavior. In this context it is important to promote better knowledge of the atypical nature of mania in youth.

A second target may be the identification of bipolar depression, in other words depressive episodes emerging in patients who will later develop BPD. Some recent publications have suggested that some characteristics (such as rapid onset and offset or physical retardation) may be more common in bipolar depression that in unipolar depression, and some authors have recently developed a tool allowing the exploration of such characteristics (10). Such identification could be useful in guiding treatment choice, considering that antidepressant medication which may induce manic episodes in such individuals should be avoided in favor of mood stabilisers.

The third early intervention target would be to identify BPD before subjects have reached diagnostic threshold level, in other words to identify the “prodromal phase” to bipolar disorder. While the concept of prodrome to first-episode psychosis is reasonably easy to define as the period preceding the first time when a patient reaches threshold level for psychotic symptoms, it is harder to define a clear target in the context of BPD, due to the many forms its onset can take, ranging from a depressive episode to mania. For this reason, a consensus is currently building to consider that the prodrome to the first manic episode is the most realistic target (11).

Prodrome to first manic episode

Knowledge of the early stages of BPD stems from 2 types of studies (11). A first group of papers is based on prospective follow-up of various samples of subjects, either considered as “at risk for bipolar disorder” (because of a family history of BPD or due to the presence of various psychopathological
manifestations) or belonging to larger prospective follow up of community samples. A second group of publications is based on retrospective studies, reconstructing the early phase of the disorder either in patients who recently presented with a first manic episode or in samples of patients already diagnosed with BPD for some years. Based on these papers, two main conclusions emerge.

The first conclusion is that a prodromal phase to first-episode mania actually does exist. Indeed, the great majority of patients seem to go through a period of noticeable change before the onset of the first manic episode, changes that are clearly detected by those who are in contact with the patient and by patients themselves. This period seems to have a relatively wide range of duration but data on this aspect has only been provided in two studies. Correll et al. (12) found that onset was insidious (>1 year) in 52% of patients, sub-acute (1 year-1 month) in 45% and that it was acute (<1 month) in a very limited number of patients (3%). Conus et al. (13) similarly reported a mean duration of 21 weeks for the prodrome, which lasted less than 10 weeks in 50% of patients and ranged between 24 and 49 weeks for the others. However, the focus of this latter study was on the 12 months preceding mania onset and this may have biased the results.

The second conclusion is that the prodrome to first episode mania is marked by the presence of symptoms which globally fall into 3 categories. First, patients present with mood symptoms, mainly in the form of mood swings, cyclothymic features or depressed mood. Second, they display sleep modification with reduction of sleep or decreased need for sleep. Third, they display behavioral and other types of changes in the form mainly of anger and irritability. While they are present in the vast majority of patients, such symptoms are likely to have rather low specificity in prospective samples. This is, indeed, supported by observation by Correll et al. (12) who found that when comparing samples of patients at high risk for psychosis who developed schizophrenia and those who developed BPD, there was an important overlap in phenomenological manifestations. In addition, the same group reported in a later study (14) that high-risk patients who developed schizophrenia and those who developed bipolar disorder had a very similar cognitive profile during the prodromal phase. In summary, if patients who develop first-episode mania do go through a prodromal phase, its phenomenological characteristics seem too nonspecific to allow reliable identification of patients who are specifically at risk of mania in a prospective approach. In this context, two main initiatives have been proposed, which will be developed in the next section.

Definition of high risk profiles: the BAR criteria

In a strategy derived from the development of Ultra High Risk criteria for psychosis, Bechdolf et al. (15) have reported the conceptualization of at-risk criteria for bipolar disorder (BAR; Bipolar At Risk criteria). Three groups are defined, among subjects who share the characteristics of being aged 15 to 25 and help-seeking for mental health issues: 1) Sub-threshold mania; 2) Depression and cyclothymic features; 3) Depression and genetic risk. The details of these profiles are depicted in table 1.

In order to explore the validity of these profiles, the authors conducted a retrospective file audit study through which they applied BAR criteria to 173 successive help-seeker adolescents who had been admitted to a youth health centre. According to the files, twenty two patients (12.7%) met BAR criteria at admission to the center, while 151 (87.3%) did not. After a mean follow-up duration of 165 days, it was found that only one (0.7%) of the patients who did not meet BAR criteria at baseline had developed a first manic episode during the follow-up period, while 5 (22.7%) of those who met BAR criteria did so. These encouraging results suggested that meeting BAR criteria when presenting as a help-seeking adolescent or young adult was linked with an increased risk of developing mania, and motivated the implementation of a prospective study, currently underway, in a population of help-seeking patients aged 15 to 25, comparing the rate of development of first-episode mania according to BAR status at program entry.

Development of a high-risk scale for first-episode mania

Considering the limited specificity of symptoms observed during the prodrome to first episode mania, Conus et al. (13) followed another strategy, based on the principle that the predictive value of
these symptoms might increase if they were to occur in a patient who also has certain characteristics that are common in patients with bipolar disorders. For example, the presence of mood swings and irritability in a young person whose father has BPD would seem more likely to announce an impending first episode of mania than if it occurred in a patient without such a family background. On the basis of a literature review (11), these authors identified various factors that could be classified within 2 groups.

First, they found mention in the literature of a certain number of risk factors, such as family history of BPD or exposure to trauma during childhood. Risk factors are not early manifestations of the disorder per se; they are demographic attributes, family characteristics or life events that either retrospectively have been observed to be more frequent in the life history of subjects who later present with BPD, or that prospectively have proven to confer a higher risk to develop the disorder.

Second, they identified, in the literature, biological characteristics as well as certain early developmental, behavioral or personality patterns that are more frequently reported in the life history of BPD subjects. Although they may be early manifestations of the disorder itself, they do not clearly present as attenuated manifestations of BPD and could therefore be considered as “markers of potential vulnerability to BPD” until further research provides sufficient evidence to identify them either as elements of the bipolar spectrum of disorders or as a defined stage in the development of BPD.

In a sample of 22 patients with first-episode mania, these authors conducted detailed retrospective interviews both with patients and their relatives, and explored which of the factors described above were reported in the majority of cases (13). This selection of items has been combined with the most common phenomenological characteristics of first-episode mania prodrome to build a scale (the First Episode Mania At Risk Questionnaire, FEMARQ), validity of which is currently being studied.

Conclusions

On the basis of the very few studies available to date, it seems that the identification of a prodromal phase to first-episode mania could be identified. This phase is marked by the presence of mood swings, depressed mood, cyclothymic features and sleep disruption as well as irritability or anger dyscontrol. However, such symptoms have very limited specificity, and strategies based on their sole presence are very unlikely to allow the identification of at-risk patients. Two main strategies have been recently developed in order to shed some additional light on this domain, and are currently under investigation in order to see if they have any validity in the prospective identification of patients who will develop first-episode mania.

Until these tools, or others to be developed, have proven their validity, the identification of patients at ultra-high risk to develop BPD during the prodromal phase to the first manic episode, is not possible. At present, the best clinical strategy to promote early intervention in BPD is therefore to improve identification of first-episode mania in young people in order to decrease the duration of untreated illness, during which many of the secondary complications develop which, in turn, seriously impede the recovery potential of such young patients.

GP Comment

What have I learned from this paper?

This article introduces the idea of a prodromal phase before the first manic episode during which patients undergo noticeable changes in mood, sleep and behaviour. However, such symptoms have limited specificity and further research is needed before this prodromal phase can be used to identify at-risk patients reliably. At present, we must identify the first episode of mania quickly and implement early intervention with mood stabilisers to improve long-term outcome.

Dr Jenny Hopwood, GP Trainee.
References

Table 1:
BAR Criteria (adapted from Bechdolf et al. (15))

I. Age 15-25 years

II. Fulfill criteria of at least one of three groups within the last 12 months:

Group 1: Sub-threshold mania
Mania-like symptoms for at least two consecutive days but less than 4 days: period of abnormally and persistently elevated, expansive or irritable mood + at least 2 criteria from the list: (1) inflated self-esteem or grandiosity, (2) decreased need for sleep (e.g. feels rested after only three hours sleep), (3) more talkative than usual or pressure to keep talking, (4) flight of ideas or subjective experience that thought are racing, (5) distractibility, (6) increase goal-directed activity (either socially, at work, or sexually) or psychomotor agitation.

Group 2: Depression + Cyclothymic features:
Depression for at least 1 week: depressed mood, or loss of interest or pleasure + at least 2 criteria from the list: (1) significant weight loss, (2) insomnia or hypersomnia nearly every day, (3) psychomotor retardation or agitation, (4) fatigue or loss of energy, (5) feelings of worthlessness or excessive or inappropriate guilt, (6) diminished ability to think or concentrate, (7) recurrent thoughts of death, recurrent suicidal ideation

+ Cyclothymic features: Numerous episodes with sub-threshold manic symptoms not meeting group I criteria. e.g. sub-threshold mania as defined in group I only for 4 hours within a 24-hour period and at least 4 cumulative lifetime days meeting the criteria

Group 3: Depression + Genetic Risk:
Depression for at least 1 week: depressed mood, or loss of interest or pleasure + at least 2 criteria from the list: (1) significant weight loss, (2) insomnia or hypersomnia nearly every day, (3) psychomotor retardation or agitation, (4) fatigue or loss of energy, (5) feelings of worthlessness or excessive or inappropriate guilt, (6) diminished ability to think or concentrate, (7) recurrent thoughts of death, recurrent suicidal ideation

+ Genetic Risk: First degree relative with bipolar disorder.

Figure 1:
Natural history of the development of BPD and potential early intervention targets. (Adapted from Berk et al. (9))
Proving that a patient has bipolar disorder

Mark Agius (1) (2) (3), Helen Murphy (4) (5)
(1) Department of Psychiatry, University of Cambridge, (2) South Essex Partnership University Foundation Trust, (3) Clare College, Cambridge.
(4) School of Clinical Medicine, University of Cambridge, (5) Magdalene College, Cambridge.

Abstract

Bipolar disorder (BPD) is commonly misdiagnosed; this article concisely outlines the sub-types of BPD, important criteria essential for diagnosis and then demonstrates the most effective method of extracting the necessary information. Using the twenty-nine questions provided, health professionals can be confident they have checked sufficiently for symptomatology that is often missed; this should help to confirm whether a patient has BPD. The aim should remain to reduce morbidity and mortality due to misdiagnosis, by improving the sensitivity of screening, enabling faster access to the correct treatment for these vulnerable patients.

Key words: bipolar disorder, diagnosis

Introduction

Bipolar disorder (BPD) is a recurrent, cyclical disorder that combines opposite, but related, mood states, including depression, mania or hypomania and mixed states. It is further differentiated into sub-syndromes (bipolar I and II). Current diagnostic criteria using the DSM-IV for BPD type-I requires the occurrence of one or more manic episodes or mixed episodes. Patients may also have one or more depressive episodes. Importantly, in the period between these episodes, most patients return to their normal state of wellbeing. Bipolar II disorder is characterised by at least one hypomanic episode as well as one or more major depressive episodes.

Epidemiological studies have indicated that the lifetime prevalence is 1% across all populations. However, additional studies (1) have suggested that BPD is more common than originally thought. This is due to the recognition that BPD has a spectrum of expression, resulting in sub-threshold BPD, not completely fulfilling DSM criteria (2), being under-detected.

The importance of diagnosing bipolar disorders correctly could play a role in the public health challenge of reducing the associated premature mortality due to suicide (3-4). Furthermore, the comorbidity of BPD often includes anxiety disorders and substance abuse. It has been suggested that substance abuse in bipolar disorder represents unregulated self-medication by these patients (5).

In this article, we discuss an effective method of diagnosing BPD in clinical practice that has been developed for use in patients who have been referred to secondary care in a euthymic state. Diagnosis is often obscured by uncertainties. Asking: “Do you get moods which go up and down?” is simply not enough.

Management of BPD requires long-term treatments, mood stabilisers, which have important, often life-changing adverse effects. Increased suicidality in BPD means that it is essential that the diagnosis is confirmed and that the correct, effective treatment is provided.
Classification of BPD
Definition of Hypomania subtypes

<table>
<thead>
<tr>
<th>ICD 10/13</th>
<th>DSM-IV2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two episodes of Mood Disturbance</td>
<td>One episode of mood disturbance</td>
</tr>
<tr>
<td>Hypomania &amp; Mania Distinct</td>
<td>Describes degrees of Mania</td>
</tr>
<tr>
<td>Single entity of BPD</td>
<td>Bipolar I – Mania Bipolar II – Hypomania</td>
</tr>
<tr>
<td>Different classifications for present state</td>
<td>Different classifications for present state</td>
</tr>
</tbody>
</table>

Detection, Misdiagnosis & Screening

The first symptom of BPD in ~50% of patients is depression (6). Long-term follow-up studies (12.8 years) conducted by Judd et al. (7) found patients with BPD were symptomatic, (depressed, manic, hypomanic or in a mixed state) approximately 47% of their lives.

Misdiagnosis is, however, a very common problem. The Depressive and Bipolar Support Alliance (DBSA) found that large-scale retrospective studies (8) indicated the most frequent misdiagnosis was unipolar depression, and also that >35% of misdiagnosed patients reported experiencing BPD symptomatology ~10 years prior to BPD diagnosis (9). These findings are supported by Ghaemi et al. (10) who showed patients wait 9 years, on average, for a BPD diagnosis.

Hirschfield et al. (9) showed that the Mood Disorder Questionnaire (MDQ) overall positive screen rate, for BPD, was 3.7% (when adjusted for non-response bias) across a population of 83,358 US citizens (>18yrs). Of those for whom the MDQ suggested BPD, only 19.8% had previously received a diagnosis from a physician, 31.2% had a unipolar depression diagnosis, and 49.0% had no BPD or unipolar diagnosis. Positive screens were highest amongst young adults from lower socio-economic areas in this study. These patients were also significantly more likely to suffer from migraine and asthma. Substance misuse was also higher in this cohort.

BPD – Subtypes or Spectrum?

The spectrum concept of BPD was first proposed in 1977 when a prospective study showed that people with cyclothymic mood disorder go on to develop unipolar depression (UPD) or BPD (11). Another showed that 12% of patients in the study went on to develop BPD type II; having had a UPD diagnosis 15 years earlier (12).

Sub-threshold bipolar patients have also been seen to progress towards BPD, one study indicating a progression of 7% of such patients with BPD type II advancing to BPD type I, over 15 years (14).
The Importance of Bipolar II

Hypomania often goes undiagnosed, due to the reduced impact on the patient's life. These patients tend to present in a euthymic condition or when experiencing depressive symptoms. Often a history of hypomania may be missed, or BPD type II (mixed state) may be misdiagnosed as an agitated depression (15). This poses a very real risk to patients; undiagnosed patients with BPD may progress to manic/hypomanic or mixed states as a result of treatment with antidepressants, in particular venlafaxine. This dramatically increases suicide risk in these patients (16).

**Bipolar markers in major depressive episode (8, 17)**

<table>
<thead>
<tr>
<th>Historical Markers</th>
<th>Cross-Sectional Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH of Bipolar I/II disorder (suicide)**</td>
<td>Retardation*</td>
</tr>
<tr>
<td>Past hypomania (≥ 2 days, incl. iatrogenic)**</td>
<td>Psychotic features*</td>
</tr>
<tr>
<td>&gt; 3 depressive episodes</td>
<td>Catatonic features*</td>
</tr>
<tr>
<td>Seasonal onset (Winter ≈ BPD II, Summer ≈ BPD I)</td>
<td>Early onset</td>
</tr>
<tr>
<td>Panic attacks, GAD, OCD/OC symptoms**</td>
<td>Atypical features**</td>
</tr>
<tr>
<td>Cyclothymia hyperthymia**</td>
<td>Depressive mixed states/agitated depression**</td>
</tr>
<tr>
<td></td>
<td>Panic attacks/disorder, 2 or more anx. disorder.**</td>
</tr>
</tbody>
</table>

Figure 1 *Mostly BPD Type I, ** Mostly BPD Type II

“Is my patient bipolar?”

We have developed a method for assessing patients referred in a euthymic state by their GP, to secondary care, in order to ascertain whether they have BPD. The mood disorder is investigated in the following order.

- High moods: intensity & frequency.
- Depressive moods.
- Mixed states.
- Disorders often associated with BPD.
- Family history.
- Substance abuse.
- Current depressive episode.

The questions asked will be presented in bold print and beneath them is given in normal print the rationale for the question.
Q.1 You are aware of how it feels when you are depressed. How old were you when you had your first depressive episode (treated or untreated)?
From experience, we often find patients report a primary depressive episode during their early to mid-teenage years. This is supported by research which has shown:

- BPD is known to be diagnosed on average 6 years prior to UPD (unipolar depression) (18).
- BPD diagnoses may take ~10 years after onset BPD symptomatology (9).

Q.2 After that, did you proceed to suffer recurrent depressive episodes?
 Patients with recurrent depressive disorder may develop BPD Type II over time (7,14).

Q.3 Looking back, when was your first hypomanic episode?
UPD has been proven occasionally to develop over time into BPD type II with the first episode of hypomania (14).

Q.4 How long do the hypomanic episodes last?
The DSM Criteria (2) suggest 4 days is diagnostic; and 2 days would be sub-syndromal. However, on investigation, often patients say that they are aware of a day when there is an upward shift in their mood, prior to full mania/hypomania, and another day where their mood is returning to their prior state.

Q.5 When you are high, hypomanic, do you find:
- You need less sleep?
- Experience racing thoughts?
- Talk quickly and hop from one thought to another?
- Spend excessively perhaps accruing debt?
- Find you mix with lots of new people, or are more flirtatious than usual?
- Take more risks than usual?

In order to validate the responses to these questions PHQ-919 and GAD-720 can usually also be administered at this point.

Q.6 When you are depressed do you find you comfort eat?
This is common, as atypical depression is linked with BPD (21).

Q.7 When you are depressed do you find you sleep a lot during the day?
Also common as atypical depression is linked with BPD (20).

Q.8 When you are depressed can you concentrate?
Patients often experience difficulties with concentration and attention span when depressed (2).

Q.9 When you are depressed, can you enjoy things?
Patients often experience anhedonia when depressed (2).

Q.10 How long do your periods of depression last?
Often weeks or months; in BPD low moods last longer than high moods. However, evidence suggests episodes of unipolar depression last longer (21).

Q.11 When you are depressed, do you get suicidal thoughts?
In practice, patients are often forthcoming about their thoughts; suicidal ideation is a common aspect of BPD (2).

Q.12 When you are depressed, do you ever get severe retardation (being slowed down), paranoia, or have hallucinations.
Psychotic depression, including catatonia may be a concomitant of bipolar disorder (2).
Q.13 Do you often get irritable or angry?
This is a common feature; often such irritability is linked with a mixed state15.

Q.14 Does it sometimes happen that your mood changes rapidly from high to low within a day?
These mixed affective episodes are one subtype of mixed affective state15.

Q.15 Do you sometimes find that you are happy and crying at the same time?
Dysphoric mania is a form of mixed affective state16.

Q.16 Do you sometimes find that you are depressed and very irritable at the same time?
Agitated Depression is a form of mixed affective state16.

Q.17 When you are in a mixed state, as we have just described, do you often find that you have marked suicidal ideation?
Patients are more likely to commit suicide when in a mixed state, and thus experience greater suicidal ideation16.

Q.18 In one year, do you get 4 or more changes of mood; at least 2 highs and 2 lows?
Often patients find this to be the case, and it implies rapid cycling. Rapid cycling patients are more difficult to treat and have increased suicidality10.

Q.19 Do you suffer from migraine?
There are genetic links between BPD and migraine, so this may increase likelihood that BPD is the cause9.

Q.20 Do you suffer with anxiety or panic disorder?
Comorbid anxiety disorders are common in bipolar disorder20.

Q.21 Do you suffer from OCD symptoms?
OCD is often linked with BPD and such patients are particularly difficult to treat with medication1.

Q.22 You may have been told that you have ‘borderline’ symptoms but do you also have episodes of HIGH mood, lasting >4 days?
Borderline personality disorder patients have mood ‘swings’ from low to normal - not high2. Therefore if they have high moods they are comorbid borderline/bipolar.

Q.23 Do you suffer from irritable bowel syndrome (IBS) or colitis?
This is another common co-morbidity. There may be immunological links, in association with levels of inflammation, between these conditions and BPD1.

Q.24 Do you suffer muscular tension?
This is another common co-morbidity2.

Q.25 Do you have a family history of BPD, suicide, or psychosis?
Patients often report that a family member spent periods of time as an inpatient, or that their relative suffered with depression. However, they are often unaware of the concept of mania.

Q.26 Do you drink alcohol to excess?
Many persons who suffer from depression use alcohol. Alcohol is a depressant. On the other hand there may be other causes of the depression. Other substances such as cocaine cause euphoria and depression when withdrawn. Cannabis has many effects on mood, often complicating diagnosis5.

Q.27 Do you find episodes of high/low mood are particularly associated with different seasons?
BPD Type I is worst in summer, and BPD Type II is worst in winter22.
Q.28 Do you think of yourself as creative?

Patients with BPD are often very creative individuals.

Q.29 Have antidepressants ever caused your mood to become high?

BPD often presents with mania/hypomania caused by antidepressants: BPD type III (iatrogenic) (15).

It is important to ascertain whether the patient is depressed at the present time. This should be investigated by repeating questions related to depression in the present tense and validating these responses using the PHQ9 and GAD7. It is important at this stage to investigate any current suicidal ideation and planning. Once all these questions have been asked, all the information needed to diagnose BPD will be available. The whole interview should take <60 minutes to complete.

We believe that every patient who is suspected of having bipolar disorder or who suffers from depression, recurrent depression, and ‘depression with anxiety’ should be evaluated as above. The details of the answers to these questions should be recorded in notes, the letter to the GP, or in the ward discharge summary. A mood stabiliser is required for patients diagnosed with BPD; this will be a life-long treatment, and may have adverse effects that will need to be monitored and managed.

Patients with BPD should only be treated with antidepressants while depressed (15). Specific drugs are effective in bipolar depression e.g. quetiapine, lamotrigine. Patients with BPD are often initially considered to have treatment-resistant depression; however, antidepressants may induce rapid cycling or increase the incidence of mixed states, increasing the risk of suicide. It is important to engage the patient in treatment, by giving them literature about the mood-stabilisers and their adverse effects in a clear format, as found in patient-friendly websites. The clinician should meet with the patient again after one week, once they have had sufficient time to weigh the benefits and adverse effects of the proposed medication, with the aim of allowing them to come to an informed decision.

When patients with BPD are receiving antidepressants for a depressive phase, they should be seen every 2-3 weeks so that the antidepressant medication can be stopped once their mood has improved. This is in line with current guidelines for BPD, in order to prevent inducing mania (15). Patients experiencing mixed states, due to their increased risk of suicide, should be assigned a care co-ordinator and then be followed up by the crisis team or Community Mental Health Team. When experiencing mixed states it is important to stop antidepressants, as previously mentioned, increase the mood stabilizer (if possible), and start an atypical antipsychotic if they are not on one already (15).

In conclusion, BPD is an unpleasant disorder, the treatment of which is complicated and still imperfect. By following these guidelines, we believe that misdiagnosis can be reduced, quality of life can be improved and, because suicide risk is likely to be increased with poor management, that some lives can even be saved. It is vital that appropriate follow up and monitoring is in place to protect these very vulnerable patients.

GP Comment

What have I learned from this paper?

This article reinforces the importance of avoiding the incorrect diagnosis of unipolar depression in patients with bipolar disorder, if they are to be treated effectively and safely. The authors present a series of useful questions that can be used to assess carefully for a previous history of mania/hypomania and for clinical features that increase the likelihood that the correct diagnosis is bipolar disorder.

Dr Jenny Hopwood, GP trainee.

References


Bipolar disorder and acute mania

Richard Yasotharan, FY2 Psychiatry
Weller Wing, Bedford Hospital.

Abstract

Acute mania is described as it presents in bipolar I affective disorder. The Young Mania rating scale is described as a way of assessing mania clinically.

Key Words: mania, bipolar disorder, young mania rating scale.

Bipolar disorder (historically known as manic-depressive disorder) is a serious mental illness involving a mood disorder in which people experience disruptive mood swings, that is characterized by episodes of a frenzied state known as mania (or hypomania) and, usually, symptoms of depression. It often has a long course and for many people the predominant experience is of low mood. Its occurrence is often defined by the presence of one or more episodes of abnormally elevated energy levels, cognition, and mood with or without one or more depressive episodes. In its more severe forms, bipolar disorder is associated with significant impairment of personal and social functioning.

At the lower levels of elevated mood, such as hypomania, individuals may appear energetic and excitable. At a higher level, individuals may behave erratically and impulsively, often making poor decisions due to unrealistic ideas about the future, and may have great difficulty with sleep. At the highest level, individuals can show psychotic behaviour, including violence.

The lifetime prevalence of all types of bipolar disorder is thought to be about 4% (3). The peak age of onset is in late adolescence or early adult life, with a further small increase in incidence in mid to late life. Prevalence is similar in men and women and, broadly, across different cultures and ethnic groups. Genetic factors contribute substantially to the likelihood of developing bipolar disorder. Environmental factors are also implicated.

Bipolar 1 is usually diagnosed if a person has at least two manic episodes. The episodes can last between two weeks and four to five months. Depression usually lasts longer than six months.

These are the usual diagnostic criteria for mania.

Must: (A). Mood predominantly elevated, expansive or irritable and definitely abnormal for the person concerned. Must be sustained for at least one week.

At least three of the following: (B).

- Increased activity or restlessness.
- Increased talkativeness (“pressure of speech”).
- Increased thoughts (flight of ideas/thoughts racing).
- Increasingly awake (less need for sleep).
- Increased self-esteem (grandiosity).
- Increased sexual energy (libido).
- Distractibility or constant changes in activity or plans.
- Loss of normal social inhibitions with inappropriate behaviour.
- Foolhardy/recklessness and risks subjects do not recognize, eg. spending spree, driving.

These factors lead to a severe interference with personal functioning in daily living.

Severity of manic symptoms can be measured by clinician-based Young Mania Rating Scale. The Young Mania Rating Scale (abbreviated YMRS) is an eleven-item, multiple-choice diagnostic questionnaire which psychiatrists use to measure the severity of manic episodes in patients. It was first published in 1978. This is based on the patient's subjective report of his or her clinical condition over the previous 48 hours (1).

The purpose of each item is to rate the severity of that abnormality in the patient. When several keys are given for a particular grade of severity, the presence of only one is required to qualify for that rating.
The keys provided are guides. The keys can be ignored if that is necessary to indicate severity (2). Scoring between the points given (whole or half points) is possible and encouraged after experience with the scale is acquired. This is particularly useful when severity of a particular item in a patient does not follow the progression indicated by the keys (6).

1. Elevated Mood (0-4): Absent – Euphoric (continuous excitement).

2. Increased Motor Activity-Energy (0-4): Absent –Motor excitement (continuous hyperactivity).


4. Sleep (0-4): No decrease-Denies need for sleep.

5. Irritability (0-8): Absent-Hostile.

6. Speech-Rate and Amount (0-8): No increase-pressured.

7. Language-Thought Disorder (0-4): Absent-Incoherent.


10. Appearance (0-4): Appropriate-Completely unkempt.

11. Insight (0-4): Present-Denies any behaviour change.

The following drugs have UK marketing authorisation for use in bipolar disorder (5).

For treatment of mania: lithium, olanzapine, quetiapine, risperidone, and valproate
For prophylaxis: lithium and olanzapine
For prophylaxis of bipolar disorder unresponsive to lithium: carbamazepine.

If a severely disturbed patient with bipolar disorder cannot be effectively managed with oral medication and rapid tranquillisation is needed, intramuscular olanzapine (10 mg), lorazepam (2 mg) or haloperidol (2-10 mg) should be considered, wherever possible as a single agent. When making the choice of drug, the clinician should take into account the following.

That olanzapine and lorazepam are preferable to haloperidol because of the risk of movement disorders (particularly acute dystonia and akathisia) with haloperidol.
That olanzapine and benzodiazepines should not be given intramuscularly within one hour of each other.
That repeat intramuscular doses can be given up to 20 mg per day (olanzapine), 4 mg per day (lorazepam), or 18 mg per day (haloperidol) - the total daily dose including concurrent oral medication should not normally exceed the British National Formulary (BNF) limit.

**GP Comment**

**What have I learned from this paper?**

The diagnostic and severity criteria questionnaires were new to me and could be useful tools in primary care to screen patients who are concerned they may be suffering from bipolar disorder prior to a decision whether or not to refer them to the psychiatric clinic.
I was also interested in the overview of the drug treatment of acute mania. This will help in decisions about which emergency drugs to carry, especially for out of hours cover.

Dr Stephen Cakebread, GP, Bedfordshire.

References

4. The ICD-10 Classification of Mental and Behavioural Disorders, World Health Organization
Bipolar III

Holly Cakebread
Foundation Doctor, Eastern Deanery.

Abstract

Bipolar III is an emerging diagnosis used to describe mania induced by antidepressant therapy prescribed for bipolar patients in a depressive episode. This article reviews the evidence and summarises the safest way to treat bipolar depression.

Key words: bipolar disorder, antidepressant agents, depressive disorder, manic episode

What is Bipolar III?

The term Bipolar III is controversial. It is not included in DSM-IV-TR or ICD-10 criteria. It is not recognised by NICE, the Royal College of Psychiatrists or any of the bipolar charities. However, the Akiskal Schema of bipolar subtypes (1) uses the definition: Hypomania induced by the use of antidepressant drugs.

The aetiology of Bipolar III

Bipolar III has an ambiguous aetiology. On one hand, it might be purely iatrogenic, that is, a hypomanic state induced in someone in whom the bipolar diagnosis been missed previously. On the other hand, the antidepressant might just have created a hypomanic state earlier than it would have presented naturally. Research indicates that 12% of unipolar patients go on to develop hypomanic/manic symptoms within 15 years (2). Does bipolar III represent a quicker development of this or is it, in fact, a separate diagnosis?

What is the evidence for Bipolar III?

It has not been possible to find literature on hypomania being induced in non-diagnosed bipolar patients by antidepressant use. This is not entirely surprising, since it is not possible to identify that a patient has a diagnosis of bipolar disorder before the first hypomanic/manic episode. The available publications have been case studies and papers describing the “switch” to hypomania/mania in patients with known bipolar disorder.

The table below shows information from a meta-analysis of the prevalence of mania induced by different antidepressant treatments when used in bipolar patients (3).

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Patients reporting Trials</th>
<th>% Patients reporting trials with affective shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>All SSRI Trials</td>
<td>706</td>
<td>22%</td>
</tr>
<tr>
<td>One or more SSRI</td>
<td>353</td>
<td>33%</td>
</tr>
<tr>
<td>Bupropion</td>
<td>209</td>
<td>18%</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>102</td>
<td>17%</td>
</tr>
<tr>
<td>Heterocyclics</td>
<td>83</td>
<td>23%</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>67</td>
<td>7%</td>
</tr>
<tr>
<td>ECT</td>
<td>49</td>
<td>14%</td>
</tr>
<tr>
<td>MAOIs</td>
<td>48</td>
<td>15%</td>
</tr>
<tr>
<td>Mirtazepine</td>
<td>35</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Total Antidepressant Trials</strong></td>
<td><strong>1250</strong></td>
<td><strong>19.5%</strong></td>
</tr>
</tbody>
</table>

After Truman (3).
This data shows that all types of treatment for depression are potentially dangerous when used in bipolar patients; on average, they cause a ‘switch’ in 1 out of every 5 patients treated. The table also highlights that the risk differs, depending on which treatment is used. However, it does not take into account the other adverse effects of the treatments. For example, the ‘safest’ treatment in terms of “switch”, nefazodone, is not used widely due to the rare but severe risk of hepatotoxicity. It would be of interest to carry out further research comparing the use of the overall safest antidepressant, for the shortest duration (with regular clinic appointments to determine the end of the depression accurately), compared to other treatment options and placebo.

It is interesting to consider the stance that different countries have taken on the literature available. The American and Canadian guidelines changed in 2002 to discourage antidepressant use in bipolar patients; in contrast, the European guidelines allow the use of antidepressants for the depressive phase of bipolar disorders. The current NICE guidelines state that treatment should only be started in moderate/severe depressive episodes and can be either a SSRI antidepressant or quetiapine (4).

How can the risk of Bipolar III be reduced?

The risk of “switch” with antidepressant treatment can be reduced by 60% by adding a mood stabiliser as illustrated by the table below.

<table>
<thead>
<tr>
<th>Without MS</th>
<th>With MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>351</td>
</tr>
<tr>
<td>Hypomanic/manic “switch”</td>
<td>33 – 68 %</td>
</tr>
</tbody>
</table>

However, this research does not consider whether it would be just as effective to use a mood stabiliser without the antidepressant or in combination with a different drug, for example, an antipsychotic (as advised in the NICE guidelines). This combination has been proved to be effective and is the first-line of treatment for bipolar depression with psychotic features (9). It could also be argued that the antidepressant itself has mood de-stabilising effects as antidepressants have been noted to push bipolar patients into a mixed state (10). Before prescribing an antidepressant it is also important to consider the type of patient because the ‘switch’ is more likely to happen in certain patients, as follows (11).

- Specific subtypes of bipolar - mixed episodes, rapid cycling courses. Low risk in bipolar II.
- Specific patients - comorbidities, a recent history of mania/hypomania, early beginning, psychotic features, a positive genetic load.

Conclusion

Treatment is based on a balance of risks. The aetiology of Bipolar III is iatrogenic and so it contradicts the guiding principle: “First, do no harm”. Antidepressants have not been proved to be superior to placebo or mood stabilisers combined with an antipsychotic for the treatment of bipolar depression. If a drug is ineffective and harmful to 1 in 5 patients then why use it? However, we cannot simply decide not to prescribe antidepressants, as in the correct context they have proven efficacy and cost-effectiveness. Clinicians need to gather as much information about the patient as possible to ensure that the risk of bipolar disorder is minimal. If there are traits suggestive of bipolar disorder, the risks and benefits of using an antidepressant must be weighed against those of other therapies. These are summarised in the following table.
How to prescribe antidepressants safely

If antidepressants are used to treat bipolar depression, start with a low dose and titrate up as required. The patient needs to be reviewed regularly (ideally every 2 weeks) so that the antidepressant can be stopped when symptoms improve. The antidepressant needs to be stopped as per the guidelines – when significantly less severe symptoms have been present for 8 weeks, start slowly to reduce the dose over several weeks while maintaining anti-manic medication (Royal College of Psychiatrists guidelines). Particular care is needed with venlafaxine and paroxetine as they are associated with a higher risk of withdrawal symptoms (NICE guidelines).

When diagnosing unipolar depression it is essential to take a longitudinal history, asking specifically about a history of any possible hypomanic/manic episodes. The mood disorders questionnaire can be of value in helping to elicit these elements of the history. This practice should facilitate the early diagnosis of bipolar disorder which should, in turn, assist the clinician in deciding on the possible risks and benefits of prescribing antidepressant medication. Whether hypomania/mania precipitated by the prescription of an antidepressant should be categorised as “Bipolar III” remains open to debate but there is no doubt about the importance of clinicians recognising the risk that elevated mood states may result from prescribing antidepressants in bipolar disorder.

GP Comment

What have I learned from this paper?

“Bipolar III” has been defined as a hypomanic/manic state induced by prescribing an antidepressant in a patient with bipolar disorder.

Although the diagnostic category of “Bipolar III” is not universally accepted, it remains important to be aware of the risk of antidepressant-induced hypomania/mania when prescribing for patients with bipolar disorder.

Mayruja Santhirakumar, GP Trainee

References

3. Truman et al, APA 2003
7. Serretti et al, Clinical features of antidepressant associated manic and hypomanic switches in bipolar


Rapid Cycling Bipolar Affective disorder: Diagnosis and management - A brief review

Madhavan Seshadri (1)  
Daniel Davies (2) (3)  
(1) SEPT: South Essex Partnership University NHS Foundation Trust  
(2) School of Clinical Medicine, University of Cambridge  
(3) Clare College Cambridge  

MS produced the data and an original draft  
DD edited the data and the draft.

Abstract

Bipolar affective disorders are highly prevalent in the general population. The course of bipolar affective disorder is characterised by episodes of mania or hypomania, and periods of depression. One clear-cut manic episode is enough for the diagnosis of bipolar disorder (according to DSM IV criteria) but many patients have two or more episodes. When a patient has 4 or more pathological mood episodes in one year, the course is defined as ‘rapid cycling’. It is important to identify rapid cycling in clinical practice as these patients do not respond as well to conventional treatment. Outcomes can be improved by a combination of management of risk factors for rapid cycling and the use of appropriate pharmacological intervention. This article focuses on the diagnostic criteria, clinical features, risk factors and management of rapid cycling bipolar disorder.  

Key words: bipolar disorder, rapid cycling, risk factors, treatment.

Introduction

Bipolar affective disorders are highly prevalent in the general population. European studies have reported a prevalence of between 0.1% and 2.4% (1,2,3,4,5). The course of bipolar affective disorder is characterised by episodes of mania or hypomania and episodes of depression. According to DSM IV criteria, one clear-cut manic episode is enough for the diagnosis of bipolar disorder (6). However, many patients have two or more manic episodes.

The term rapid cycling is used to describe a particular course of bipolar disorder. In 1974, Dunner and Fieve (7) studied a group of bipolar patients who had a poor response to lithium and other conventional treatments. Many of these patients experienced at least 4 episodes of mania and/or depression per year. They coined the term ‘rapid cycling’ to describe this particular pattern. These criteria were validated, incorporated and described in the DSM-IV (6) as a course specifier for bipolar disorder. Rapid cycling has not been described in ICD 10 (8). However many patients who fulfill the diagnostic criteria under ICD 10 code F38.00, i.e. mixed affective episode, are likely to fall into this category.

It is important to clarify the use of the term rapid cycling, because very rapid, i.e. daily alterations in mood episodes, have been described as rapid cycling as well as ultrarapid cycling and ultradian cycling (9) (the term ultradian refers to a cycle of shorter than 24 hours). The relationship between ultradian cycling and rapid cycling bipolar disorder is not yet clear. It is possible that ultradian cycling represents an acceleration of rapid cycling bipolar disorder.

Epidemiology

The prevalence of rapid cycling disorder varies from 13% to 56% of patients with bipolar disorder. This wide range reported could be due to many reasons (9). In particular:

a) The criteria for rapid cycling bipolar disorder could be interpreted differently; using less...
stringent criteria, more patients could be described as rapid cycling. b) The data are derived from studies on patients who are treatment resistant and are inpatients in tertiary care units, where rapid cycling is more common. Community studies across ten countries showed a 12-month prevalence of rapid-cycling bipolar disorder as 0.3% in the general population. Of patients diagnosed with bipolar disorder, 30-40% fulfilled criteria for rapid cycling. Rapid cycling bipolar disorder was associated with younger age of onset, more severe depressive symptoms, increased number of lifetime episodes and persistence of symptoms. With an increase in the number of depressive episodes experienced, there is an increased risk of suicide. Important predictors for suicide are the change from a manic or hypomanic to a depressive episode.

Table: 1 Diagnostic criteria for rapid cycling bipolar disorder

1. The patient should have presented with clinical features meeting the criteria for bipolar disorder
2. There should have been at least 4 discrete mood episodes in the past year; these could be manic, hypomanic or depressive episodes.
3. Between the episodes there should have been a remission period of 2 months or a switch of mood episode to the opposite pole e.g. depression to mania or hypomania.
(Adapted from: Diagnostic and Statistical Manual of Mental Disorders DSM IV. American Psychiatric Association, 2000.)

Table: 2 Risk factors associated with rapid cycling bipolar disorder

1. Bipolar II disorder.
2. Depressive episode in bipolar disorder.
3. Antidepressant therapy for depression in bipolar disorder.
4. Comorbid alcohol and substance misuse.
5. Significant life events.
7. Hypothyroidism.
8. Female sex.
10. Number of previous episodes.

Aetiology of rapid cycling

The aetiology of rapid cycling bipolar disorder remains unclear. Studies investigating the development of this disorder have so far failed to identify genetic factors that differentiate rapid cycling from non-rapid cycling bipolar disorders. Biological factors, such as like medical illnesses, hypothyroidism and substance misuse, are associated with an increased risk of rapid cycling bipolar disorder. Among the hypotheses for rapid cycling pathoaetiology, two of the most commonly accepted are kindling and sensitisation.

1. Studies have shown that the risk of rapid cycling increases with the number of previous episodes. Post et al. (11) analysed this subset of patients and found that, initially, relapse of episodes was associated with similar social circumstances or life events and the presenting symptoms were similar. As the illness progressed, these episodes started to occur more spontaneously. This was similar to the kindling phenomenon seen in animal models of epilepsy. The hypothesis is that changes occur in the brain with psychosocial stressors leading the precipitation of mood episodes. After a few episodes, these brain changes might persist, leading to spontaneous mood episodes. The changes could be
electrophysiological or neurochemical.

2. Sensitisation is a learning phenomenon in which repeated exposure to a stimulus heightens the 
behavioural response to it. It is best understood in drug abusers, especially amphetamine users. 
With repeated use of amphetamines there is an exaggeration of behavioural responses to the drug 
and to drug associated stimuli. The phenomenon of sensitisation is also studied with respect to 
antidepressants.

In bipolar disorder, repeated exposure to psychosocial stressors may cause sensitisation, resulting in 
greater shift in mood and perhaps contributing to the development of rapid cycling (11).

Management

Rapid cycling disorder is a complex phenomenon and studies examining long-term treatments show 
less favourable outcome than in non-rapid-cycling bipolar disorder (12). 
A diagnosis of rapid cycling should not be made without first excluding thyroid dysfunction, 
antidepressant-induced mood switching, suboptimal medication regimes and poor compliance with 
medication (13).

Treatment for bipolar disorder aims to reduce the severity of symptoms, stabilise mood and prevent 
relapse.

The optimal choice of drug depends on individual variation and response, such as the experience 
of adverse effects or mood switching. NICE guidelines recommend a combination of lithium and 
valproate as first-line treatment. However, there are specific considerations for patients with rapid 
cycling.

Most important, the focus should be on prevention of treatment-induced switching from one pole to 
another and on long-term outcomes, rather than treating individual episodes. 
Many patients with rapid cycling bipolar disorder fall into the category of bipolar II and a high 
proportion of these patients are likely to be taking a combination of mood stabilisers and 
antidepressants. Antidepressant therapies have been associated with mood switching; treatment 
regimes should seek to avoid mood switching in rapid cycling bipolar disorder. NICE guidelines 
suggest antidepressants should not be used in individuals with rapid cycling, but rather recommend 
an increase in dose of an anti-manic agent or the addition of another mood-stabilising agent such as 
lamotrigine. If antidepressants are used in rapid cycling, these should be reviewed and stopped when 
no longer necessary, i.e. when in remission after a depressive episode, to reduce the risk of inducing 
mania.

Trials of medications should last at least 6 months, unless severe adverse effects are experienced. This 
reduces the risk of inducing rapid mood switching. 
A specific history of possible risk factors should be taken. These are listed in Table 2, and include 
substance misuse or comorbid medical conditions. The patient should, with appropriate support, try 
to minimise, manage or eliminate any risk factors.

Course and Prognosis

Rapid cycling bipolar disorder responds poorly to pharmacological management. Although the 
STEP-BD study (14) reported that out of 1742 patients who entered the study with a diagnosis of rapid 
cycling bipolar disorder, only 5% experienced four or more discrete mood episodes over the next year, 
it should be noted that 61% of rapid cycling patients did experience between one and three discrete 
mood episodes in the next year. A younger onset of disease, more severe initial symptoms and the use 
of antidepressants were associated with an increased likelihood of experiencing a mood episode in 
the follow-up year. These results suggest that cycling may represent a continuum and that treatment 
may reduce the rate at which cycling occurs. Only a small proportion of patients still qualified as ‘rapid 
cycling’ after a year, but care should still be taken to avoid medication-induced mood switching, even 
when the patient no longer appears to be rapid cycling. This evidence is also in accordance with NICE
guidelines that warn against the use of antidepressant therapies in individuals with rapid cycling.

Conclusion

Rapid cycling refers to one particular course of bipolar disorder. Rapid cycling bipolar disorder responds poorly to medication and many of these patients have comorbid medical conditions. Minimising the use of antidepressants and increasing the use of antimanic agents may reduce the frequency and severity of the pathological mood episodes.

GP Comment

What have I learned from this paper?

Patients with rapid cycling will inevitably be heavy users of both primary and secondary care services and so identifying such patients and providing early intervention are vital.

I was interested to note the association with hypothyroidism, antidepressant-induced mood switching and sub-optimal medication regimes. Such patients need close co-operation between GPs and mental health services.

Dr Stephen Cakebread, GP, Bedfordshire.

References

7. Clinical Factors in Lithium Carbonate Prophylaxis Failure David L. Dunner, MD; Ronald R. Fieve, MD Arch Gen Psychiatry 1974;30 (2):229-233.
Some somatic symptoms are important evidence for an early diagnosis of bipolar spectrum mood disorders

Giuseppe Tavormina, M.D.
President of “Psychiatric Studies Centre” (Cen.Stu.Psi.)
Piazza Portici, 11 - 25050 Provaglio d’Iseo (BS) – Italy
E-mail: dr.tavormina.g@libero.it

Abstract

Patients with bipolar disorder often present with somatic symptoms, including colitis, gastritis, eczema, psoriasis and migraine. The identification of these symptoms is a very useful aid to early diagnosis of bipolar disorder.

Key words: bipolar spectrum, colitis, gastritis, eczema, psoriasis, migraine.

Bipolar patients are often misdiagnosed and undertreated or inappropriately treated (1) (2) (3). Patients with bipolar spectrum disorder are more prevalent than was previously thought (8) (9). Such patients very often present with somatic symptoms (“somatizations”), and a high percentage these symptoms are misdiagnosed or mistaken for somatic symptoms caused by organic diseases. Instead, the internal tension, the agitation and the emotional lability of patients with a bipolar diagnosis are the cause. In a study of 423 patients, only 20% did not present any somatization at their “first visit”; almost all of this “no-somatization” group were men, only 16% were women (12).

The consequence of these somatic symptoms being misdiagnosed and mistaken for physical illness is typically a long series of blood and instrumental tests, which are often of no value in the management of the patient. However, in the case of colitis, it is important that, on at least the first occasion, the patient be appropriately investigated to exclude organic illness. Baig has presented evidence in the 2012 European Psychiatric Congress about the relationship of colitis to affective disorders (4). Eczema and psoriasis may, like colitis, be associated with bipolar disorder, because of the association between inflammation and affective disorders (5) (6). Furthermore, migraine has genetic links with bipolar disorder (7).

The chronic presence in the life of the patients of some somatizations (the above colitis, gastritis and migraine but also including an increase of psoriasis and eczema reactions) are key symptoms that should alert the psychiatrist and/or the GP to the possibility of an early diagnosis of bipolar spectrum mood disorder (12). Treatment of the bipolar disorder may improve the somatic symptoms.

In an observational study on a group of 423 patients, 161 men and 239 women (12) (15), all the somatic symptoms disappeared during pharmacological treatment of their bipolar mood disorders, except for some residual and soft symptoms that periodically increased together with other mood disorder symptoms during phases of exacerbation of the bipolar disorder.

The subthreshold presence of hyperthymic, dysthymic and cyclothymic temperaments (10-13) revealed in the history of the patients with bipolar spectrum disorders allows us to consider their presence as an important means of early diagnosis of the bipolar disorder. However, the chronic presence in the life of the patients of some of the somatic/somatization symptoms which we have described (above all, colitis, gastritis and migraine) are very important pointers that can lead to an early diagnosis of bipolar spectrum mood disorders. Early diagnosis of bipolar disorder is important because there is a public health issue regarding the correct diagnosis: the failure to treat bipolar mood disorders may sometimes result in serious consequences: not only impaired quality of life but also increased risk of suicide (14).
GP Comment

What have I learned from this paper?

Before presenting with an obvious diagnosis of bipolar disorder, patients may come with symptoms of colitis, gastritis and migraine. If there is any suggestion that these symptoms might be accompanied by a mood disorder, I shall now seek a psychiatric opinion so that the treatment of bipolar disorder, if this diagnosis is confirmed, is not unnecessarily delayed.

Mayruja Santhirakumar, GP Trainee.

References

Bipolar spectrum: somatizations in 400 pt.

- Migraine: 8%
- Gastritis: 25%
- Colitis: 45%
- Other somat.: 2%
- No somat.: 20%
Mixed affective state: a diagnostic and therapeutic challenge

Singh S1, Ho JYH2, Agius M3

1Dr Saurabh Singh BA (Hons), MB BChir, Department of General Surgery, Barnet and Chase Farm Hospitals NHS Trusts, London.
2Dr Jasmine H Y Ho, BA (Hons)MB BChir, Department of Paediatrics, National University Hospital, Singapore.
3Dr Mark Agius MD., Department of Psychiatry, University of Cambridge, South Essex Partnership University Foundation Trust. Clare College Cambridge.

Abstract

Mixed affective states are important phases in bipolar affective disorder. This paper describes the nature of these states and their importance, which is because of the increased risk of suicidal thoughts and actions. Stopping antidepressants, optimising treatment with mood stabilisers and adding an atypical antipsychotic to treatment is effective in treating mixed affective states, reducing suicidal ideation and actions.

Key words: mixed affective state, mixed bipolar depression, dysphoric mania, antidepressants, management of mixed affective state, antipsychotics

The mixed affective state remains both a diagnostic and therapeutic challenge. In mixed affective states, patients experience both symptoms of depression and mania. It is widely accepted that these patients exhibit an increased risk of suicide. Although it is recognised that these states are important, there is no adequate consensus on the diagnostic criteria or management.

Many terms including ‘mixed affective state’, ‘dysphoric mania’, ‘mixed bipolar depression’ and ‘agitated depression’ have been used in the literature. These terms allude to different proportions of manic and depressive symptoms that may be classified into three phenotypes; mixed affective episodes (when the proportion of manic and depressive symptoms is equal), dysphoric mania (when manic symptoms are prominent), and mixed (bipolar) depression (when depressive symptoms predominate). These phenotypes are generated because both mania and depression are active processes that can occur both successively and simultaneously (1) (2). Furthermore, agitated depression can be reconceptualised as an affective mixed state (3).

Evidence for a spectrum which encompasses such states is provided by Akiskal et al. (3) who showed that a significant percentage (19.7%) of patients diagnosed with Unipolar depression (n=254) experience ‘agitated depression’. In addition, those 19.7% showed a strong clustering of ‘non-euphoric hypomanic’ symptoms, which suggests a bipolar spectrum link. In fact, Tavormina et al. showed that 28% of bipolar patients had agitated depression (n=300) (4). The overlap in the symptomatology in such patients suggests that mixed affective states are part of the bipolar affective disorder spectrum. Indeed, mixed states can be thought of as transition states between manic and depressive episodes. The notion of a “bipolar spectrum” appeared in the literature in a 1977 paper on a prospective follow-up of cyclothymic individuals (5). Akiskal et al. conceptualised unipolar and bipolar mixed states as ‘depressive mixed state’ and a part of the bipolar affective spectrum (3).

A conceptual model was proposed by Rhimer et al. who described three entities produced by the combination of two different outputs from two distinct ‘mood generators’ (1). The manic mood generator produces a manic mood and a depressive mood generator a depressed state. When the dominant input is from the manic mood generator with a smaller input from the depressive mood generator; a state of ‘dysphoric mania’ is produced. Conversely, in ‘mixed bipolar depression’ the depressive mood generator dominates over the manic. Equal inputs from both mood generators produce the ‘mixed affective state’.

Several studies have shown that patients have a high risk of suicide when in a mixed affective state (6). Therefore clinically it is imperative to find strategies to resolve mixed states quickly. Balázs J et al.
showed that psychomotor agitation and irritability are strong predictors of increased suicide risk (6). There is scant literature about the management of mixed states. A few principles emerge from the limited studies available. The need to discontinue antidepressants is apparent (7). Logically there is a need to stabilise the mood and among mood stabilisers, divalproate has been more effective (7). There is little evidence on the use of adjuncts. A recent case series suggested three-pronged regimens, including increasing/addition mood stabilisers and/or increasing/addition antipsychotics as well as decreasing antidepressants (8).

From reviewing the literature, a mixed affective state should be considered when symptoms of mania and depression occur; especially agitation, insomnia, changes in appetite, psychotic symptoms and suicidal ideation (ICD-10: F31.6, DSM-IV: 296.6x). Agitation is a powerful predictor of increased suicide risk.

If a patient experiences such a mental state, it is likely they lie on the bipolar affective disorder spectrum. Hence it is important to take a longitudinal history, screening for hypomanic and manic episodes. Given an increased risk of suicide, a comprehensive suicide risk assessment is necessary. As already discussed, three treatment strategies emerge from the literature which could be used simultaneously. In essence, it is necessary to decrease or discontinue medication that may push the patient’s mood in one direction, for example antidepressants, and also stabilise the mood. If a patient is on an antidepressant then a decreasing and subsequent discontinuing it is helpful. To stabilise the mood, if a patient is currently on a mood stabiliser, the dose should be increased. If not, then a mood stabiliser such as divalproate should be started. Because of the necessity of stabilising the mood, an adjunct such as an antipsychotic may be required.

Regular review is necessary to screen for adverse effects and to assess suicide risk. The following algorithm summarises our recommendations (Depakote=semisodium valproate=divalproate, Antiψ = Antipsychotic drug).
GP Comment

What have I learned from this paper?

I was interested to learn that agitated depression is part of the bipolar spectrum and associated with a high risk of suicide. Also that it is best treated, not with antidepressants but with mood stabilisers. These facts would encourage me to refer these patients early to the mental health services.

Dr Stephen Cakebread, GP, Bedfordshire.

References

Part 5. Treatment of Bipolar Disorder

Treatment of acute mania: an article for the General Practitioner

Dr Olivia Balding MBBS and Dr Soosamma Varghese MBBS, MD Psychiatry, PhD.

Abstract

Guidance, mainly intended for GPs, is provided on the treatment of acute mania. Mania is a state of elevated mood and excitable behaviour. Elevated mood can be classified as hypomania or mania, depending on severity. The treatment depends upon whether the patient is already on antimanic drugs. If a patient is not taking any antimanic medication then the first-line treatment is with an antipsychotic or a mood stabiliser such as lithium or valproate. Benzodiazepines can also be used at initial presentation if required. If the patient is already on antimanic medication then either dose increments of existing medication or the addition of adjuvant medication should be considered. Depot antipsychotic medication is also an option if compliance with oral medication is an issue. This article will expand on all of these options and provide further discussion on the subject of acute mania management.

Key Words: mania, hypomania, bipolar affective disorder, antipsychotic, mood stabilisers; lithium and valproate.

Introduction

The aim of this paper is to provide a succinct and useful guide on the treatment of acute mania. We discuss the causes and presentation of mania/hypomania and the treatment of the acutely manic patient. This includes guidance on when to refer to specialist psychiatric services and when management within the community will suffice.

What is mania?

Mania is a state of elevated mood, characterised by irritability, excess anger and/or happiness. The patient has high levels of energy and may put themselves or others at risk. They may also exhibit delusional beliefs; most commonly grandiose in nature. Dependent on the severity of the symptoms, this can be described as either hypomania or mania. Hypomania is a disorder characterised by a persistent mild elevation of mood, increased energy and marked feelings of wellbeing. There is typically increased sociability, talkativeness and a decreased need for sleep but not to the extent that these characteristics lead to severe disruption of work or result in social rejection. There is no clear psychosis in hypomania. In mania the mood is elevated out of keeping with the patient’s circumstances and may vary from carefree joviality to almost uncontrollable excitement. The patient may also act in a disinhibited manner. Signs include pressure of speech, flight of ideas and loose associations. Self-esteem is often inflated, with grandiose ideas and overconfidence. Psychotic symptoms can be present in mania; and they can be defined as either mood-congruent or mood-incongruent.

Causes of mania

There are few causes of mania. The patient may have an affective disorder; in this instance mania is most commonly associated with bipolar affective disorder (ICD-10 F31), where periods of mania alternate with periods of severe depression. For the diagnosis of bipolar affective disorder to be made there must be two or more episodes in which the patient’s mood and activity levels are significantly...
disturbed. Where a patient presents with first-episode mania and no previous depressive episodes the diagnosis of Mania (ICD-10 F30) can be made. This diagnosis exists as some patients have only one episode of mania, without recurrence.

Other causes include drug-induced mania, commonly due to stimulants, such as cocaine; or as an adverse effect of medications, including antidepressants and steroids. Thyroid dysfunction can also induce a state of mania.

**Treatment**

There are extensive options for the treatment of acute mania. It is of the utmost importance to understand these medications and which are used as the first line.

**Treatment of acute mania and hypomania**

The drug treatment depends on the severity of symptoms and whether the patient is currently taking antimanic drugs. Clinicians should be guided by current medication doses and previous response. Only lithium, olanzapine, quetiapine, risperidone and valproate semisodium (Depakote) are licensed for the treatment of acute mania in the UK.

(i). General advice

To help reduce the negative consequences of manic symptoms, healthcare professionals should consider advising patients to avoid excessive stimulation, to engage in calming activities, to delay important decisions and to establish a structured routine, incorporating regular sleep and reduced activity levels.

If a patient is taking an antidepressant at the onset of an acute manic episode, the antidepressant should be stopped. The discontinuation of the antidepressant can be gradual, depending on the patient’s current clinical need and previous experience of discontinuation/withdrawal symptoms from that antidepressant.

(ii) Drug treatment for those not taking antimanic medication.

a) Options include starting an antipsychotic, valproate or lithium.

Consider:

- Prescribing an atypical antipsychotic if there are severe manic symptoms or marked behavioural disturbance. However, in the initial stage, if there is severe agitation, prescribing a first-generation antipsychotic (typical) such as haloperidol or chlorpromazine is advised.
- Prescribing a mood stabiliser such as valproate or lithium if the symptoms have responded to these drugs before.

b) In the initial management of acute behavioural disturbance or agitation, the short-term use of a benzodiazepine (such as lorazepam or diazepam) should be considered.

c) If treating acute mania with antipsychotics; olanzapine, quetiapine or risperidone should normally be used, and the following should be taken into account:

- Individual risk factors for adverse effects.
- The need to initiate treatment at the lower end of the therapeutic dose range.
- If an antipsychotic proves ineffective, augmenting it with valproate or lithium should be considered.

d) Carbamazepine should not be routinely used for treating acute mania. Gabapentin, lamotrigine and topiramate are not recommended.
e) Drug treatment for those already taking antimanic medication:

- If a patient is already being treated with any antipsychotic, the dose should be increased if necessary. If there is no improvement following this, the addition of lithium or valproate should be considered.
- If a patient already taking lithium has a manic episode, plasma lithium levels should be checked. If levels are suboptimal (<0.8 mmol/L) the dose should normally be increased to a maximum blood level of 1.0 mmol/L, provided there are no unacceptable adverse effects. If the response is not adequate, augmenting lithium with an antipsychotic should be considered.
- If a patient is already taking valproate the dose should be increased until either the symptoms improve or adverse effects restrict further dose increments. If there are no signs of improvement, the addition of olanzapine, quetiapine or risperidone should be considered. Patients taking >45 mg/kg should be monitored carefully.

NB – If quetiapine is used it should be at a high dose, as lower doses are recommended in the treatment of depression and can induce mania.

d) For patients already taking lithium or valproate, adding an antipsychotic should be considered at the same time as gradually increasing the dose of lithium or valproate.

e) If any of the oral atypical antipsychotics are not producing the desired effect, then an antipsychotic depot injection, such as zuclopenthixol or flupenthixol should be considered.

f) For patients who present with mania when already taking carbamazepine, the dose should not routinely be increased. Adding an antipsychotic should be considered, depending on the severity of mania and the current dose of carbamazepine. Interactions with other medications are common with carbamazepine, and doses should be adjusted as necessary.

g) The use of ECT is only considered to achieve rapid and short-term improvement of severe symptoms. It is only used rarely, in cases of prolonged or severe mania. This, however, would only be considered once the patient has been assessed by a specialist.

Special attention

Valproate should not be prescribed routinely for women of child-bearing potential. If no effective alternative is available, adequate contraception should be used and the risks of taking valproate during pregnancy should be explained.

If a pregnant woman develops acute mania an atypical or typical antipsychotic should be considered. The dose should be kept as low as possible and the woman monitored carefully.

(iii). Drug treatment of acute mania in children and adolescents

When prescribing medication for children or adolescents with an acute manic episode, the recommendations for adults, as discussed above, should be followed. The only difference is that drugs should be initiated at lower doses. At initial presentation:

- Height and weight should be checked (and monitored regularly).
- Prolactin levels should be measured.
- When considering an antipsychotic, the risk of increased prolactin levels with risperidone and weight gain with olanzapine should be considered.
- Where there is an inadequate response to an antipsychotic, adding lithium or valproate should be considered. Valproate should normally be avoided in girls and young woman because of risks to the foetus during pregnancy and risk of polycystic ovary syndrome.

Drug treatment after recovery from an acute episode.

1. Prescribers should consider starting long-term treatment for bipolar disorder:
• After a manic episode that was associated with significant risk.
• When a patient with bipolar I has had two or more acute episodes.
• When a patient with bipolar II has significant functional impairment, risk of suicide or rapid cycling.

2. Lithium, olanzapine or valproate should be considered for long-term treatment of bipolar disorder. The choice should depend on:

• Response to previous treatment.
• Relative risk.
• Known precipitants of manic versus depressive relapse.
• Physical risk factors (particularly renal disease, obesity and diabetes).
• The patient’s preference.
• History of adherence.
• Gender.
• A brief assessment of cognitive state (MMSE).

If oral treatment fails, then consider antipsychotic depot medication.

3. If the patient has frequent relapses or symptoms continue to cause functional impairment, switching to an alternative monotherapy or adding a second prophylactic agent (lithium, olanzapine or valproate) should be considered. Possible combinations are:

• Lithium with valproate.
• Lithium with olanzapine.
• Valproate with olanzapine.

4. If a trial of a combination of prophylactic agents proves ineffective, the following should be considered:
• Consulting with, or referring the patient to a clinician with expertise in the drug treatment of bipolar disorder.
• Prescribing lamotrigine (especially is the patient has bipolar II disorder) or carbamazepine.

Long-term drug treatment should normally continue for at least 2 years after an episode of bipolar disorder and up to 5 years if the person has risk factors for relapse. This should be discussed with the patient and there should be regular reviews. Patients who wish to stop medication early should be encouraged to discuss this with their psychiatrist.

**Psychological therapy after recovery from an acute episode**

Psychological interventions should be considered for people with bipolar disorder who are relatively stable but experiencing mild to moderate affective symptoms. The patient must possess the necessary motivation for this therapy to be successful. The therapy should be in addition to prophylactic medications and be at least 16 sessions over 6-9 months. It should include psychoeducation about the illness, mood monitoring and enhance general coping strategies.

Focused family intervention could also be of value. This should also take place over 6-9 months. It should include psychoeducation, ways to improve communication and problem solving.

**When to admit**

Admission to an inpatient unit should be considered for patients with bipolar disorder at significant risk of harm to themselves or others. The unit should provide facilities for containment within a supportive, low-stimulation environment, including access to a psychiatric intensive care unit. The inpatient service should seek to provide an emotionally warm, safe, culturally sensitive and supportive environment, with high levels of positive engagement between staff and patients.
Acute day hospitals should be considered, as an alternative to inpatient care and to facilitate early discharge from inpatient care.

Admission for children and adolescents should be considered for those at risk of suicide or other serious harm.

**Conclusion**

The diagram below gives a summary of all of the main treatment options discussed within this article. It serves as a quick, easy visual reference to use in clinics. When all of the treatment options discussed here have been tried without positive effect or if the patient is at extreme risk then they must be referred to the psychiatric services.

**GP Comment**

**What have I learned from this paper?**

This was a good paper to read right through. It was very clear and gave a basic working knowledge about management of acute mania in primary care, providing most of the answers to common management problems faced in day to day practice.

The comprehensive treatment plans have been presented in a very simplified manner.

**Dr Roshan Jayalath, GP.**

**References**

1. ICD-10 Classification of Mental and Behavioural Disorders, Churchill Livingstone.
Lithium therapy - from monitoring to shared care

Helen Wear, Guy's Hospital London.
Clare Holt, Kingston Hospital.
Mark Agius, South Essex Partnership University Trust; Clare College, Cambridge; Department of Psychiatry, University of Cambridge.

Abstract

Lithium is a mood stabiliser that is generally regarded as ‘gold standard’ for the treatment of bipolar affective disorder. However, lithium has a narrow therapeutic index. This necessitates regular testing of lithium levels as well as of renal and thyroid function, which can be affected by chronic lithium use. An audit was conducted by the Bedfordshire Community Mental Health Team (BCMHT) to investigate the monitoring of lithium therapy. Blood tests (for lithium levels, renal function and thyroid function) were conducted more infrequently than is currently recommended. However, there was also some evidence for alternative explanations for the apparent lack of monitoring, such as the fact that blood tests were now being conducted by GPs rather than psychiatrists. Lithium therapy falls into the remit of shared care: the responsibility for the management of patients is shared between hospital specialists and GPs. One tool to improve communication between the various teams involved in patient care is the shared-care card.

Key words: lithium, bipolar affective disorder, drug monitoring, shared-care.

Background

Lithium is the ‘gold-standard’ mood stabiliser for the treatment of bipolar affective disorder. However, strict monitoring is required, both of lithium levels and of other biochemical markers such as renal function (urea and creatinine) and thyroid function tests. This is because lithium has a narrow therapeutic index: too high a level leads to toxicity, while too low a level will not be effective.

Current recommendations are that lithium levels are checked every three months and lithium dosing adjusted accordingly, to maintain a serum lithium concentration of 0.4 to 1.0 mmol/l. Note that the lower end of the treatment range is preferable in the context of maintenance therapy and in the treatment of elderly patients. In addition, both renal function and thyroid function tests should be performed every six months.

In terms of renal effects, the most common association with lithium is nephrogenic diabetes insipidus, which typically presents as polyuria and polydipsia and is due to a failure of the kidneys to respond to antidiuretic hormone (ADH), which controls water re-absorption in the collecting ducts. Hypothyroidism is the most frequent endocrine implication of long-term lithium use and appears to be primarily due to inhibition of the release of thyroid hormones (T3 and T4).

Lithium monitoring in practice

The clear recommendations for monitoring blood tests in patients on lithium therapy mean that, at least in theory, monitoring should be relatively straightforward to implement. However, an audit conducted by the Bedfordshire Community Mental Health Team (BCMHT) provides an illustration of some key areas of difficulty with the practicalities of lithium monitoring. Details of the methods and results of this audit are outlined below.

Methods

The target population was patients being treated by a community mental health team (the BCMHT) with a catchment area of 60,000 population. A database of all patients attending outpatient...
psychiatric appointments at Bedford Hospital was used to identify patients for inclusion in the audit. At the time of the audit, there were 69 patients with bipolar affective disorder out of a total of 500 patients with any psychiatric disorder being treated by the BCMHT. Of these 69 patients, 19 were receiving lithium therapy. For each of the 19 patients, the paper notes were reviewed and all monitoring blood tests, i.e. lithium blood levels, renal function tests and thyroid function tests, carried out over a two-year period (January 2006 to January 2008) were recorded.

Results

a) Recording of lithium levels

Graph 1

![Graph 1](attachment://last_recorded_lithium_level.png)

Graph 2

![Graph 2](attachment://lithium_levels_from_jan_2006.png)

The target was that all patients should have a recorded lithium level within the last three months and that all patients should have eight recorded lithium levels over a two-year period, starting in January 2006, in line with recommendations for three-monthly lithium monitoring. Graphs 1 and 2 clearly illustrate the failure to meet these targets. Only 7/19 patients had recorded lithium levels within the last three months, and only 3/19 patients had eight or more recorded lithium levels over the two-year period.
b) Recording of thyroid function tests

Graph 3

The target was that all patients should have recorded thyroid function tests within the last six months and that all patients should have four recorded thyroid function tests over a two-year period starting in January 2006, in line with recommendations for six-monthly monitoring of thyroid function tests. As with the monitoring of lithium levels, targets were not met. Only 7/19 patients had recorded thyroid function tests within the last six months (graph 3) and only 4/19 patients had four or more recorded thyroid function tests over the two-year period.

c) Recording of renal function tests
The target was that all patients should have recorded renal function tests within the last six months and that all patients should have four recorded renal function tests over a two-year period starting in January 2006, in line with recommendations for six-monthly monitoring of renal function tests. Once again these targets were not met. Only 8/19 patients had recorded renal function tests within the last six months and only 6/19 patients had four or more recorded renal function tests over the two-year period.

**Interpretation**

The obvious conclusion is that all aspects of lithium monitoring were consistently carried out more infrequently than is currently recommended for patients on long-term lithium therapy. However, there are alternative explanations for the apparent failure to carry out monitoring. For example, blood tests may have been performed but the results may either never have been documented in the notes or may have simply been recorded as normal rather than the actual level being stated in the notes. Also, it is possible that doctors other than psychiatrists (i.e. general practitioners) may have taken over responsibility for lithium monitoring.
The above graphs provide support for ‘alternative explanations’ accounting, at least in part, for the apparent lack of recorded lithium blood-level results. According to graph 7, 12/19 patients had lithium levels measured but the results were then not adequately documented in the notes. According to graph 8, for 11/19 patients the psychiatrist had asked the GP to take over the monitoring of lithium levels.

Taking all the results together it would appear that while lithium monitoring was indeed carried out less frequently than recommended, it was also under-reported. This highlights the need for both better documentation in the notes and improved communication between psychiatrists and GPs.

Moving forward – the need for coordinated shared care

Lithium monitoring falls into the remit of shared-care: the responsibility for the management of patients is shared between hospital specialists and community GPs. While psychiatrists continue to review patients with bipolar affective disorder being treated with lithium therapy, GPs often take on the monitoring of lithium levels. However, as the audit indicated, when this happens, psychiatrists are not always aware of the results of blood tests arranged by GPs. The narrow therapeutic index of lithium has already been discussed. This implies that there is a high potential either for under-treatment or for toxicity if the blood levels are not within the recommended range. Unless the
psychiatrist responsible for adjusting the dose of the lithium is aware of the blood level results and 
also of the results of the renal and thyroid function tests, patient safety could be compromised. 
Good communication between the psychiatrist and the GP is essential if risks to the patient are to be 
minimised.

One tool to facilitate communication between GPs and hospital specialists is the shared-care card. 
This is a card for recording test results, which the patient takes both to the GP and to hospital 
outpatient appointments. The results of any tests carried out by the GP can subsequently be viewed 
and documented by the hospital doctors. The use of shared-care cards is not confined to psychiatry. 
For instance, they are given to rheumatology patients on disease modifying drugs (DMARDs) such as 
methotrexate and gold, which, like lithium, have a narrow therapeutic index and can lead to toxicity.

A lithium pack, including a shared-care card and psycho-education material, has now been 
implemented by the Department of Health for patients on long-term lithium therapy. However, prior 
to this development, the BCMHT had already introduced a shared-care card at a local level and a 
sample of this card is included for reference.

**GP Comment**

**What have I learned from this paper?**

Because lithium has a narrow therapeutic index, regular blood monitoring is necessary, not only 
to check that the lithium blood level is in the right range but also to ensure that renal and thyroid 
function are not compromised.

Good communication between the GP and the hospital psychiatrist is essential if the results of blood 
monitoring are to be used fully for safe and effective lithium treatment. Communication can be 
facilitated by the use of a shared-care card, carried by the patient and taken to appointments both 
with the psychiatrist and with the GP.

**Mayruja Santhirakumar, GP Trainee.**

**References**

The Treatment of Bipolar Depression

Dr Jenny Hopwood (1) and Dr Mark Agius (2) (3) (4)
(1) Eastern Deanery
(2) Department of Psychiatry University of Cambridge
(3) South Essex Partnerships University NHS Trust.
(4) Clare College Cambridge

Abstract

The treatment of bipolar disorder, including management of mania and depression in primary and secondary care, is well described in the NICE guidance on this subject1. This article summarises and updates the guidance on the treatment of bipolar depression, describing the use of mood stabilisers in combination with antidepressants as well as the use of quetiapine and lamotrigine and thus provides practical advice on how bipolar depression can be managed in primary care.

Key words: bipolar disorder, bipolar depression, treatment, primary care, NICE

Key points

• Patients with bipolar depression should not be prescribed antidepressants alone due to risk of switching into mania and causing rapid cycling or mixed states, with increased risk of suicide.
• When prescribing an antidepressant, a mood stabiliser should also be prescribed.
• Antidepressants should be given during the depressive phase only and stopped when a patient is in remission from depression.
• Alternatives to antidepressants include lamotrigine and quetiapine; the latter is recommended in pregnant women.

Bipolar depression is an episode of depressive symptoms occurring on a background of mania or hypomania with previous depressive episodes. It is important to distinguish the management of bipolar depression from that of unipolar depression, as it is somewhat different. Often bipolar depression is misdiagnosed and managed as unipolar depression. It is important to avoid this misdiagnosis by taking a thorough history enquiring about previous manic or hypomanic episodes (2,3).

For many people with bipolar disorder the predominant experience of their illness is low mood and depression. Patients may tell professionals that the depression phase of bipolar disorder is of very severe intensity and is very debilitating, impacting profoundly on themselves and their families (2). During this depressive phase, patients often have atypical features, such as tendency to overeat for comfort and to sleep more than usual, especially during the day.

The treatment of bipolar depression differs from unipolar depression in that people with bipolar depression should not be prescribed antidepressants alone1. Patients treated with antidepressants only may be ‘switched’ into mania, rapid cycling or mixed states (4), with increased risk of suicide. Therefore antidepressants should be prescribed with a mood stabiliser. NICE also advises that antidepressants should only be prescribed during the depressive phase and should be stopped once the patient is in remission from depressive symptoms or when symptoms have been significantly less severe for eight weeks1. The dose of antidepressant should be reduced gradually over several weeks, while maintaining the mood stabiliser.

NICE guidance advises that if a patient is already taking a mood stabiliser and presents with an acute depressive episode, initially the dose of the mood stabiliser should be assessed to ensure that it is optimal. Lithium, as well as being a mood stabiliser, also has antidepressant properties, so it can contribute to treating bipolar depression5. If the patient has mild symptoms and is not considered to be at risk of developing severe symptoms, a ‘watchful waiting’ approach can be considered with...
regular review. If symptoms are moderate or severe and the patient is already taking a dose-optimised mood stabiliser, prescribing an SSRI can be considered. Any patients started on an antidepressant should be reviewed regularly.

When an antidepressant is initiated, patients should be warned about a number of possible consequences:

- The possibility of switching to hypomania or mania
- The fact that it can take “at least” two weeks for antidepressants to have an effect.
- The risks of stopping the medication and the need to take it as prescribed.
- The need to monitor for suicidal ideation, anxiety, agitation and akathisia.
- The need to seek help promptly for distressing adverse effects

Antidepressants should be avoided for patients with depressive symptoms who have rapid-cycling bipolar disorder, a recent hypomanic episode or recent functionally-impairing rapid mood fluctuations. NICE instead advises optimising the dose of mood stabiliser or the addition of a second mood-stabilising agent.

There is some evidence that antidepressants may be less effective in relieving depressive symptoms in patients with bipolar depression than in unipolar depression. If the depression is not adequately treated with an antidepressant in combination with a mood stabiliser, lamotrigine or quetiapine can be used. There is considerable data for the efficacy of these two medications and quetiapine is recommended by NICE for severe bipolar depression which is not responding to antidepressants alone. For moderate to severe bipolar depressive symptoms in pregnant women, quetiapine alone, or SSRIs (but not paroxetine) in combination with a mood stabiliser (but not valproate and preferably not lithium because of the risk of teratogenesis) can be used. These women should be monitored closely for signs of switching and the SSRI should be stopped if manic or hypomanic symptoms develop.

In summary, the management of a depressive episode in bipolar disorder is initially to recognise that this is bipolar depression rather than unipolar depression, to give antidepressants only in conjunction with mood stabilisers and to use atypical antipsychotics, particularly quetiapine, or to prescribe lamotrigine for those not responding to treatment. The importance of regular review and promptly stopping antidepressant medication following remission to prevent switching to mania has been highlighted.

**GP Comments**

**What have I learned from this paper?**

A key challenge for GPs and psychiatrists alike is to differentiate unrecognised bipolar depression from unipolar depression, as this has important treatment ramifications. Bipolar depression carries a much higher suicide risk and these patients may not respond to or may worsen with antidepressant monotherapy.

Mania is a straightforward diagnosis but bipolar depression (which is far commoner and may be more disabling than manic/hypomanic symptoms) is difficult to recognise because hypomanic episodes may not be noted by the patient or sought by their doctor. Collateral history with consent may be especially valuable. Patients with ‘depression’ who have a family history of bipolar disorder, young age of onset and atypical features (e.g. marked fatigue, lead-like limb heaviness, hypersomnia, and hyperphagia) may actually have bipolar depression and should be referred for further evaluation. Pharmacotherapy, with a mood stabiliser, rather than an antidepressant (or if an antidepressant is needed, limiting treatment only to the depressed phase) requires expertise and GPs should work closely with their psychiatrist colleagues to optimise diagnosis and treatment for these patients. It would be good practice to conduct a regular practice-based audit of patients with bipolar disorder who are taking antidepressants to ascertain if these are still required.

Dr Daniel Dietch, Lonsdale Medical Centre, London.
References

1. NICE Guidance CG38: Bipolar disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care
Psychotherapeutic interventions and Bipolar Disorder: Impact of bipolar disorder on individual’s families and wider society.

Michelle Branford, Sharn Tomlinson, Systemic Family Psychotherapist MA. (With Dist) in Systemic Teaching Training and Supervision
SEPT: South Essex Partnership University Foundation Trust and Mind in Mid Herts

Abstract

This paper discusses Psychotherapeutic intervention used to treat bipolar disorder. It aims to highlight the importance of psychotherapeutic treatment interventions for individuals with bipolar and the benefits to their families and society. These benefits include improved quality of life, financial status and engagement with psychiatric service, resulting in better medication adherence. In this paper we look at psychotherapeutic interventions both as an adjunct to pharmacology and as an independent treatment of bipolar disorder.

Key words: bipolar, psychotherapeutic, pharmacology, cognitive behaviour therapy, psychoeducation, family therapy, social rhythm therapy.

Introduction

Psychotherapeutic interventions support the symptom management and relapse prevention of bipolar disorder. According to Miklowitz they are recommended as an adjunct to pharmacology (medication) in the treatment of bipolar (1). Mood-stabilising medication is used to aid the stabilizing of all phases of bipolar to manage mood swings effectively and is the main recommended treatment. It is estimated that one third of persons diagnosed with bipolar disorder take less than 30% of their medication and non-adherence to medication is associated with relapse and suicide (2). The aim of psychotherapeutic approaches working with patients diagnosed with bipolar disorder is to: increase medication compliance, reduce relapse episodes and social risks, along with improving overall life experience. This paper is a brief overview, identifying psychotherapeutic approaches that assist in both symptom management and relapse prevention of bipolar disorder.

Bipolar disorder

Bipolar disorder was historically known as manic depression; the current diagnostic criteria are outlined in the clinical descriptions guidelines of ICD-10 (3) under mood disorders. There are varying degrees in severity and frequency of manic and depressive states ICD-10 (3). Therefore psychiatric diagnosis and classification of bipolar disorder is on the basis of mood episodes DSM-IV (21). Bipolar disorder is defined by ‘manic’ episodes of abnormally elevated energy levels with increased activity and alternate low mood states associated with depression. Some severe manic states can lead to psychotic episodes and, along with depressive states, can result in suicidal ideation and action with risk of death. Both of these states lead to a disturbance in cognition, mood, behaviour and overall individual functioning. Variations in mood are unique to the different types of bipolar disorder. The main four types include: bipolar 1 which is the most severe. The individual would have one or more manic and depressive episodes. Second, there is bipolar II, where there is at least one depressive episode alternating with a hypomanic state. Third there is cyclothymic disorder, which involves milder mood states than bipolar II, but still consists of both depressive and hypomanic symptoms (episodes) with lesser severity. Finally there is Unspecified bipolar disorder, where the mood states exist outside of the identified diagnostic criteria of the other types mentioned. This disorder can be problematic both for the individual and their family, psychologically and financially.
Impact of bipolar disorder on individuals, their families, friends and wider society

The bipolar disorder diagnosis is proposed to reach a lifetime prevalence of 4% of the population, approximately half divided between Bipolar I and II, with the remaining 2% Bipolar Disorder Not Otherwise Specified (4). The associated risks are high and can be devastating. According to Scott et al., there is a 6% death by suicide rate and 30% - 40% of patients deliberately self-harm (5). A wider study found the suicide rate to total 12.6% which was higher than schizophrenia and depression (5). In addition, there are those who are not yet diagnosed so their associated struggles go unrecorded. An individual experiencing an episode can face interpersonal conflicts, social isolation, cognitive deficits and distortions, affecting the way they are able to relate to themselves and others, in addition to influencing the way in which they perceive and interact with the world. The symptoms also have challenging implications for society generally.

The effect of bipolar disorder for the individual within the context of wider society includes negative effects on: relationships, family, likelihood of criminal activity, social stigma, a range of psychosocial problems and unemployment. In the manic states there can be an increase in abnormally optimistic thinking that can lead to unhelpful behaviours. These thoughts and mood swings can lead to disruptive behaviours, which can include over (erratic) spending, promiscuity, violence, excessive multiple tasking and impulsive actions. During the depressive states there can be a tendency for what can be described as a crash in mood. Subsequently, the individual can experience pessimistic thoughts that will be followed by associated behaviours such as: withdrawal from social support networks (isolation), substance misuse, reduced self-care and decreased environmental care. For both states the contemplation and action of suicide can be prevalent. Disruptions to functioning can result in unemployment prior to, during and post hospitalization. It is reported that approximately one third of bipolar patients had impaired work functioning 2 years after hospitalization (6). With employment problems, treatment costs and behavior disruptions, there are financial implications to the individual living with the disorder and an economic impact on society as a whole. These are serious negative consequences, highlighting the importance of effective management of this psychiatric disorder. Even though it is emphasized that pharmacology is the favoured treatment of bipolar symptoms, the integration of other treatments is also recommended in psychiatric practice guidelines (6). Non-adherence to taking medication has been identified as a major factor contributing to relapse and increased overall wider economic cost (2).

Cognitive Behavioural Therapy

Cognitive Behavioural Therapy (CBT) works with the relationship between thoughts, beliefs, feelings and behaviours. Individuals experiencing manic and depressive episodes can have associated distorted perception, thinking and subsequent unhelpful action. The aim of this therapy is to reframe faulty thinking both to increase awareness (medication compliance) and to support subsequent mood and behavioural responses (7). Miklowitz (1) cites Cochran who examined CBT treatment in a randomized controlled trial, that was reported to be successful in promoting lithium (mood stabilizer) compliance. Subsequently this reduced individual hospitalization and reported mood episodes. Another example of CBT effectiveness can be seen in Lam et al. who found a decrease in relapse rate: 44% for CBT treatment group as opposed to 75% for a routine treatment group (7).

Studies have found CBT to be more effective in managing depressive symptoms than mania. Focusing on these symptoms, techniques such as: challenging unhelpful beliefs and thoughts connected with helplessness or hopelessness, behavioural activation, goal setting and exercise tools are used (8). Ball (7) found patients attending CBT had lower depression scores and tended to have longer times between depressive episodes and relapse over 18 months; however the benefits of the treatment were reported to diminish over time. This indicated that, even though valuable, this treatment, may have been time limited and therefore subsequent top-up sessions could be recommended. Also, CBT was found to be most effectively delivered in the recovery period rather than in an acute episode. This
study further showed that CBT was most effective in patients that had fewer than 12 previous episodes (7).

There are additional Psychotherapeutic interventions that are also evidentially supported as being useful in managing symptoms.

**Individual psychoeducation**

Psychoeducation aims to use didactic (directional) teaching about bipolar disorder to facilitate learning about the symptoms, development of relapse prevention plans, and learning the importance of adherence to medication and illness-management strategies (7). Miklowitz (1,11) mentions a randomized study by Perr et al. that looked into the value of this intervention with bipolar patients. This study found ‘clear benefits’ after 18 months. The likelihood of manic recurrences was 27% of patients in the psychoeducation group relapsed as opposed to 57% of patients in the routine care group. However, there was no time delay in depressive recurrences, unlike the CBT interventions. Even though the value of psychoeducational interventions is recognized, other therapies that specifically target bipolar-related activity have also been reported.

**Interpersonal therapy and social rhythm therapy**

Interpersonal therapy aims to enable the patient to identify their different emotional states. It focuses on the social situation in which stressors may emerge, with the purpose of identifying the problematic patterns of communications and to propose possible alternatives (4). Two studies revealed greater periods of stability and psychosocial functioning in patients who received interpersonal therapy treatment than those who did not.

Social rhythm therapy derives from interpersonal therapy and two main behavioural observations of bipolar disorder. Bipolar disorder is often associated with poor interpersonal functioning and there are typically sleep disruptions, involving poor sleep and wake cycles. These inconsistencies or instabilities can perpetuate manic episodes (1). The main objective of this therapy is to resolve key interpersonal problems related to: bereavement, role disputes, interpersonal conflicts or deficits. It aims to help stabilize moods and to steady ‘social rhythm’ that includes irregularities - sleep patterns, exercise and socializing. It does this by monitoring routines, such as keeping track of patterns (disruptive and stabilizing) and the identification and regulating of events that can provoke episodes (1). Miklowitz (1) reported a trial in which acutely ill patients were assigned randomly to pharmacology and weekly interpersonal and social rhythm therapy (IASRT) or pharmacology and weekly clinical management sessions. Also patients, who were in the recovery period, were randomly assigned to interpersonal and social rhythm therapy (IASRT) or clinical management for a two-year maintenance period. Patients who received IASRT during the acute phase had longer intervals of being well in the maintenance phase. IASRT was most effective in delaying recurrences in the maintenance phase and succeeded in stabilizing their social rhythms during the acute phase and for mania. IASRT initiated during the recovery period was no more effective than clinical management in preventing recurrences over two years. Therefore, IASRT presented as being most effective when administered during an acute episode.

**Psychodynamic Interventions**

Even though there are only a few studies identifying the benefits of this type of therapy, due to its unquantifiable nature, there is still an indication of its benefits in supporting individuals with bipolar disorder. When working with patients who have bipolar disorder, this approach aims to: establish a therapeutic relationship which helps patients overcome denial of illness, address relationship issues and manage medication. The clinician’s aim is to explore the more traditional themes of psychotherapy and build on the therapeutic alliance. Rothbaum and Astin (6) reported that a group on a combination of lithium and couple psychodynamic therapy had fewer relapses and better social outcomes than two other groups on lithium alone.
Although the approach is adaptable to individuals and groups there are specific therapy models identified to be more effective, with broader interventions.

Systemic Care models

These models are multicomponent programs for the treatment of bipolar disorder that cover a combination of psychosocial interventions. They include those with a psychoeducation character and simple treatment procedures. These interventions include: psychoeducation, encouraging an active role in treatment and permitting the patient easy access to and holistic inclusion with the medical services and team. Lolich et al. (4, 46, 48, 49, 50, 5) found, in controlled studies as stated in the literature review, that there was a significant reduction in severity and frequency of manic episodes and better levels of functionality for patients within the multi-care systems program. The improvements in quality of life and functionality were shown to have a better or longer lasting effect 2 to 3 years after initiation of the intervention; however like the psychoeducational study there was no reduction of depressive symptoms.

Family Therapy

In considering the individual’s interaction with their environment, family therapeutic treatments include both the diagnosed individual and their family unit. There are various approaches within this therapy including family psychoeducation and multifamily group psychotherapy. The baseline objectives of this treatment include supporting the individual to regulate their emotions and enhancing interpersonal communication when facing conflict. Also this intervention aims to improve family functioning through psychoeducation and understanding of the nature of the symptoms, disease course and treatment. It aims to develop the skills of the individuals and families and to enable them to acquire knowledge to manage the disorder more effectively. The focus of research studies is on improving communication, problem solving and seeking to prevent or decrease possible conflicts. Family therapy has been most effective when implemented after an acute episode and but can begin in moderate or acute states.

Lolich et al. (4, 9, 31) reported on a study that was carried out in 2003 with 101 patients diagnosed with bipolar disorder. She compared family therapy with family education as an adjunct to medication (pharmacological treatment). The family therapy group had a longer time between episodes, better pharmacological treatment compliance and increased relapse prevention.

There is evidence to suggest that family therapy is identified as an effective adjunct to medication in delaying psychotic reoccurrences in patients with schizophrenia and in relapse prevention of bipolar disorder (1, 16). An example of this is reported by Miklowitz in a small scale trial (N=33) that found acutely ill patients receiving an 11-month psychoeducational marital intervention had better medication adherence and greater improvements in functioning than those receiving pharmacology alone (1, 17).

Miklowitz (1) reports on three trials of family focused therapy (psycho-education, communication enhancement training and problem solving). The first trial focused on medication with family focused therapy or family-based crisis management. Patients in a family-focused therapy had a greater likelihood of survival without disease relapse (52%) unlike those in the crisis management (17%). For those with depressive symptoms there was a stronger benefit than for those with manic symptoms. The effects reported included improved communication. The second trial over a 1-2 year period had two groups of family-focused therapy and pharmacology versus individual therapy and pharmacology. It was found that patients in the family-focused therapy had fewer recurrences (28%) and re-hospitalization (12% rate), compared to individual therapy with a 60% recurrence and re-hospitalization rate. The third trial looked at adolescents who were assigned to family-focused therapy and medication compared with psychoeducation and medication. Those in the family-focused therapy group had quicker recoveries from depressive mood states and spent less time in acute depressive episodes over 2 years.
**Multifamily psychoeducation groups**

This treatment has the same aims as family therapy but includes multiple families being seen together. The advantage of this treatment is its cost effectiveness along with its suggested clinical effectiveness. Patients from families that were initially high in conflict or low in problem-solving and who family therapy had approximately half as many depressive episodes per year and spent less time in depressive episodes than those who received medication alone. There were no effects of either family intervention on mania symptoms and no differences in the outcomes between patients who received were in single family therapy or in multifamily groups. In summary, this treatment was found to have stronger effects on depression symptoms than manic episodes; there was no difference in outcomes between multifamily psychoeducation groups that worked with more than one family at once and single family therapy. The benefit of the multifamily approach was that it allowed for more cost-effective management of affected individuals and their families (1).

**Dialectical behaviour therapy (DBT) and mindfulness cognitive behaviour therapy**

In this review, cognitive behavioural therapy, psychoeducation and family focused therapy presented as the approaches with most evidence to indicate usefulness in managing bipolar disorder as an adjunct to pharmacology. There is also some indication that dialectical behavioural therapy (DBT) and one of its components, ‘Mindfulness’, has benefits but there is currently limited empirical evidence.

DBT is the recommended treatment for borderline personality disorder but, using similar principles of supporting emotional regulation, it has been applied to bipolar disorder (9). Its aims are to support individuals with bipolar disorder to develop skills to monitor judgments based on thinking and utilizing rational thought rather than the ‘emotional mind’. Also, it encourages the identification of self-destructive behaviours and awareness of self and states. DBT also works on the individual’s perception of both the social and interpersonal triggers.

The main skills which DBT supports are: interpersonal effectiveness, emotional regulation, distress tolerance and core mindfulness, which will be discussed later in this paper. It utilizes tools such as feeling (emotion) and behavior, identifying the link between thoughts, observations, life charting, mood charting, validation of thoughts, goal setting and progressive relaxation to achieve individual symptom management (9). Van Dijk (9) reported on a study by Goldstein et al. in which DBT was used to treat bipolar disorder with results indicating significant improvements in emotional regulation, depressive symptoms and maladaptive behaviours, including suicide.

The mindfulness component of this approach is outlined by its objectives to support the individual’s sense of self, awareness of symptoms, concentration, thought control and attention (9). Mindfulness in this context aims to improve the individual’s moment-to-moment awareness of mood and energy levels changes with acceptance and anxiety management.

In a study on mindfulness-based CBT (10), participants showed increased mindfulness, lower residual depressive mood symptoms, less attention difficulties and increased emotional-regulation abilities, improved psychological wellbeing and improved psychosocial functioning. The focus on attention training, the here and now and the present moment could be the factor that challenges the racing thoughts associated with mania and concentration difficulties. The identification and self-acceptance of depressive-related mood states and thoughts may influence the stabilizing of related symptoms.

**Bipolar disorder and substance misuse**

Bipolar often coexists with substance misuse disorders (11). Weiss et al. created a manual-based group psychotherapy for patients with bipolar and substance dependency. The treatment used was integrated group therapy (IGT). Patients receiving IGT had significantly better outcomes on addiction severity index (p<.03), abstinence (p<.01) and likelihood of achieving 2 (< .002) or 3 (p<.004)
consecutive months of abstaining (11). However, not all individuals diagnosed with bipolar would consistently see their substance misuse and other behaviours as a being problems.

**Proposed benefits of bipolar II**

Fieve describes the perceived benefits of the hypomanic state of bipolar II in individuals valuing the heightened energy states. This includes their lively moods, socializing ability, increased creativity and productivity. He describes many individuals being the ‘movers and shakers in society’ and categorizes them as bipolar IIB (B for beneficial). However, the cost is the episodes of periodic depression and possible escalation to more severe mania (12).

**Conclusion**

There is evidence to suggest that psychotherapeutic interventions have significant benefits for bipolar disorder (13). The most evidence is for CBT which targets symptoms, social functioning and risk of relapse, as an adjunct or independent treatment (14). Psychotherapy can be utilized to improve the quality of life of those who have bipolar disorder and others in society directly or indirectly affected by the individual with the disorder. This can have a positive consequence for the patient’s social, health and financial circumstances. However, the different approaches discussed present with unique and combined benefits, depending on the needs of the individual, type of diagnosis and subsequent degree of symptoms. Further research and more exploration into psychotherapeutic approaches is required for a more accurate understanding of what is best to treat and in whom. For example, the rates of depression and total time spent in depressive episodes may be as much as 3 times higher than manic episodes (Judd et al. (10)). Therefore, for those cases, a treatment evidenced to be more beneficial at targeting depression would be more suitable. Family therapy can only be effective when the patient, their family, carers and other relevant people are willing to participate.

Research indicates that the cognitive behavioural treatment approach and family therapy may be the most suitable to target depression (depressive episodes), whereas ‘social rhythm therapy’ has presented as more suitable when a patient presents with symptoms of mania. However, Colom et al. have suggested that the psychoeducation approach combined with CBT techniques seems the most promising, focusing on education, information, treatment compliance and illness management (15). Although there is strong evidence that pharmacology is effective treatment, it may not be enough. For example, in patients with bipolar episodes, recurrence rates are up to 60% in 2 years even when medicated (Gitlen et al.) (10). Adherence to medication can be affected by factors including relationship and social status, educational level, stigma, denial and personal attitudes towards medication. Psychotherapeutic interventions can be utilized to support the potential barriers to effective recovery. Research has indicated the value of psychotherapeutic interventions relating to an improvement in adherence to taking medication and to aid relapse prevention. However, further research is needed to investigate which treatment is suited to individual needs to achieve an improved outcome for this disorder.

Bipolar mood states (episodes) can be triggered by activating events. Episode trigger factors include life events, economic pressures (socioeconomic status), high-pressured work environments, diet and lifestyle. As well as providing the appropriate treatment to suit the symptoms, factors such as triggers and therapeutic management of them need to be considered. Further exploration is required to establish what treatments would be most effective in relation to these factors. Other triggers include family difficulties, social relationship breakdowns, communication difficulties and bereavement; these can all be destabilizing factors that contribute to triggering or to maintaining an episode. Targeting the individual’s ability to manage and cope with these life events and situations are areas in which psychotherapeutic interventions are proven to be successful.

As individuals in the media (celebrities) work to reduce the social stigma of bipolar disorder by making their diagnosis public, open discussion or talking therapies may increase acceptance in a wider social context for the individual patient with this diagnosis. Psychotherapeutic models need to be developed, researched and should be based on clear therapeutic advantages for reducing bipolar symptoms and improving effectiveness of treatment.


GP Comment

What have I learned from this paper?

Psychotherapeutic interventions for bipolar disorder have to been shown to be effective in the management of patients with bipolar disorder. It seems that CBT has the most evidence and its impact is not only in symptoms but also in social functioning and quality of life. Patients who benefit the most from psychotherapy are the ones suffering more depressive episodes than manic ones. As family physicians we have the possibility to explore the family as a potential alliance to help in the therapeutic process.

Dr Juan Mendive, Family Physician, Barcelona.

References

7. Fieve RR. Bipolar II: Enhance Highs, Boost Creativity, Escape Cycles (book on order)
9. DYT ref
10. Mindfulness based CBT
17. Jones E, Asen E. Systemic Couple Therapy and Depression; Systemic Thinking And Practice Series, Edited by David Campbell and Ros Draper; Karnac; 2002.
19. ICD-10
20. Secondly there is Hypomania, where a lesser elevated mood state is present without hallucinations or delusions but increased social activity and talkatively.
21. DSM-IV
Ongoing Management of bipolar disorder

Dr Snehal Khajuria

Abstract

Bipolar (affective) disorder is a challenging psychiatric illness to manage and is associated with significant risk of morbidity and mortality. A meta-analysis has revealed that suicide is 20 times higher in patients with bipolar than the general population (7). Acute relapses of bipolar are often managed in secondary care with hospitalisation whereas long-term maintenance management is achieved largely in primary care. This paper discusses the ways in which lifestyle, psychotherapy and pharmacotherapy can be utilised in maintenance management, how they are advantageous in patients and what obstacles are faced.

Key words: bipolar disorder, maintenance management, pharmacotherapy, psychotherapy, lifestyle management, non-compliance, monitoring bipolar, primary care.

Introduction

Bipolar (affective) disorder is considered one of the most challenging psychiatric conditions to manage due to its characteristic fluctuations of mood and chronic relapsing and remitting course. The prevalence of bipolar I and II disorder varies from 0.4-0.6% and 0.5% respectively (1). Equal ratios of males and females are diagnosed with bipolar I in opposition to a higher ratio of females diagnosed in Bipolar II (1). Presentation of bipolar is often also different between the sexes; males predominantly present with a manic episode on first presentations whereas females often present with depression (1).

Bipolar disorder is usually treated acutely by specialist psychiatric services, leaving primary care to manage the condition long-term. Although it has been associated with the ability to display impressive creativity in some patients, it has also had a negative impact on the lives of most patients. Greater than 4% of women and 7% of men die through suicide attempts within two decades of diagnosis (2). Studies have also shown that untreated illness for prolonged periods can provoke poor response to treatment, poor social adjustment, higher hospitalisation rates and development of comorbidities (3, 4). Appropriate long-term management is therefore crucial as episodes become more frequent and difficult to treat in both types (3). These multiple implications of bipolar disorder make it imperative that it is diagnosed correctly and managed appropriately. Good management can prevent major disruption and morbidity in the lives of patients. However, one of the biggest challenges facing bipolar treatment is the lack of patient compliance. It has been reported that patients experience symptoms 47% of their life, more so in depressive states (29). Moreover, only 40% of patients comply with drug treatments one year following an episode (30).

Non-compliance in maintenance of bipolar disorder

Despite the morbidity associated with bipolar disorder, long-term treatment, which almost always involves medication, does not make it easy for a patient to comply with maintenance treatment and the unfavourable side effects of medication. A study conducted to assess adherence by collection of prescriptions suggested that only 54.1% were fully adherent to maintenance drugs, 24.5% were partially adherent whereas another 21.4% were not adherent (22). Non-adherent individuals were more likely to be homeless, young in age, unmarried, non-caucasian or have a substance use disorder; they attended fewer outpatient psychiatry visits (22). In addition it was found that those on combination therapies had better adherence than those given prescriptions for monotherapy (22). Unfavourable side-effect profiles of popularly prescribed mood stabilisers, e.g lithium (which requires meticulous monitoring) and antipsychotics, e.g. olanzapine (weight gain) significantly contribute to non-compliance and require regular review.
Treatment Options

The core objectives of treating patients with bipolar disorder include: reduction of symptoms and risk, stabilisation of mood and prevention of relapse (9). In addition, patients should be educated with awareness into their mental health. Aims of education are directed towards identifying coping strategies and enabling them to consult for advice as early as possible, when needed. Despite significant developments in pharmacological management of bipolar disorder, most patients are unable to recover using drug treatments alone (28). Three forms of treatment have been developed to incorporate all of these objectives and should be implemented collectively. These include lifestyle modification, psychotherapy and pharmacology. Risks of suicide are shown to be lower when patients are satisfied with their level of care, are treated for alcohol and tobacco abuse and take lithium (6, 7, 8). This illustrates the combined importance of lifestyle modification, psychotherapy and pharmacology in managing patients. In ideal circumstances the patient should feel they are able to live their lives as normally as possible with support from primary and secondary mental health teams (5).

Lifestyle management, psychotherapy and community care

Psychosocial stress is known to instigate symptoms of mania and depression. Psychotherapy can go hand in hand with pharmacotherapy and lifestyle management to identify early warning signs and patient awareness into their own mental health. This can reduce relapse rates, frequency of hospitalisations and improve social functioning (6, 27, 31, 32). Rates of relapse average between 40-60% in 1-2 years, despite being treated with pharmacotherapy (11). It is therefore important that psychotherapy is used as an adjunct to pharmacotherapy. Psychological support should be provided to patients with bipolar disorder in the form of psychotherapy for at least 16 sessions over a period of six to nine months. This enables exploration of management and coping strategies such as the recognition of changing mood and its triggers. The patient should be assigned a care co-ordinator in the community who will conduct weekly visits for 6 months to support them until their condition has stabilised. Management, progress and coping strategies can be discussed with the care co-ordinator to ensure optimal advancement in their mental health. The patient should also be informed of self-help and bipolar groups. Through these, they can share their experiences with patients who have a similar diagnosis, enabling them to feel more supported and achieving greater insight into their condition. It has been shown that patients who undergo intensive psychotherapy (6) or group therapy (27) are less likely to relapse and have longer spells of ‘wellness’ compared to those who have had only brief therapy. Moreover, those who have more manic symptoms are more likely to improve with strategies to promote medication adherence and early recognition of symptoms; whereas those with depressive symptoms are more likely to improve with CBT and interpersonal coping strategies (9, 28). With the help of the patient’s family, carers and care co-ordinator, identification of suicidal or homicidal ideation should be addressed immediately and promptly managed (9).

Lifestyle adjustments can also help prevent triggers of relapse. NICE guidelines have suggested good sleep hygiene, relaxation techniques and avoidance of excessive stimulation (5). Sleep is particularly important, as sleep deprivation can potentiate manic episodes. Overnight shift work is discouraged.

Maintenance pharmacotherapy

The prognosis of bipolar disorder is dependent upon early diagnosis and treatment. This reduces the risk of relapse and doubles the response rate of medications (9, 26). Indefinite treatment (once appropriate mood stabilisers have been identified) should continue because of the risk of relapse. A study by one group suggested that relapse can occur in one third of patients in the first year following presentation, and in more than 70% within 5 years in patients that are not treated (11). Psychiatrist involvement is often requisite in management of patients, due to psychiatric comorbidities, treatment resistance, relapse and risks of harm to themselves and others (9). Women who require treatment must be educated about teratogenic side-effects of mood stabilisers and the importance of contraception whilst taking them (9). Antidepressant monotherapy carries a risk of cycle acceleration,
treatment related mania, and hypomania (12, 13); it is not recommended. Co-administration of a mood-stabilising agent with antidepressants has been shown to decrease cycle acceleration and treatment-emergent mania (13, 15, 16). Despite this research, risk is not completely eliminated and hence antidepressants should only be used with mood stabilisers and only for the time when the patient is depressed, whereas mood stabilisers should be used throughout every phase of the illness, including when the patient is euthymic (17, 18).

NICE has published recommendations for long-term treatment based upon the type of bipolar disorder and number of presentations. They advise maintenance treatment in bipolar I patients following two acute episodes, or a single severe episode with consequences (5). They also suggest prophylactic treatment in patients with bipolar II disorder who relapse frequently, have functional impairment or are at risk of suicide (5). Choice of prophylactic drug(s) is often dictated by the leading pattern of relapse (25). Use of lithium, lamotrigine, valproate, quetiapine and olanzapine has been supported well by particular studies for bipolar disorder (9, 19-21). However, combinations of quetiapine with lithium or valproate are considered more effective than using either of the latter in isolation (9, 19). Each medication possesses its own specific side effects, which may make one medication favourable over another. Lithium, for example, is associated with a low therapeutic index and requires three-monthly blood tests for serum lithium concentrations, as well as six-monthly thyroid and renal function blood tests (25). Rapid withdrawal can induce relapses and it must therefore be stopped gradually when a decision is made to end treatment (25). All of this needs to be discussed with the patient so they have a clear awareness of when to seek help, and how to manage their medications in the best way.

Non-prescribed medications have also shown benefit in maintenance therapies. Omega-3 fatty acids can help aid reduction of depressive symptoms in patients with bipolar disorder via similar mechanisms to lithium and valproate (9, 23). Lifestyle modifications can also be adopted to combat adverse effects of medications. A randomized controlled study showed that a moderate exercise program with active management of body weight improved weight loss and lipid profiles in patients taking olanzapine compared to controls (24). Such strategies can be advised in clinics when starting patients on a particular therapy.

Monitoring bipolar disorder

Regular clinical examination and assessment of physical health is recommended (9). Bipolar disorder is associated with higher rates of general medical comorbidities. These include diabetes, cardiovascular disease and obesity (compared to age-matched individuals) (34). Bipolar disorder is also associated with higher risks of cardiovascular disease than other psychiatric diagnoses (9, 34). Assessment of depressive, manic and sleep symptoms, suicidal risk, comorbidities and substance abuse must be conducted frequently to alert the services of any changes in mental state (9). The weight and lipid profile should be consistently assessed, particularly in those taking antipsychotic medications such as olanzapine, risperidone or quetiapine, due to alterations in metabolism. Antipsychotics have been said to accelerate cardiometabolic risk accumulation, thereby contributing to premature death rates (35). These factors must be monitored closely, particularly in those with co-existent general medical morbidities. Other adverse effects frequently associated with antipsychotics include extrapyramidal symptoms (akathisia, parkinsonism, and other movement disorders such as dystonias and dyskinesias). Tardive dyskinesia can occur within months of initiation and is potentially irreversible, particularly affecting those that are elderly with cardiovascular disease, stroke or neurological vulnerability (9). Symptoms should be monitored using the Abnormal Involuntary Movement Scale during follow-up visits (9).

Selection of medications and dosage adjustments should always be explored during each follow-up visit, to ensure patients are not skewing to a manic, hypomanic or depressive episode. Lower doses may be indicated in children, underweight patients, the elderly and those with chronic disease (9). Higher doses may be required for those who are severely psychotic (9, 10).
Conclusion

Bipolar disorder remains a debilitating psychological disorder associated with significant risk of morbidity and mortality. It has one of the highest suicide rates among all psychiatric diagnoses; one third of patients attempt suicide (33). Prophylactic treatment is mostly administered in the primary care sector and is fundamental in preventing relapses. Bipolar disorder can be managed using lifestyle changes, psychotherapy and pharmacotherapy in order to prevent relapse, reduce risk and stabilise mood. An educated awareness of bipolar disorder can also help identify any symptoms early so they can be suitably treated. Doses of medications must always be monitored and enquiry should always be made about possible adverse effects. Regular blood checks and physical examinations will also assist in identifying any adverse reactions. Although bipolar disorder is associated with significant morbidity, if it is managed well, many patients respond successfully to treatment and live a full life.

GP Comment

What have I learned from this paper?

This paper helped me to refresh my knowledge on bipolar disorders at a time when many of us in primary care find it difficult to distinguish bipolar from general mood swings.

It was also interesting to see the evidence behind effectiveness of using lifestyle and psychotherapeutic interventions in reducing relapses in bipolar disorder. This evidence will encourage me to use such therapies in my own practice.

Altogether I think the paper was well balanced in providing information required by the general practitioner.

Dr Roshan Jayalath, GP.

References

2. Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. Arch Gen Psychiatry 2011;68:1058-64
17. Ghaemi SN, Sachs GS, Goodwin FK. What is to be done? Controversies in the diagnosis and treatment of manic-depressive illness. World J Biol Psychiatry 2000; 1; 65-74
Part 6. Recovery from Bipolar Disorder

Self-management in the treatment of bipolar disorders

Benjamin Philip Martin
The Princess Royal Hospital, Shrewsbury and Telford NHS Trust.

Abstract

There is a significant shift in the focus of care throughout the medical profession, where care in the community, alongside patient education and empowerment are being prioritised. We, as care providers, should be looking to reflect this in the management of bipolar disorder by empowering our patients to manage their own condition. Of course the difficulty with this is that with any psychiatric disorder, self-monitoring and patient-led care is dependent on the patient being competent to make appropriate decisions and having insight into the effect of their condition on their life. It is therefore a difficult balance to control, between clinician-led and patient-led care, but one that could be potentially liberating for many of our patients trying to run their lives alongside their condition.

Key words: bipolar disorder, community, empowerment, self-monitoring, insight.

We are practising in a time where there is rapid and significant change within the healthcare system. Policy setters are encouraging individualised care and care within the community; this is affecting how we are able to provide care for our patients. These features are being reflected in the clinical guidelines that are being published and should therefore also be reflected in the manner in which we practice.

National institute for health and clinical excellence (NICE) guideline for bipolar disorder

This guideline (1), published in 2006, gives us a clear outline of how care should be provided for patients with bipolar disorder. It includes pharmacological management using acute antimanic drugs and long-term prophylaxis. The guidance highlights triggers that suggest when referral from primary to secondary care may be clinically indicated, aiming to boost the confidence of those managing patients in primary care. The guideline provides clear information about the monitoring of biological parameters, particularly related to drug adverse effects. The advice for particular patient groups, such as pregnant women, children and adolescents is particularly useful.

This paper will focus on three points from the guidance that allude to the changes in care that are being recommended and how such changes could be reflected in our care provision.

• ‘Healthcare professionals should aim to develop a therapeutic relationship with all patients with bipolar disorder, and advise them on careful and regular self-monitoring of symptoms (including triggers and early warning signs), lifestyle (including sleep hygiene and work patterns) and coping strategies.’

• ‘If a patient is at risk of suicide, exploitation or severe self-neglect, is a significant risk to others (including neglect of dependents), or has a history of recurrent admissions, particularly compulsory admissions, a crisis plan should be developed in collaboration with the patient, covering:

  - a list of identified or potential personal, social or environmental triggers, and early warning symptoms of relapse
  - a protocol for increasing the dose of medication or taking additional medication (which may be given to the patient in advance) for patients who are at risk of rapid onset of mania and for whom clear early warning signs can be identified – protocols should be monitored regularly,
and are not a substitute for an urgent review’
• ‘…care programmes should include; written treatment plans that promote the principles of self-management, and are shared with the patient and, where appropriate, with families and carers.’

When reading through these sections of the guidance it is clear that there should be an element of ‘self-management’ of bipolar disorder. The difficulty with this is that self-management is very much a soft marker, something that will be experienced by both the clinician and the patient, but is very hard to measure. This leads to it being a part of care that is unquantifiable, difficult to research objectively, and therefore less readily implemented. I will look to suggest that despite these hurdles, it remains something that we as clinicians should be adopting as a part of the care we provide, in the hope that it will eventually translate into better patient care. More importantly, the outcome will be that it should lead to lives changed for the better, as patients are no longer controlled by a condition, but able to balance managing life alongside their condition.

**Evidence for self-management**

There has been a climate shift in the management of a number of other conditions over the past decade where patients are being encouraged to manage their conditions themselves. The aims of this are not only to make treatment and care more cost effective but also to increase patient satisfaction and, importantly, to improve patient outcome.

**Hypertension** is a condition that has gone from being perceived as a mystery by many, to something of which the general public is more aware. The provision of care has changed from a condition controlled by the general practitioner, where patients present to have their blood pressure checked, to a condition where patients have been monitoring their own blood pressure and present with a trend of their recent ambulatory readings. This reflects the change in clinical guidance (2) where a diagnostic requirement is to ‘offer ambulatory blood pressure monitoring to confirm the diagnosis of hypertension’ and management advice includes ‘encouraging people to monitor their condition’. Building on this, a recent study by McManus et al (2010) (3) has proposed that encouraging patients to titrate their medication based on home blood pressure monitoring has led to significantly tighter control of the condition.

Similar clinical outcomes have been noted in the management of asthma. When patients are encouraged to manage their own condition, through symptom monitoring, peak flow monitoring, and the availability of oral steroids for the management of an exacerbation, clinical outcomes significantly improve. This has been expressed in a host of trials, including Osman et al (2002) (4) who looked at the impact of empowering patients following a hospital admission for acute asthma, on their clinical outcome. This is reflected in the content of the most recent British Thoracic Society guidelines (5) for asthma, which states:

‘The purpose of education is to empower patients and/or carers to undertake self-management more appropriately and effectively. Information given should be tailored to individual patient’s social, emotional and disease status, and age. Different approaches are needed for different ages.’

It also provides an outline of points that should be considered in a patient education session:

- ‘Nature of the disease
- Nature of the treatment
- Identify areas where patient most wants treatment to have effect
- How to use the treatment
- Development of self-monitoring/self-assessment skills
- Negotiation of the personalised action plan in light of identified patient goals
- Recognition and management of acute exacerbations
- Appropriate allergen or trigger avoidance.’

The degree of patient involvement in care has also grown in chronic obstructive pulmonary disease (COPD). Open discussions between GPs and their patients leads to some patients having an ‘exacerbation kit’ as advised by NICE guidance (6):
‘Patients at risk of having an exacerbation of COPD should be given a course of antibiotic and corticosteroid tablets to keep at home for use as part of a self-management strategy.’ This gives the patient confidence that they are able to manage their condition further, and also is shown to decrease hospital attendance, improve outcome and therefore improve the patient’s quality of life in an exacerbation (7).

The provision of oral anticoagulation therapy shows particular similarities to the pharmacological management of bipolar disorder in the monitoring and dosing changes that are required. Patients on warfarin are often protective over the management of their dosing, and are well informed about the risks of treatment being subtherapeutic or supra-therapeutic. The advent of a ‘warfarin card’ has encouraged the atmosphere in which the patient is the expert and the clinician is the service provider. Titration of dosing to achieve appropriate plasma concentration of lithium is closely aligned to the monitoring of the international normalised ratio (INR) in anticoagulation. Two developments within the management of anticoagulation that could be applied to the management of bipolar disorder are finger prick monitoring, which could be also applied to lithium blood-level measurement and using agents that do not require blood monitoring. An initial focus for improvement of clinical care for patients being treated with warfarin was the development of finger prick INR readings. This reduced the invasiveness of testing, and also permitted informed and appropriate patients to monitor and dose their warfarin themselves by following an algorithm (8). Being able to develop a similar test for capillary lithium levels that relates to serum lithium levels would permit quicker and easier testing for therapeutic dosing, and would also prove useful in monitoring for levels of toxicity.

More recently research has been looking into other oral anticoagulants such as Rivaroxaban, a direct factor Xa inhibitor. Implementing the routine use of drugs such as this aims to save on the costs of monitoring and to reduce adverse events, although there is an increase in cost of the drug itself. This is comparable to the broadening of therapeutic strategy for treating bipolar disorder, from the widespread use of lithium, to the use of mood stabilisers and atypical antipsychotics. There is still a need for further research into which pharmacological intervention is most effective, as currently decisions are made on an individual basis.

Diabetes management lies at the forefront of self-management, because it entails symptomatic monitoring, physiological testing, and pharmacological interventions. Interestingly paediatric diabetes patients demonstrate variable insight into the beneficial effect of treatment on their condition, in a similar way to the variable insight that patients with bipolar disorder show into their condition. Research into the role of self-management in paediatric patients with diabetes, I would suggest, is highly relevant when considering applying the same management principles to those patients with bipolar disorder.

NICE (9) has incorporated the idea of empowerment and self-management into their guidelines, even for young children as below:

‘Children and young people with type 1 diabetes and their families should be offered timely and ongoing opportunities to access information about the development, management and effects of type 1 diabetes. The information provided should be accurate and consistent and it should support informed decision-making.’

The issue of insight is pertinent. It was noted by Rewers et al (2009) (10) that often children under 6 have poor hypoglycaemic awareness, and consequently they are less suitable for self-monitoring. This would be comparable to bipolar patients that have poor insight into whether or not they are in a manic, or a depressive phase. In the same way that those younger children are not suitable for self-monitoring glucose levels, this would suggest that patients with bipolar disorder that have poor insight would be unsuitable for self-management.

How can this apply to the management of bipolar disorder? The recommendations for monitoring of therapy in patients with bipolar disorder are demanding. As a consequence of this, it is difficult for clinicians to provide appropriate monitoring, especially when...
liaising between primary and secondary care in the monitoring process. I would suggest that involving patients with this monitoring process is an obvious area where we can look to empower patients to take a management role in their condition.

To aid this transition, further research into the relationship between serum lithium and capillary lithium, salivary lithium, or urinary lithium in patients on lithium therapy is needed. This would help to clarify if there is scope in the future to use salivary, urinary, or capillary samples to monitor therapeutic dosing of lithium. This would reduce the need for blood testing for levels within primary or secondary care, which may or may not be a current hurdle for patients, although there would of course still be the need for renal and thyroid function monitoring. This also does not help the patients with bipolar disorder who are not using lithium for therapy.

It is particularly worth noting that there is no benefit in self-monitoring if the patients are not compliant with their medication. Self-management is something that would put the ball into the patient’s court in terms of shaping their recovery. Carter et al (2005) (11) highlighted the fact that clinicians are providing a service that the patient may or may not engage with, and that this will vary from patient to patient and from condition to condition. They found that compliance with medication was correlated to the perceived need for treatment. In specialties such as oncology, adherence was highest, whereas this fell with conditions such as asthma. Although medication use in psychiatric conditions was not included in the study, I would suggest there would be a wide variety of opinions among psychiatric condition patients, ranging from patients that have respect and gratitude for their medications, to patients that detest the need to take medications to be ‘normal’. I would expect this variety to be reflected in their compliance. This further highlights the need to select out patients that would not be suitable for self-management. NICE guidance has picked up on this finding, and has produced generic guidance for ‘medicines adherence’ (12) which suggests:

‘Patient involvement in the decision-making process requires that healthcare professionals acknowledge patients’ views about their condition and its treatment, and that both healthcare professional and patient have a role in making decisions about treatment. Simple interventions to increase patient involvement do not necessarily increase the overall length of consultation and may be justified by benefits, particularly over the course of a long-term condition.’

This guidance clearly encourages patient empowerment, and reflects evidence that patient involvement increases medication compliance, something that is a constant battle for patients with bipolar disorder.

Current situation

The current situation with self-management in patients with bipolar disorder is that there is great variability from patient to patient and from clinician to clinician. Interventions such as the ‘lithium card’ start to encourage patients to take ownership over their condition and to feel like they have an element of control over their management. However there remains great scope for increasing the degree of patient involvement, and for the extent to which the patient leads changes in therapeutic strategy to grow.

How things could be different?

As mentioned above, development of devices to enable fingerprick monitoring for lithium levels, or accessible monitoring for sodium valproate or carbamazepine could allow more power to be shared with, or given to the patients. That said, the main development I feel needs to come from inclusiveness and shared decision-making rather than technological advances.

The intervention that I feel would be most beneficial in increasing the involvement of the patient in their care is provision of a clear plan for increasing a patient’s mood stabilisation medication, appropriately using antidepressants, and recognising triggers that may be an indication for anti-psychotic medication or inpatient care. This would increase the confidence and ownership of the
patient, as well as equipping the approved mental health professional and GP to manage the condition when required. This could be undertaken using a refined version of the empowerment strategy from the BTS/SIGN guidelines included above.

What would be the benefits?

• Improved patient outcome – in many other chronic conditions, as shown above, incorporating self-management and patient empowerment into the therapeutic strategy leads to improved patient outcomes. The interventions in bipolar disorder are less clear, and the patient group more difficult to manage, but potential benefits could make the change worthwhile.
• Improved quality of life – this is the marker that we as clinicians should be always aiming to improve. Freedom from hospital monitoring, the independence to make informed health decisions, and tighter therapeutic control would start to contribute to an improved quality of life.
• Reduced clinician input – secondary care clinicians would continue to be involved in the management of difficult cases, and would provide more of a planning and equipping service. This would liberate primary care physicians, and the patients themselves, to manage their condition in the community.
• Empowered patients would recognise and respond to warning signs at an earlier point in time, facilitating prompt intervention. This would lead to less oscillation between manic and depressive phases, and more of a steady state. This concept was highlighted by Agius et al (13) in a paper which particularly focussed on identification of early warning signs and developing a relapse prevention plan.

What would be the difficulties?

The significant difference between patients with bipolar disorder and most of the patient groups above, for which there is clear evidence for self-management, is that of insight into their condition. Giving a patient the power and authority to control and change their therapy requires an understanding of the illness, the effect of treatment on the condition and essentially an appreciation that there is a condition that needs treating. With disorders that bridge the boundary between a psychotic and neurotic condition, it will not always be possible to affirm that patients appreciate the illness, the treatment, or the link between the two.

Clinical improvement as a consequence of patient-led care needs intelligence for appropriate decision making, a desire to see improvement in health, and insight into the condition and how it affects them. The clinician will assess indicators of each of these attributes from their interactions with the patient. It then requires a judgement to be made by the doctor as to whether the patient is suitable to take a leading role in his or her own therapeutic management. This judgement will be heavily influenced by an open discussion between the patient and clinician.

There is, of course, a risk that the judgements might be incorrect and that patients that should not be given such freedom take an inappropriate lead in their care. It could be proposed that this would raise a risk that poor patient selection would lead to manic patients being a risk to the public, or patients in the depressive phase are at increased risk to themselves. I would highlight the fact that short of treating patients under the Mental Health Act, we are never able to enforce treatment. We do not therefore ensure that patients take their medications or engage with treatment. There will therefore be little change in the treatment provided but a major shift in the attitude with which that treatment is received.

It seems unlikely that encouraging self-management will increase the risk of non-compliance in this patient group. On the contrary, I feel that empowering the patients will give them an ownership that leads to greater engagement with healthcare professionals and the treatment they are able to advise.
Conclusions and recommendations

I am not able to provide clear guidelines as to what will be successful in the management of bipolar disorder. My role is to highlight the success that has been proven in other conditions, to note the suggestion in current guidance for bipolar disorder to ‘promote principles of self-management’, and to propose avenues by which this can be implemented. The interventions that can be patient led are less clear-cut than in many of the other conditions that I have explored above. That said, I would hope that in developing a therapeutic relationship, and empowering the patient, it will lead to patients feeling more equipped to tackle life alongside managing their condition. I feel that self-management is a vision that allows the clinician the role of becoming an overseer and enabler rather than a dictator in the management of a patient’s condition. This is something that should, over time, significantly improve patient care.

GP Comment

What have I learned from this paper?

This is an interesting article highlighting the evolution of clinical medicine to a shared treatment platform between patient and doctor. A doctor may prescribe but to be effective, the clinician needs the patient to be concordant with the treatment plan. Unlike the other medical conditions listed hypertension, asthma, COPD there is no objective numeric measurement tool, that could be utilised. There are downloadable smartphone applications called ‘Mood Trackers’ which allow a patient to tap on a visual representation of their mood i.e. smiling face=happy etc. This is a good starting point but perhaps initiating a ‘buddy-up’ with an objective member of the patient’s family to help assess their mood and symptoms as described in the article would be better. This could increase understanding, awareness and participation of the patient and their family & friends. It might also help to break the social stigma of mental health disorders in the community and make it comparable to checking BP daily.

Simple monitoring of lithium levels would be excellent. However, R&D is too often focussed on the next big ‘pharmaceutical’ compound that can be licensed and become an income generator for the company. Monitoring may not be on the priority list of many multi-national pharmaceutical companies.

Dr Vishal Naidoo, GP.

References

7. Jeppesen E, Brurberg KG, Vist GE, Wedzicha JA, Wright JJ, Greenstone M, Walters JA. Hospital
Psychoeducation for Bipolar Disorders’ Patients: The “Porta Aberta” Programme

Catarina Klut*, Salomé Xavier*, João Graça*, Gonçalo Carreteiro* and João C. Melo*
* Department of Psychiatry, Hospital Prof. Dr. Fernando da Fonseca, EPE, Amadora, Portugal

Abstract

Psychoeducation is currently considered to be a fundamental intervention in the management of bipolar disorders. A psychoeducation group programme for patients with bipolar disorders, aimed at euthymic patients just prior to their discharge from the acute psychiatric inpatient unit, named “Porta Aberta” (Open Door), has been implemented since 2007 at the day-hospital of our psychiatric department (Amadora, Portugal). In this article, the authors provide a brief review of the relevant literature on this subject and also assess the effectiveness of the “Porta Aberta” programme in reducing the average number and duration of readmissions; they determine whether individual characteristics (gender, marital status and disorder subtype) may influence outcome.

Key words: psychoeducation, bipolar disorders, treatment adherence, relapse prevention

Introduction

Psychoeducation (PE) in combination with psychopharmacological treatment is becoming an increasingly popular intervention in the management of bipolar disorders. It is currently recommended by the British Association for Psychopharmacology (1) and the National Institute for Health and Clinical Excellence (2) for the long-term treatment of patients with these disorders. PE has been defined by Francesc Colom as “a patient’s empowering training targeted at promoting awareness and proactivity, providing tools to manage, cope and live with a chronic condition (i.e. adherence enhancement, early warning sign identification, lifestyle, crisis management, communication), and changing behaviors and attitudes related to the condition” (3). This sort of intervention has also been shown to be useful in non-psychiatric conditions such as diabetes (4) and coronary heart disease (5).

The first structured PE intervention for patients with bipolar disorders that was tested in a randomized control study was reported by Perry et al. It consisted of 7-12 individual sessions of training on the recognition of early warning signs of recurrence and the importance of seeking prompt medical help. It was associated with important clinical improvements such as a significant increase in time to manic relapse, a decrease in the total number of manic episodes over 18 months and also better overall social functioning and employment status. No significant change in the number or length of depressive relapses was found (6).

More recently, Colom, Vieta et al. carried out a well-designed randomized controlled trial to assess the effectiveness of structured group PE for patients with bipolar disorder types I and II. This seminal study compared PE with an equivalent group experience that consisted in unstructured supportive discussion. One hundred and twenty euthymic patients were included and randomly divided between the two groups. Each patient underwent 21 sessions, in 8 to 12 participant groups, over a period of 6 months. In the PE group, the following topics, also named by the authors as the “big five” ingredients, were covered: illness awareness, treatment adherence, early warning signs identification, substance misuse avoidance and regularity of habits. This intervention significantly decreased the total number of recurrences (manic, hypomanic and depressive episodes), increased the time to any recurrence, and decreased the mean number of admissions per patient, and the mean duration of admissions, both at 2 (7) and 5 years (8) after the intervention. A significant reduction in the time spent acutely ill was also found after 5 years. Despite the initial increase in the utilization of health care resources during the implementation phase of the PE programme, in the long term this intervention has been shown to be less costly and more effective. It increased the planned outpatient appointments but the estimated mean cost of emergency consultation and inpatient care utilization was significantly lower (9).
Miklowitz et al. studied the effectiveness of a family-focused PE in enhancing mood stability during maintenance treatment, with a 2-year time frame. The patients that received this intervention had fewer relapses, showed greater reductions in mood disorder symptoms and better medication adherence (10).

The “Porta Aberta” Programme

A psychoeducational programme for patients with bipolar disorders named “Porta Aberta” (Open Door) has been implemented at the Day Hospital of the Hospital Prof. Dr. Fernando Fonseca’s Department of Psychiatry (Amadora, Portugal) since 2007.

“Porta Aberta” was designed as a group PE programme which can occasionally include individual sessions, depending on the number of eligible patients at that time. It is aimed at euthymic patients that show reasonable insight and good motivation, just prior to their discharge from the acute psychiatric inpatient unit. The purpose of this early intervention is to create a link with the Day-Hospital unit and its healthcare workers, which can then be maintained in the outpatient setting, in order to improve adherence. The programme is composed of eight independent sessions, held four times a week during a two-week period, in which several topics are presented and discussed, in the following order: Signs and Symptoms of the disease; Coping with Stigma; Treatment Plan; Promoting Wellbeing; Risk Behaviors; Family Intervention; Daily Activities Planning and Open Session.

In this article, the authors aim to assess the effectiveness of the “Porta Aberta” programme in reducing the average number and duration of readmissions and to determine if individual characteristics (gender, marital status and disorder subtype) may influence outcome.

Methods

For this observational study, the clinical records of all the patients diagnosed with bipolar disorder, that attended at least 4 out of 8 sessions of the “Porta Aberta” programme, from 2007 to 2010, were reviewed. The variables assessed were socio-demographic (age, gender, marital status) and clinical (type of bipolar disease - I vs. II or NOS and number and duration of admissions to the inpatient unit in the 1-year period before and after programme enrollment, respectively). The analyzed data was made anonymous and confidentiality was assured. Statistical analysis was performed using the SPSS for Windows, version 14.0, and significance was tested, using the Chi-square and Student’s t tests, for nominal and continuous variables, respectively. Data was collected in the last semester of 2011. There was no missing data in the clinical records.

Results

A total of 69 patients were included. They were more frequently female, not married and diagnosed with bipolar disorder type I (Table 1). The mean age was 37.2 years (sd=10.6). In the 1-year period prior to programme enrollment, these patients had a mean number of 1.28±0.66 admissions per patient, which was significantly reduced to 0.28±0.59 (p=.032) in the following year (Graph 1). There was also a significant reduction in the mean duration of admissions in the 15 patients who were readmitted, decreasing from 25.7 to 17.3 days (p=.028) (Graph 2).
Graph 1: Mean number of admissions per patient one year before and one year after programme enrollment (n=69, *p=.032).

Graph 2: Mean duration of admissions one year before and one year after programme enrollment (n=15, *p=.028)

When comparing the patients who were readmitted to the acute psychiatric inpatient unit (n=15) during the study time-frame with those who were not (n=54), no significant differences were found regarding the socio-demographic variables or the type of bipolar disorder (Table 1).

Table 1: Socio-demographical and clinical characteristics of the sample (n=69) and their influence on readmission NS=non significant. NOS= Not otherwise specified
Concluding Remarks

PE for bipolar disorders has been shown to be effective in enhancing treatment compliance, promoting symptom reduction, preventing depressive, manic and hypomanic relapse, increasing the time interval before the next episode, diminishing the number and length of hospitalizations and improving socio-professional functioning and quality of life (11).

Our data is consistent with the literature on PE and shows that the “Porta Aberta” programme has significantly improved the clinical outcome of the participants in decreasing both the average number and length of readmissions. These findings are in line with previous studies concerning both individual (6) and group (7,8) PE for bipolar disorders, and support its global efficacy in these two settings.

The importance of motivation in bipolar patients engaging in PE has been highlighted previously by Cakir et al. (12). They studied motivation-related factors in bipolar patients undergoing PE and found that the presence of a family history of bipolar disorder or suicide, full medication adherence, therapeutic blood level of mood stabilizers, more regular follow-up visits, more mixed episodes and less number of total episodes were associated with a better level of attendance. Although such particular factors were not assessed in our population, motivation to participate was an essential aspect in patient selection, which may have contributed to the positive results by improving attendance.
Most studies on PE were held in an outpatient setting and required a minimum period of euthymia, usually from 3 months (12) to 6 months (7,8), in order to ensure a better assimilation and integration of the educational dimensions. Despite this common inclusion criterion for clinical studies, Colom and Vieta have stated that “in routine clinical practice it may be enough that the patient is not acutely ill and reasonably stable according to the clinician” (13). It is our belief that the earlier enrolment in our PE programme and the links established with the day-hospital staff, as long as clinical stability was assured, could have improved attendance and outcome.

This study has some limitations, such as its retrospective design, not being controlled, having a short follow-up period and not specifying the type of affective episode, which may impact the extent to which the results might be generalised. Nevertheless, it supports our clinical impression of a significantly improved outcome and suggests that enrolment in a PE programme at an earlier stage of the recovery process may also be associated with positive results.

Investigation directed at evaluating the effectiveness of non-pharmacological interventions for the management of psychiatric disorders is becoming a trend in psychiatric research which is certain to benefit future clinical practice.

**GP Comment**

*What I have learnt from this paper*

A psychoeducational programme for bipolar disorders has been shown to be effective for treatment compliance, to promote symptom reduction, to prevent relapses, to diminish the number and length of hospitalizations and to improve functioning and quality of life. Motivation of patients to participate was a key factor in contributing to positive results of the programme.

*Dr. Juan Mendive, Family Physician, Barcelona.*

**References**

10. Miklowitz DJ, George EL, Richards JA et al: A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Arch Gen Psychiatry
2003; 60: 904-912.
‘Craziness and Creativity’: a review of bipolar disorder and the artistic temperament

Hankir, A (1); Agius M (2,3,4); Zaman, R (2,3)
(1) The Royal Oldham Hospital, Oldham, England, UK
(2) South Essex Partnership University Foundation NHS Trust, UK
(3) Department of Psychiatry University of Cambridge, UK
(4) Clare College Cambridge, Cambridge, UK

Abstract

“We of the craft [poets] are all crazy,” remarked the 18th century British romantic Lord Byron about himself and his fellow poets (1). Implied in this statement is the notion that there exists a special kind of relationship between creativity and being “crazy”. Moreover, there is a certain form of “craziness” in particular that generally tends to be associated with the arts, certainly in the public mind, and that is namely manic-depressive illness. The ancient Greek philosopher Socrates discussed artistic “madness” or possession by the Muses as follows: “If a man comes to the door of poetry untouched by the madness of the Muses… he and his sane compositions never reach perfection, but are utterly eclipsed by the performances of the inspired madman.” (4). More recent empirical research employing systematic and biographical methodologies reveals that there is an association between manic-depressive illness and the artistic temperament. Professor Kay Redfield Jamison spearheaded research on live artists and revealed that there is considerable overlap between intense creative states and hypomania (42). The purpose of this systematic review is to present historical perspectives and contemporary research evidence that supports or refutes John Dryden’s notion that: “Great wits are sure to madness near allied, and thin partitions do their bounds divide”.

Key words: manic-depression, bipolar disorder, poetry, artistic temperament, melancholia.

Introduction

“We of the craft [poets] are all crazy,” remarked the 18th century British romantic Lord Byron about himself and his fellow poets (1). Implied in this statement is the notion that there exists a special kind of relationship between creativity and being “crazy”. Moreover, there is a certain form of “craziness” in particular that generally tends to be associated with the arts, certainly in the public mind, and that is namely manic-depressive illness. The association between ‘creativity and craziness’ is one of the oldest and most contentious of cultural notions. Given that the litany, both historical and contemporary, of eminent poets, playwrights and other artists who suffer from mental illness is substantial (2) the purpose of our investigation is to clarify if there is empirical evidence that supports that there is, indeed, an association between bipolar disorder and the artistic temperament.

Method

A literature search on bipolar disorder and creativity was performed. Arguments that were the most compelling in supporting or refuting an association between the artistic temperament and psychopathology were extracted and coalesced.

Historical perspectives

In Greek mythology, Dionysus, son of Zeus, and a mortal mother, was afflicted with madness while young and episodically subject to both great ecstasies and suffering. As the god of wine (3) Dionysus induced frenzied ecstasies, madness, and savage brutality in those around him. Significantly, much of the greatest poetry in Greece was written for Dionysus.
By the time of Plato and Socrates, common lore held that priests and poets communicated with the gods through inspired “madness”. Socrates discussed artistic “madness” or possession by the Muses: “If a man comes to the door of poetry untouched by the madness of the Muses, believing that technique alone will make him a good poet, he and his sane compositions never reach perfection, but are utterly eclipsed by the performances of the inspired madman.” (4).

The eighteenth century, which associated moderation with genius, was almost completely reversed by the nineteenth century Romantics, who once again emphasized not only the melancholic side, but also the more spontaneous and inspired qualities of genius.

Defining and assessing creativity

One of the challenges faced by researchers on creativity is defining the term creativity itself. Up until the early 20th century, “creative” individuals were said to have “genius.” The landmark study of Lewis Terman, who prospectively followed a group of highly gifted children over many decades, was entitled “Genetic Studies of Genius.” (5)

In Terman’s study “genius” was defined as having a high intelligence quotient (IQ) on the TQ tests that Terman himself had pioneered. Interestingly, as Terman and his group followed these high-IQ participants longitudinally into adulthood, they observed that they were generally more successful than average, but that very few of them actually made significant creative contributions, thereby supporting the argument that having a high IQ is not the same as being creative. That is to say, strictly speaking, ‘creativity’ and ‘intelligence’ are not necessarily one and the same, albeit they may share similar features. It is thought-provoking that in a separate study, hypomania has been found to increase intellectual functioning on the Wechsler Adult Intelligence Scale (6). The relationship between intelligence, creativity and bipolar disorder is beyond the scope of this article. However, future studies in this area would be an interesting line of research.

Although there may be lack of consensus amongst those engaged in research on creativity studies, a definition that the authors favour is one that purports that creativity is the ability to produce something that is novel and also useful in a very general sense (7). In fact, most definitions of creativity emphasize novelty and originality, balanced against utility. That is, creativity can be thought of as: “The development of novel solutions that work” (8).

The literature on creativity provides a vast array of paradigms and approaches to assessing the different definitions of creativity. Scientists have conducted research on the abilities that support creative thinking and problem-solving in laboratory paradigms. At a broad level, tasks can be divided into tests of convergent thinking, in which there is one correct answer, and tests of divergent thinking, designed to measure the ability to generate unique and diverse solutions. Many of these measures are based on conceptual models of creative thought.

It is noteworthy that in a meta-analysis of 36 studies, psychopathology scores were found to be robustly related to higher scores on measures of divergent thinking, $g=.50$ (9). Divergent thinking has been found to be positively related to mania risk, but was not found to be elevated among persons diagnosed with bipolar disorder (10).

Autobiographical narrative

Far and away the commonest methodology utilized to understand whether bipolar disorder is associated with creativity has been to analyse biographical and/or autobiographical narratives of eminent personages with notable creative accomplishments who were suspected of having mood symptoms. In these samples bipolar disorder is clearly overrepresented, particularly when milder forms of the disorder are considered. These findings seem to be consistent across methodologies, in that similar results materialize from research that has a more direct assessment of bipolar symptoms. However, given the concerns about reliability, bias and small sample size, findings on studies of biographical and autobiographical narratives must be considered tentative at best.
The role of psychological pain in creativity

Learning through intense, extreme, and often painful experiences, and using what has been learned to add meaning and depth to creative work, is probably the most widely accepted and written about aspect of the relationship between melancholy, madness and the artistic temperament. John Berryman, a poet and manic-depressive who eventually committed suicide, described the role of ordeal in his artistic work. "My idea is this: The artist is extremely lucky who is presented with the worst possible ordeal which will not actually kill him" (12). Poet Antonin Artaud's view - that art first heals the artist and subsequently helps to heal others - is an ancient one, inextricably bound to the belief that “madness” and the arts are causally linked.

Creative work can act not only as a means of escape from pain, but also as a way of structuring chaotic emotions and thoughts, numbing pain through abstraction and the rigors of disciplined thought, and creating a distance from the source of despair. To the extent that an artist survives, describes and then transforms psychological pain into an experience with more universal meaning, his or her own journey becomes one that others thus can better protected take (42).

Research methodologies in bipolar disorder and creativity

In one of the most widely cited studies of creativity in bipolar disorder, Richards and her colleagues reported findings using the Lifetime Creativity Scale (13) a comprehensive structured interview for assessing lifetime creative accomplishments, as defined by major endeavours that are original and objectively recognized by others as meaningful contributions. Peak lifetime ratings of accomplishment were higher among 33 persons with bipolar disorder than among the controls with no history of mood disorders or schizophrenia (14).

Choosing a creative occupation and achieving success in that area could be the end product of many different qualities of an individual or his or her context and circumstances. In a meta-analysis of 29 studies involving a sample size of 4,397 participants on personality attributes associated with choosing artistic occupations, Feist et al. (15) discovered the largest effect sizes were for the character trait of impulsivity (mean d=.75). An explanation for this is that impulsivity may help promote expression without constraint, fostering the creation of more unique ideas.

Several studies have documented heightened impulsivity within bipolar disorder, during manic episodes (16) as well as during remission. (17) Perhaps of most significance and importance, studies now suggest that impulsivity can predict the onset of the disorder among those with subsyndromal symptoms (18).

Beyond the personality feature of impulsivity in occupational choice, Feist (19) also found that persons in creative occupations obtained consistently higher scores on measures of Openness to Experience (d=.44). Openness to Experience has been related to many aspects of creativity, including creative accomplishment, engagement in creative daily activities, and divergent thinking (20). Several studies have suggested that Openness to Experience is elevated among individuals with bipolar disorder compared to controls with no mood disorder (21). Openness to Experience also appears to be positively correlated with risk for mania (22).

It has been argued that commitment and effort are major predictors of success in creative efforts (23). In meta-analyses of the predictors of creative accomplishments in both science and arts, Feist et al. identified substantial evidence for the importance of ambition and drive (24). A large body of evidence indicates that bipolar disorder is related to a drive to succeed in achieving goals. A number of studies have also documented that bipolar disorder is related to self-critical attitudes about the need to attain lofty goals (25).

It is important also to add that large-scale studies have documented higher rates of accomplishment in first degree relatives of those with bipolar disorder compared to the general population (26). One idea is that family members may experience the heightened ambition but be unencumbered by
symptoms, resulting in unusual levels of success (27). Heightened levels of accomplishment also appear to be a pre-onset characteristic of bipolar disorder; a recent study found that extremely high levels of scholastic accomplishment were predictors of the onset of the disorder (28).

The role of the depressive dimension of bipolar disorder in creativity

Because bipolar disorder can involve depressive episodes as well as manic symptoms, the potential role of negative affectivity and depression has been the focus of inquiry when considering if there is an association between manic-depressive illness and the artistic temperament. Indeed, Sir George Pickering has argued that, while depressed, a creative person may be in an incubation phase during which ideas may grow (29). This is then followed by a very creative period after the person emerges from the depression; he cites Charles Darwin, Marcel Proust, Sigmund Freud and Florence Nightingale as examples. Such examples are, of course, anecdotal and come with their attendant limitations.

It has been theorized that negative emotions may be useful for creativity, particularly for critical thinking (30) and perseverance (31). This idea has been a major research focus, with more than 63 studies considering the role of affect on creativity (32). The findings of two meta-analyses have identified no impact of negative affect or sadness on creativity tasks (33).

Beyond negative affective states, it has long been argued that depression might be related to higher creativity. Researchers conducting biographical studies, for example, have noted high rates of depression in authors, musicians and other artistic groups (34). Despite this, in studies with direct assessments of depression, depressive symptoms were negatively related to lifetime ratings of creativity (35), to measures of divergent thinking such as the Torrance Creativity scales (36) and to self-ratings of creativity (37). Given these findings, it would seem unlikely that the elevations of creativity within bipolar disorder would be explained by negative affectivity or depressive symptoms.

The role of the mania in creativity

Positive emotional states, in contrast, may broaden attention and thinking, widening the array of percepts, thoughts, and images that come into awareness (38). Fredrickson's broaden-and-build theory of positive emotions (39) proposed that the momentarily broadened mindsets triggered by positive emotions have a range of positive consequences, including enhanced creativity and cognitive flexibility. Drawing on this literature, one would expect that positive affect would enhance performance on measures of creativity. Consistent with this postulation, positive affect is related to better performance on tests that assess creativity such as a willingness to allow more atypical exemplars on the Rosch category inclusion task (40). These results therefore suggest that positive affect enhances creativity.

One of the common symptoms of manic episodes is intense euphoria. Beyond episodes, positive affectivity is elevated for some people with bipolar disorder during remission (41). Henceforth, bipolar disorder enhances performance on measures of creativity by virtue of positive affectivity, a symptom of its clinical diagnostic criteria.

The psychologist, J.P. Guilford, who carried out a long series of systematic psychological studies into the nature of creativity, found that several factors were involved in creative thinking; many of these relate directly to the cognitive changes that take place during mild manias as well. Fluency of thinking, as defined by Guilford, is made up of several related and empirically derived concepts, measured by specific tasks:

1. Word fluency, which is the ability to produce words each, for example, containing a specific letter or combination of letters.
2. Associational fluency, which is the production of as many synonyms as possible for a given word in a limited amount of time; expressional fluency, the production and rapid juxtaposition of phrases or sentences.
3. Ideational fluency, which is the ability to produce ideas to fulfil certain requirements in a limited
amount of time.

It may be that elevations in mood such as those caused by hypomania result in more creative thought; likewise, depressed mood and thinking may well lead to periods relatively bereft of creative work.

In all these aspects of creative thought, the elements of fluidity and flexibility of cognitive processing are pronounced in hypomanic states. It can be argued that the quickening and opening up of thought in an otherwise unimaginative person will not result in creative achievement. If, however, a highly imaginative person's thinking processes are hastened and loosened by mild manic states, it is likely that a distinctive quality will be added to the creative process. The grandiosity of spirit and vision so characteristic of mania, coupled with manic drive and intensity, can add an expansiveness and boldness as well (42).

A study on eminent British writers and artists

Professor Jamison studied a group of 47 eminent British writers and artists. She was interested in looking at rates of treatment for mood disorders within these groups, as well as the nature of intensely creative episodes, the similarities between such episodes and hypomania, and the perceived role of very intense moods in the work of the writers and the artists. Virtually all the creative writers and artists (89%) said they had experienced intense, highly productive, and creative episodes. These "intensely creative" episodes were characterized by pronounced increases in enthusiasm, energy, self-confidence, speed of mental association, fluency of thoughts and elevated mood, and a strong sense of well-being. A comparison of these changes with the DSM-III criteria for hypomania reveals that mood, energy and cognitive symptoms show the greatest degree of overlap between the intensely creative and hypomanic episodes. Several of the more behavioural changes typically associated with hypomania (increased libido, talkativeness, increased spending sprees of money) were reported by only a minority of subjects. Mood changes were profound. One-half reported a sharp increase in mood just prior to the beginning of an intensely creative period. The fact that the elevation in mood often preceded the creative periods rather than being entirely a result of them is important in understanding the relationship between moods and the creative process. When the subjects were asked specifically about the importance of very intense moods in the development and execution of their work, 60% stated that such moods were integral and necessary, and 30% stated said that it was very important. The rate of treatment for affective illness (38%) was extremely high in this sample of distinguished British writers and artists. Lifetime prevalence rates for manic-depressive and depressive illness in the general population are 1% and 5%, respectively. The proportion of individuals who actually seek or receive treatment is far smaller. Therefore, the findings of this study represent a conservative estimate of the actual rate of mood disorders in the sample (42).

These findings would suggest that mildly positive moods and energy increases may be more beneficial for creativity than full-blown manic episodes. This profile fits with case reports that lithium can increase productivity for those with severe symptoms of bipolar disorder (43). These results suggest that if manic symptoms provide an advantage for creativity, it may be the mild watered-down manic symptoms that do so. That is, positive affect and energy are beneficial, but treating severe symptoms could enhance creativity.

Mixed states

Kraepelin, in his 1921 classic textbook about manic-depressive illness, described mixed states, in which depressive and manic symptoms coexist; he conceptualized these mixed states as primarily transitional phenomena, that is, they tended to occur when an individual was going into or out of a depressive or manic state (46). Such states represent an important link between manic-depressive illness, artistic temperament, creativity, and the rhythms and temperament of the natural world. Other studies support the suggestion that these types of shifts in affect might contribute to creative processes (47).
Causes of diminished creativity

Creativity may decline over time for those diagnosed with bipolar disorder; the neurocognitive, psychological, and social consequences of bipolar disorder could diminish creative cognition, confidence, and motivation. In the only study to examine developmental course, preferences for complex figures were lower among those adolescents who had been ill for more years (48).

It is not known whether this pattern is observed across measures of creativity. Related to state-dependent changes, little is known about the effects of medications. Some evidence suggests that lithium can lower fluency for those with bipolar disorder. Stoll et al. described seven clients who felt that divalproex was more protective for creativity than lithium was (49).

Mogens Schou, however, who is the person largely credited for developing lithium as a treatment for bipolar disorder (50), studied a group of 24 artists. Using measures of productivity and quality of work, he found that the artists fell into three groups. Half of the subjects (12) showed great improvement; these were people who had very severe bipolar illness and found that, treatment actually enhanced their ability to create. A second group (N=6) had unaltered productivity. A third group, 6 people or 25% of the sample, had lowered productivity, although this did not necessarily occur throughout the period of treatment. Overall, notwithstanding the small sample size, these results suggest that adequate and appropriate treatment is likely to be helpful for the majority of creative people with bipolar disorder.

Conclusion

Most of the controversy surrounding the “mad genius” versus “healthy artist” debate arises from confusion about what is actually meant by “madness” as well as from a fundamental lack of understanding about the nature of manic-depressive illness.

Any attempt to polarize thought, behaviour, and emotion arbitrarily into clear-cut “sanity” or “insanity” is destined to fail; it is contrary to what we know about the infinite gradations of disease in general and psychiatric illness in particular. Most people with manic-depressive illness never become psychotic. Manic-depressive disorder, unlike schizophrenia or Alzheimer disease is not a dementing illness; bouts of mania are almost always temporary and periods of full remission exist between episodes of illness (51).

People often believe that the creative benefits of bipolar disorder stem from cognitive processes that emerge during mania. This belief, which may deter seeking treatment, may not be true. Several studies suggest that milder symptoms may be more crucial for creativity than severe symptoms. Other findings indicate that creativity may be common among family members and those at risk for the disorder who do not experience full-blown mania.

Mounting evidence that bipolar disorder can actually be advantageous by conferring creativity can be a step towards improving public conceptualizations of this disorder and reducing stigma. Above and beyond influencing public attitudes, research demonstrates that a focus on the strengths of bipolar disorder can enhance therapeutic outcomes (52).

The clinician who treats creative people with mood disorders must, of course, be a sensitive and supportive listener. Patients are likely to work best if the psychiatrist understands the challenges and difficulties that creative people confront in the pursuit of their art (53).
GP Comment

What have I learned from this paper?

This is a well-written paper, putting into context the suspicion that a clinician must often have harboured of the ‘mad genius’. We may come across a patient with radical thoughts who, if given the appropriate support, would perhaps reach greatness in life. If we could be less restrictive in our concept of ‘normality’ we could be more embracing of potentially-gifted patients, which would encourage them to realize their full potential. This is worth considering the next time we consult with a ‘bipolar’ patient.

In hindsight, the patient might also be considered non-conformist and hence could be stigmatized at the time, as all too often genius is only recognized posthumously.

Vishal Naidoo, GP.

References

4. Ibid. p 48.
20. McCrae RR, Ingraham LJ. Creativity, divergent thinking, and openness to experience. Journal of
45. Srivastava S, Ketter TA. The link between bipolar disorders and creativity: evidence from personality


51. Psychoanalyst Albert Rothenberg, for example, has been critical of studies whose findings purport to show a relationship between psychopathology and artistic creativity. This is a view at odds with most of the available historical, biographical, and scientific evidence. Some of his confusion appears to be based on a lack of appreciation for the subtlety, complexity, and fluctuation in the symptom patterns of manic-depressive illness, as well as insufficient awareness of the cyclic or episodic nature of these disorders.


‘The Melodies of Manic-Depressive Illness’: a case study of bipolar disorder

Hankir, AK
The Royal Oldham Hospital, Oldham, UK

Abstract

The purpose of this manuscript is to provide the reader with a qualitative insight into the, ‘mind of a medic who has manic-depressive illness’. The article contains a succinct description of the cultural and spiritual factors that have shaped my mindset. I then go on to signpost my own personal trajectory and I also refer to diverse source material, from Dante to Kipling, to illustrate how bipolar disorder has transformed the inner landscapes of my mind and how it has profoundly influenced my values and attitude towards life. It is my hope that my exposition will be comforting for those who derive solace from shared experience. I also hope that it will aid me in my quest to banish the stigma, certainly in the medical profession, towards doctors who have a psychiatric disorder.

Key words: autobiographical narrative, psychopathology, manic-depressive illness.

“The Saracens say that this disease [Hansen’s disease] is God’s vengeance against the vanity of our kingdom. As wretched as I am, the Arabs believe that the chastisement that awaits me in hell is far more lasting and severe. If that is true, then I call it unfair…”
King Baldwin ‘the Leper’ of Jerusalem circa 1200 AD

The epigraph of this manuscript was derived from Oscar nominated director Ridley Scott’s epic motion picture The Kingdom of Heaven. It alludes to King Baldwin’s horrendous affliction which was first suspected when his brilliant physician noticed that the King felt no pain upon sustaining trauma to his arm. It aptly illustrates, in my opinion, the immeasurable anguish that sufferers of this incapacitating illness experience. Not only are they disfigured in an aesthetic sense (to the extent that they are rendered so ghastly that they resort to, as the King did, wearing a mask to conceal their hideous appearance) but they are also, more often than not, labelled outcasts and as such ostracized from the society to which they once belonged. This social exclusion, consequently and in no small part, contributed to the torment that to which lepers were subjected. It is perhaps not superfluous to add then that the scars that can’t be seen are indeed the deepest.

The venerable Saladin was the shrewd commander of the powerful Muslim forces during the epoch of the crusades during which the Crescent and the Cross would repeatedly clash in conquest for the helm of the Kingdom of Heaven. Saladin was not oblivious to the plight of his adversary. Such was the mutual respect and chivalry between these two noble leaders, that the magnanimous Saladin would offer the valorous King Baldwin his very own personal physician. The veracity of this report is verified by a score of contemporary historians who have sifted through the works of chroniclers of the Orient (see Amin Maalouf’s ground breaking book The Crusades through Arab Eyes).

The Kurdish vicegerent was beneficiary of the Islamic Golden Age which paved the way for the European Renaissance and produced some of medical history’s most honoured and finest healers and polymaths such as the illustrious Avicenna, to name but one. Such a gesture by Saladin appeals to my psychopathology and my morality (perhaps not in equal measure depending on whereabouts I am situated on the bipolar spectrum) even centuries after the event took place. The twentieth century French thinker Michael Foucault viewed psychopathology (or ‘madness’ as he referred to it) as the natural inheritor of leprosy. Much in the same way that lepers were marginalized, those who suffer from mental illness have become today’s social outcasts and must now bear the brunt of stigma.

On a personal note, I feel that mental illness evokes negative emotions such as fear in the general public’s mind. Those who suffer from psychopathology relinquish their capacity for reason and this
may help explain the general public’s aforementioned reaction. I like to think that gone are the days that those who suffer from psychopathology are shackled to chains or are treated in any manner of inhumane ways. If anything, I feel as though my personal experiences with mental illness have made me more human and humbled me and made me realize how powerless human beings can be to the vicissitudes of life. It is my contention that we can breathe meaning into human suffering and this can help you to realize with hindsight that it wasn’t a breakdown but rather a breakthrough that you were experiencing. Psychopathology has made me realize that come what may I can never have the license to be judgmental towards another human soul. It has also made me realize how important it is to adorn my face with a smile that never fades, to bear a heart that never hates and to have a touch that never hurts…

Not only does bipolar disorder provoke you to reflect on the ontology of identity but it also prompts you to cogitate on the meaning of human existence and the purpose of life. Moreover, manic-depressive illness helps you to realize if anything how transient human existence is, as Dante so eloquently put it in his book Inferno, “Life is as ephemeral as foam in the water and as short lived as smoke in the wind.”

An inordinate amount of misconceptions about mental illness abound and my intention is to encourage people to deconstruct and reformulate their views on psychiatric illnesses in general. This should hopefully lessen the stigma if not abolish it altogether. Stigma is a recurring theme that I will expand upon in more detail later in this exposition.

I unashamedly disclose my having bipolar disorder, one of the most persistent and severe of mental illnesses, for a number of reasons. I am aware that there are employers who do not look favourably upon applicants who have a psychiatric illness and it is an established fact that sufferers of psychopathology are less likely to be employed than those who have a physical ailment. My aim is to increase awareness and dispel myths about psychopathology in general and manic-depressive illness in particular by elaborating on my personal experiences and by signposting my own journey. In the same vein as the creative David Holloway said in his moving article, My ‘Colorful’ life with Schizophrenia, “I pray that the perception of manic-depressive illness can be altered to that of a renewed awareness which evokes notions of love, peace and harmony”.

My purpose is to provide you with a qualitative insight of manic-depressive illness. As a recently qualified doctor I will attempt to do this through the dual perspectives of objectivity and subjectivity, by reconciling healer and healed and hopefully, by doing so, repudiate the unfounded perception that service provider and service user are ostensibly dichotomous. By this I intend to bridge the gap between the two.

If this article provokes you to reflect on how many of us take the stability of our moods for granted and how dysfunctional we can become when our moods do go haywire it would have served part of its purpose. However such oscillations and extremes in mood do not come without their gems for, as Khalil Gibran so wondrously put it, the more sorrow carves into your being the more joy it can contain…

Disclaimer Alert

“They learn in suffering what they teach in song. An artist survives, describes and then transforms psychological pain into an experience with more universal meaning and his or her own journey becomes one that others can, thus better protected, take.”

- Professor Kay Redfield Jamison, author of the international bestseller An Unquiet Mind, Professor of Psychiatry in Johns Hopkins University, world authority on bipolar disorder, voice of manic-depression…

I am aware that, much like myself, there are those who derive solace from shared experience and my fellow manic-depressives may find comfort and even redemption in my lines. However I lay no claim to being master of the illness that afflicts me. If you do suffer from bipolar disorder the best recourse is
to seek attention from a friendly GP or other qualified mental health practitioner for a systematic and thorough psychiatric assessment. You are not the best person to plan your assessment, treatment and referral. So although I have personally experienced psychopathology, the devastating lows and the ebullient highs, this exposition should never replace the advice, guidance and recommendation given by an expert i.e. a consultant psychiatrist.

Indeed, in the wise words of the founder of modern medicine himself, Sir William Osler, “The physician who doctors himself has a fool for a patient”.

My narrative will not delve so much into the basic science of bipolar disorder; what I want to convey is what it’s like to have manic–depressive illness, to have to grapple with this disorder of affect that “was bequeathed to me by antiquity; that has survived the ravages of time and has possessed me much in the same way that a malevolent spirit possesses its victims however despite its proclivity to cause so much carnage it is something I vacillate over exorcising from my being…” I have referred to the tools of prose and verse in an attempt to express the inexpressible anguish that manic-depressive illness causes to sufferers and their loved ones.

The written word can serve as a medium to transmit the essence of bipolar disorder to all those who wish to inform themselves about this capricious illness. Indeed the benefits can be manifold. However, that is beyond the scope of this essay. Suffice it to enumerate that famous novelists, such as William Styron and John Berryman, to name but two, both wrote candidly about their own psychopathology and reported finding this very same activity both engaging and therapeutic.

**Bipolar disorder: historical perspective**

Bipolar affective disorder has been known since ancient times. Hippocrates described patients as ‘amic’ and ‘melancholic’, and clear connections between melancholia and mania date back to the descriptions of the two syndromes by Aretaeus of Cappadocia (c. 150 BC) and Paul of Aegina (625-690). Thinking at that time reflected ‘humoral’ theories, with melancholia believed to be caused by excess of ‘black bile’ and mania by excess of yellow bile.

**The reductionism of nomenclature…**

“The clinical reality of manic-depressive illness is far more lethal and infinitely more complex than the current psychiatric nomenclature would suggest. Cycles of fluctuating moods and energy levels serve as a background to constantly changing thoughts, behaviours and feelings. The illness encompasses the extremes of human experience. Thinking can range from florid psychosis, or ‘madness’, to patterns of unusually clear, fast and creative associations, to retardation so profound that no meaningful mental activity can occur. Behaviour can be frenzied, expansive, bizarre, and seductive, or it can be seclusive, sluggish, and dangerously suicidal. Moods may swing erratically between euphoria and despair or irritability and desperation. The rapid oscillations and combinations of such extremes result in an intricately textured clinical picture. Manic patients, for example, are depressed and irritable as often as they are euphoric; the highs associated with mania are generally only pleasant and productive during the earlier milder stages”.


**Case Study: Dr Ahmed Hankir**

I was born on the 15/09/1982 in Belfast, Ireland. I lived in the picturesque city of Dublin for a spell before moving to the idyllic county of Worcestershire where I resided for half a decade prior to being whisked away to the war-torn lands of Lebanon, where I am ethnically from.

I spent my formative years in the Middle-East. I attended a school with an American curriculum and by virtue of this I assimilated into my identity aspects of the American culture: the accent, the zest for life, the gregariousness and also a passion - perhaps even an obsession - for basketball (this proved
to serve me well in fact, for I would go on to captain the Manchester University Men’s First basketball team despite my diminutive stature and it was during my tenure as team captain that the squad won the British University Sport’s Association national tournament in 2006).

I returned to the British Isles at the tender age of 17. This was a significant mark in my life; from that point on I would be totally dependent on myself in the financial sense but also in the emotional sense in that I would no longer be living in the immediate milieu of my parents. But the UK wasn’t like Lebanon where if you don’t work, you don’t eat and furthermore a good education was your birth right and I’d be damned if I squandered this golden opportunity, this decent shot at life that I had been granted because of the sacrifice that other Britons of previous generations had made in order that I live a better life than them. It didn’t take what the Columbia University Scholar C. Wright Mills called a “sociological imagination” that I would later acquire to realize at that time that I had plenty to be grateful and sanguine about.

Money didn’t grow on trees and so I worked full-time for three years prior to matriculating in higher education. The calluses on my hands were testament to the toil of my labour. You reap what you sow and it would only be a matter of time before this became apparent. Until then, I started to notice feelings of melancholia; however I feared that any expression of ennui would be tantamount to complaining so in a maladaptive manner, I repressed my feelings.

Leaving my family at a young age, migrating to a culture that was quite different to the one I was immersed and integrated in for the previous five years and having to support myself to survive were all factors that precipitated the low mood. A facet of my pre-morbid personality - my sensitivity- only perpetuated the depressive illness that I was experiencing, albeit a mild depressive illness. This was tempered more or less by another trait of my pre-morbid personality and that is to always be thankful for what I have been bestowed with and to constantly be mindful of how fortunate I am relative to so many others (in a way I was providing myself with cognitive behavioural therapy). It is important to note that, although I may have had a looming insight into how I was feeling, this was largely ineffectual at stopping me from feeling the way I did when I was in extremis. Although I was fully aware that there were people who were damned and doomed for the rest of their cursed existence in dungeons I was feeling the way I did regardless, for my persecution assumed a different guise.

I enrolled in a sixth form for the A-Level assessments since, despite graduating top of the school that I attended in Lebanon, the qualification that I was in possession of was not recognized. Even though I was in full-time employment I still managed to receive straight As and I was granted admission into Manchester Medical School. My dream had come true...

“All men dream but not equally; those who dream by night in the dusty recesses of their minds wake in the day to find that it was vanity. But it is the dreamers of the day who are dangerous men for they may act their dreams to make them possible. This I did”.

- Lawrence of Arabia

In 2006 reports started trickling in about a war that was being waged upon Lebanon. The sheer abruptness was astounding; Lebanon was only just recovering from a devastating civil war and after many, many years of reconstruction Beirut was now, once again, becoming a tourist attraction. It only took a matter of days for Lebanon’s concrete infrastructure (for Lebanon’s abstract fabric is impregnable) to be obliterated. It was around this time that I started to notice the following:

- “I was dreaming dreams that no mortal ever dared to dream before…”
- Grandiloquent ideas, racing thoughts, Knight’s Move thinking evident
- Pressurized speech
- Argumentative, irritable, impetuous, over-familiarity
- Over-generosity and spending sprees
- Reduced need for sleep
- Increased amounts of energy (subjective 11/10)
- Affective incongruity (feeling elated despite the fact that my world has turned upside down, but this will soon change…)
Predisposition: both my parents suffer from depressive illness. However, it is noteworthy that my monozygotic twin brother was spared of the disorder, highlighting the environmental role played in manic-depressive illness (my twin brother has gone on to achieve great feats of his own, obtaining a doctorate from Imperial College London and is presently a post-doctoral research fellow at The Department of Physiology Anatomy and Genetics, Oxford University).

Precipitating factor: war waged upon my country of origin was a major stressor, although there were a number of other factors that also culminated and compounded.

Perpetuating factors: refusing to seek psychiatric treatment out of fear that I was ungrateful for all of what I have been given in life and parents living overseas so they were not able to care for me and provide me with the support that they would have wanted to due to logistics.

I have devised a simple formula in an attempt to understand what was happening to me:

Lack of moral support by those closest to me
+ War waged upon my country of origin
+ 12 hours a day intense preparation for high stake assessments
= STRESS!

And never forget, “Sometimes an appropriate response to reality is to go insane…” And always remember, “Insanity is much like gravity all it takes is a little push…”

A full-blown mania ensued. When beholden to the spur, flights of fancy and notions of romanticism compel you. I came across a terse biography of Thomas Willis in the footnote of the OHCM. It outlined his many scholarly achievements, apart from his famous circle, his accomplishments in the field of academic medicine include tracing the track of the spinal accessory nerve (few have followed him I am told) and associating the sweet taste of glycosuria to diabetes mellitus.

This was all good and well but what truly inspired me was yet to come. Apparently during his lunch break whilst he was lecturing in Oxford, he developed the peculiar habit of giving his meals away to the poor and destitute. I was awe-struck by this august man’s altruism and so naturally I sought to emulate him…

Who am I to complain? I have been bestowed with so much good fortune in my life and yet still I find something to moan about. I felt like I was taking having shelter for granted. What is life like for those who are less fortunate, the homeless say? Atticus Finch in Harper Lee’s To Kill a Mocking Bird proclaimed “you can never really know a man unless you slip into their shoes and walk around in them”.

So I took heed to his calling. I crossed the Atlantic and worked as a Spare Change Newspaper vendor in Boston. I slept on the cold and hard streets of Boston. I kept on saying to myself “If I want to understand how hard it must be for the homeless I have to slip into their shoes and walk around in them…” I composed an article that was published in the same newspaper I was attempting to sell to the people of Boston. It was my first real attempt at writing. With hindsight, I realize that it wasn’t as good as I perceived it to be (indeed whilst manic grandiosity will inflate your perception of your own ability and may even cause you to become self-aggrandizing) but it does illustrate a number of salient points:

(1), those who suffer manic-depressive illness find comfort and therapy writing and reading (bibliotherapy) as mentioned above and
(2), there is a theory that there exists a correlation between manic-depressive illness and the artistic temperament. The litany of writers, artists and composers who suffer from this form of psychopathology includes some of the most creative and brilliant people in history. Not that manic-depressive illness makes me the next Lord Byron, or does it?!

The aftermath of mania is invariably melancholia… I started to sink into the murky depths of a
depressive illness, a depression too dreadful to describe. Suicidal ideation, irregular/disturbed sleeping patterns, socially withdrawn, listlessness, feelings of worthlessness, utter guilt and sheer shame, inability to concentrate and a bleak outlook for the future are all part and parcel of the depressive dimension of bipolar disorder. I was, ironically, rendered homeless consequent to the spending spree as a result of being over-generous whilst manic; for two nights I slept on the hard and cold streets of Moss Side (déjà vu?). These were the toughest times of my life and things were not going to get much better any time soon…

The namesakes that have affectionately been bestowed upon me include wandering poet, travelling healer and repository of medical mnemonics and quotes. The three vital signs of psychic life are introspection, ambivalence and turmoil. I composed some original poetry which may provide a window to my turmoil of mind at the time…

“Regard the conflagration in my wake, an inexorable inferno burning bridge after bridge! Wipe that tear, my dear I say. Stay, don’t go away. If only you know that for you I’d bleed myself dry. For you, I’d bleed myself dry…”

As I alluded to in the above stanza, whilst the bridges in Lebanon were burning quite literally, I started to burn bridges in the metaphorical sense with people who, at the time, I thought were my closest companions.

“Champagne to my real friends and real pain to my sham friends…”
- Edward Norton, 25th Hour.

It is true that my friends became fewer but firmer and my reputation tarnished apparently irrevocably so to the extent that I was ostracized by these so-called ‘sham’ friends of mine. Social exclusion had a deleterious effect on me. I was sinking deeper and deeper into the darkness…

**Stigma**

A stigma was a scar on the skin of ancient Greek criminals. It was a sign to all that they were unsafe, unclean and unwanted. Stigma stills persists today in the public’s attitude towards those who are mentally ill. We see a fundamental divide between the psychotic mind and the asthmatic lung, as if those who suffer from psychopathology do so out of their own making and as such do not deserve the same kind of sympathy we would ordinarily show to someone with another chronic or long term illness like cancer but instead they are made to endure the howls of derision that are hurled at them…

So what, might you ask, deterred me from abusing substances? Wouldn’t that help me to escape from reality (for mankind cannot bear very much reality - TS Elliot)? Simple, one word: Chief! It behoves me to make a popular culture reference at this stage:

“Every time the old man put the bottle to his mouth, he wouldn’t suck from out of it but it would suck from out of him until he was yellow and he was wrinkled and not even the dogs would recognize him”
- Chief from ‘One Flew Over the Cuckoo’s Nest’

So popular culture actually conferred protection, although my religious beliefs did have a more powerful hold on me this is not to negate this medium as a useful interface to promote public health campaigns (and perhaps promoting abstinence was not the intended effect of the scene but the outcome was a positive one in my case)…

**Medication**

Patients with manic-depressive illness may not opt to popping pills in order to cure themselves (a lot of patients don’t believe that there is anything the matter with them in the first place). The reason behind this resistance is that they perceive the taking of medication to be a sign of weakness. Also, manic-depressive illness has a profound effect on a person’s identity and some patients believe that taking medication will rob them of their character. There is also the concern of medicalising human
emotion. A person with manic-depressive illness can no longer merely be angry any more, for any manifestation of human emotion is regarded as symptomatic of his illness.

An SSRI (i.e. citalopram) was prescribed by my family doctor. However, the consequences were deleterious. An adverse reaction ensued (SSRI used to treat depressive illness in patients with bipolar disorder can cause a drug-induced hypomanic or manic episode which is what happened). Consequently I became “dysfunctional” as a result of this drug-induced hypomanic state (people at my work place were complaining about my being more assertive and inappropriate displays of ebullience). Citalopram was then discontinued. The anti-psychotic quetiapine was then instigated since it has mood-stabilising properties. Also used as an off-license sedative (which is the reason why most patients, including myself, refuse to continue complying with this medication).

AED carbamazepine was considered, since it is known to have mood-stabilising properties, yet not commenced since it is hepatotoxic and blood results revealed that I had unexplained deranged LFTs. Lamotrigine, another AED, was considered. However, it has been known to cause Stephens-Johnson syndrome and must be commenced with caution. Lithium has a narrow therapeutic index and is not advocated by some psychiatrists on the grounds of its toxic side-effect profile.

A Taste of the High life…

After having completed a fascinating special student component in Bedford with Dr Agius and Dr Zaman as my co-supervisors I received one of the most extraordinary phone calls in my life. A good friend of mine is presently serving a dual appointment as professor of political economy and international business. He is also a consultant for the United Nations on radicalization. I received an unexpected phone call from him almost immediately after my interlude in the south of England asking me if I’d like to tutor a very important person on sociology. The subject matter was not my area of expertise. However, since the student was a first year undergraduate I accepted his request and met the challenge. Before I knew it, I found myself before the presence of a powerful personage. For the purposes of discretion, a strict anonymity of my student’s true identity must be observed. I made it clear to him that the subject matter, although not esoteric enough to be beyond my capacity to fathom and teach, was not a specialist interest of mine. However, my client seemed more than content after the first tutorial and invited me to be his personal tutor for three months.

My employers generously provided me with accommodation in a five star hotel in Mayfair, London, and unlimited room service. They also remunerated me rather handsomely. The whole experience felt so surreal. Having a contact with arguably the highest echelon in society was beyond my wildest imagining. It spoke volumes about the character of my student, who proved to be a most humble and hospitable man who was not one to be perturbed and always maintained equanimity. He was also rather docile and intelligent and I have great expectations for his future.

Medication did not heal me the way reading books did and I would voraciously read whatever I could lay my hands on. Theology, sociology, psychology, English literature (my favourite of all), you name it. Whether manic-depressive illness was responsible for my unquenchable thirst to acquire knowledge is perhaps a matter for further discussion and analysis. All I know is that my life experiences have been so diverse and wide ranging, from as Rudyard Kipling so poetically puts it, talking to crowds and keeping my virtue to walking with kings and not losing that common touch. However, I still feel so terribly inadequate and I want to achieve so much more in this life. I will not despair for I know that it is the discontent that drives human progress and that when there is optimism there is nothing that cannot be transcended.

And today…

“11 years ago a young disillusioned 17 year old man arrived on these shores with nothing but two suitcases, hope and faith. He said he wanted to be a doctor and that he would do anything it takes to realize his dream. Now, as I write these lines reclined on a sofa inhaling the sweet scent of Jasmine that permeates the Mediterranean breeze I can reveal to all that hope is most certainly audacious and that with forbearance and fortitude you can overcome the seemingly formidable obstacles that may come
your way and achieve your goals, however lofty they may seem. After all, why aim for the sky when there are footprints on the moon?"

An Ode to the Salmon Family, my Saviours…

“No man is an Island, entire of itself…”
- John Donne Meditation XVII

Toby Salmon is an incredibly cultured, intelligent and confident young man whom I met when we were both in our first year in university. Toby was charming and eloquent. A firm friendship soon transpired between us. To this day, the only person I have met who has better listening skills than Toby is his father, the honourable Charles Salmon QC. When life became unbearable I turned up at Charles’s doorstep in London. Vanessa, Toby’s mother, provided for me as if she were my very own mother. They cared for me and supported me and showed me a kindness that to this day still brings tears to my eyes. I was down and out; nobody wanted to know me when I broke down. But the Salmon family wouldn’t give up on me. They remembered who I was and what I was like before the breakdown and they had unshakable belief in me. For the next five years, they would provide me with emotional and even financial support. When I was literally penniless a phone call to Charles and he would transfer the funds for me to get some food. His generosity is the like of which I have never come across before in my life. I would spend weekends in their family home where I would experience unbridled joy and unalloyed happiness basking in the warmth of their presence and I would return to Manchester with bags full of groceries.

The love that I received from the Salmon family is why I am a doctor today. I COULD NOT HAVE QUALIFIED WITHOUT THE ASSISTANCE OF THE SALMON FAMILY. If manic-depression makes you learn more about the nefarious side of the human condition, of how cruel people can be to you, it can also make you learn about how altruistic and good-hearted people can be. I owe everything to the Salmon family. There isn’t a day that goes by that I don’t think about them. It is people like them that make this world a better place to live in.

And last, but by no means the least, my older brother Khoder Hankir is the person to whom I dedicate this article. Khoder’s trajectory is one laden with pathos. However, he would never reveal this outwardly, lest he burden others with his own tales of woe. He is the most considerate, conscientious and earnest individual I have ever met and also one of the most compassionate, industrious and diligent. He is the bedrock of the Hankir family and his support, both moral and financial, helped me to realize my dreams. Thank you immeasurably, Khoder Hankir, for being the great man that you are, and for inspiring me to be a better man.

GP Comment

What have I learned from this paper?

This was an insightful, courageous and moving account of a colleague with mental illness that touched a chord within me. We all at some point question our own sanity and display traits of some of the criteria.

In this current age of dependence on pharmacologic interventions, the importance of emotional support of a family structure, should never be underestimated.

Dr Vishal Naidoo, GP.
Review and Overview: autobiographical narrative and psychopathology

Hankir, AK (1); Agius, M (2, 3, 4)
(1) The Royal Oldham Hospital, Oldham, England, UK
(2) South Essex Partnership University Foundation NHS Trust, UK
(3) Department of Psychiatry University of Cambridge, UK
(4) Clare College Cambridge, Cambridge, UK

Abstract

With the immediacy and authenticity of the first-person narrative, the mental illness memoir creates a graphic picture of human existence in the “kingdom of the sick” (Sontag, 1978). Moreover, autobiographical narratives of mental illness have an established tradition of lending themselves to the psychiatric field. Jaspers, in his General Psychopathology (1913), borrowed from Schreber’s Memoirs of My Nervous Illness (1903). Indeed, both Freud (1911) and Sass (1994) have based their own constructs of delusions and other mental illness phenomena on Schreber’s descriptions. The three vital signs of psychic life are ambivalence, introspection and turmoil. William Styron wrote candidly about his own turmoil of mind whilst in the throes of melancholia: ‘I was feeling in my mind a sensation close to, but indescribably different from actual pain’ (1990:p.16). Autobiographical narratives of mental illness provide a window into the nature of psychopathology in a way that is not possible from standard psychiatric texts. They allow psychiatrists, service users and the general public a rare qualitative insight into the richness of psychopathology as experienced first hand rather than as drawn out and described by psychiatrists. Indeed, in the preface of Oliver Sack’s book The Man who Mistook his Wife for a Hat the author contends, ‘To restore the human subject at the centre - the suffering, afflicted, fighting, human subject - we must deepen a case history to a narrative or tale…’ (1985). Perhaps it is for these reasons that the editors of Cutting Edge Psychiatry in Practice have decided to include autobiographical narrative in their journal. For the GP or psychiatrist reading them, it can be insightful and instructive. For family and friends of loved ones who suffer from psychopathology, it can be informative and illuminating. For those who actually compose the articles, it can be an effective and indeed cathartic form of therapy.

Key words: autobiographical narrative, psychiatry, health humanities

Introduction

‘In order to restore the human subject at the centre, the suffering afflicted fighting human subject; we must deepen a case history to a narrative or tale…’
- Oliver Sacks.

Cutting Edge Psychiatry in Practice (CEPiP) includes in each one of their issues an autobiographical narrative from a person who suffers from the mental illness of that particular issue’s theme. In the inaugural issue of CEPiP The Management of Schizophrenia: an Update, David Holloway authors an autobiographical narrative entitled My ‘Colorful’ Life with Schizophrenia. Tom Inskip, a General Practitioner, states that David’s manuscript “Is a very moving account from a highly articulate individual with schizophrenia… the condition [schizophrenia] can occur in wonderfully sensitive, creative and caring individuals.” (8).

It is with the immediacy and authenticity of the first person narrative that the mental illness memoir creates a graphic picture of human existence in the “kingdom of the sick” (1). Moreover, autobiographical narratives of mental illness have an established tradition of lending themselves to the psychiatric field. Jaspers, in his General Psychopathology (2), borrowed from Schreber’s Memoirs of My Nervous Illness (3). Indeed, both Freud (4) and Sass (5) have based their own constructs of delusions and other mental illness phenomena on Schreber’s works.
In many respects, psychiatrists owe an enormous debt to Schreber, whose seminal writings have helped to facilitate the illumination of psychopathology. This salient fact supports our contention that autobiographical narratives of psychopathology are beneficial. The mental illness memoir can be utilized to understand what service users are experiencing better by providing an insight into psychiatric phenomena, be that the oscillations in mood and the flights of fancy that characterize bipolar disorder, the persecutory delusions and third-person auditory hallucinations that define psychosis, or the suicidal ideation and the nihilistic thoughts that pervade and permeate the depressive mind.

Methodology

We conducted a non-systematic review of the literature. We extracted and amalgamated the passages that we found to be the most compelling from the autobiographical narratives of eminent novelists, poets and academics that suffered from the major psychiatric illnesses, namely the disorders of affect and schizophrenia. We have also offered our own humble annotations for readers’ dissection and delectation. We herein present the vivid and vivacious first-person accounts of psychopathology as experienced first-hand and in doing so hope to portray the subjective expression of mental illness more accurately. We further hope that this manuscript will help service providers, relatives of the mentally ill and the general public to understand people who have a mental illness better and in doing so help to reduce stigma.

John Perceval: an autobiographical narrative of schizophrenia

John Perceval was the progeny of Spencer Perceval, the British Prime Minister who was assassinated in the House of Commons. In his book A Narrative of the Experience of a Gentleman during a State of Mental Derangement to Explain the Causes and the Nature of Insanity, and to Expose the Injudicious Conduct Pursued towards Many Sufferers under that Calamity, Perceval evocatively describes his debilitating symptoms and the inhumane treatment he received whilst institutionalized. His brave and often disturbing account of the squalid conditions of the asylums and of the situation of his fellow patients is illustrative of the appalling treatment that mentally ill people in England had to endure at the beginning of the 19th century.

Perceval’s piercing definition of mental well-being and of having capacity, borne from his realization of what it is like to relinquish that capacity by succumbing to mental illness, should serve as a blueprint for defining a healthy psychic life. Moreover, it is testament to how it is only in sickness do we truly understand (and indeed value) the meaning of health:

A man who knows who and what he is, his position in the world, and what the persons and things are around him; who judges according to known, or intelligible rules; and who, if he has singular ideas or singular habits, can give a reason for his opinions and his conduct; a man who, however wrong he may act, is not misled by any uncontrollable impulse or passion; who does not idly squander his means; who knows the legal consequences of his actions; who can distinguish between unseemly and seemly behaviour, who feels that which is proper and that which is improper to utter, according to the circumstances in which he is placed; and who reverences the subject and the ministers of religion; a man, who, if he cannot always regulate his thoughts and his temper and his actions, is not continually in the extremes, and if he errs, errs as much from benevolence and hesitation, as from passion and excitement, and more frequently: lastly, a man who can receive reproof, and acknowledge when he has needed correction. (6)

The passage below is also derived from Perceval’s autobiography and is, in our opinion, also poignant in its effect:

If anyone knew how painful the task of self-examination and of self-control was, to which I devoted myself at the time, every minute without respite, except when I was asleep, in order that I might behave, and with the sincere desire of behaving becomingly; they would understand how cruel I felt it afterwards, when I required my liberty for the further pursuit of health and of strength of mind, to have it denied to me for fear of my doing any person any bodily harm (7).
These lines permeate with a conscientiousness of not harming another soul’s feelings. They reflect the diligence and earnestness with which Perceval was mindful of others and how imperative it was for him to function selflessly in society and to even be vigilant when regarding and considering the rights of others. It is testament to the painstaking lengths that Perceval, and indeed others who suffer with mental illness, will go to in order to promote social order in the community in which they are immersed. No doubt this account will resonate with other people who have a psychiatric disorder. It is our hope that this narrative will help to dispel the myth that all those who suffer from psychopathology are only preoccupied with refusing to abide by the law.

According to David Holloway: “I pray that the perception of schizophrenia can be altered to that of a renewed awareness which evokes more notions of love, peace and harmony… instead of the negative crime films in Hollywood and those crude depictions on television…” (8) This echoes the message that Perceval’s autobiographical narrative delivers: namely the notion that those who suffer from schizophrenia can be perceptive, sensitive and caring just like ‘normal’ people, perhaps even more.

**Memoir and Melancholia**

The three vital signs of psychic life are ambivalence, introspection and turmoil. William Styron wrote candidly about his own turmoil of mind whilst at the throes of melancholia: ‘I was feeling in my mind a sensation close to, but indescribably different from actual pain’ (9).

This analogy between depressive illness and physical pain is ubiquitous in the writings of novelists who suffer from depressive illness. Take, for instance, the 20th century American poet, Sylvia Plath, and the 19th century British novelist, Virginia Woolf, both of whom notably suffered from severe depressive illness and committed suicide, to name but two. Writing in 1902, the eminent Harvard University scholar and the father of modern psychology, William James, described the depressive dimension of his bipolar disorder as follows:

‘It is a positive and active anguish, a sort of psychical neuralgia wholly unknown to normal life’ (10).

For others, the intangibility of the emotional pain drives the individual to inflict actual physical harm upon themselves. For example, Sarah Ferguson (11) wrote:

*I slashed my wrist again and again as deeply as I could… As my writing to you comes to a close, the pain is so unbearable inside me that a force of such strength has driven me to inflict a physical pain on myself in the hope of appeasing the other.*

This excerpt is extraordinary for multifarious reasons. Foremost, it gives credence to the unbearable mental agony that a sufferer of a psychiatric illness can experience to the extent that the physical pain brought on by slashing one’s wrist is a welcome relief. Almost everyone accepts that those who suffer from physical pain are worthy of our sympathy. However, to pronounce that mental illness can be just as distressing, if not more so, is more often than not ridiculed and rejected. It seldom is judged to merit sympathy from other people.

Indeed, British television personality Trisha Goddard’s autobiographical narrative describes her experiences as an inpatient in both a psychiatric hospital and a breast cancer unit and it further illustrates how we, in general, are not as sympathetic to mental illness as we are to physical illness:

*“Both experiences were horrible… but with breast cancer people ran towards me with open arms and hugged me. With depression people ran away… When I was diagnosed with breast cancer, I was inundated with ‘Get Well Soon’ cards. When news leaked out that I was in a psychiatric hospital following a breakdown, not a peep. And certainly no cards…”*  

William Styron eloquently describes the perils of reductionism in his own autobiographical narrative by elaborating on the usage of the term depression and how it came to replace the more apt term melancholia. Styron’s account commands the attention of all those who stake a claim in wanting to understand the subjective experience of a psychiatric illness better: When I was first aware that I had been laid low by the disease, I felt the need, among other things, to **register a strong protest against the word “depression”. Depression, most people know, used to be termed “melancholia,” a word which… crops up more than once in Chaucer, who in his usage seemed to be aware**
of its pathological nuances. “Melancholia” would still appear to be a far more apt and evocative word for the blacker forms of the disorder, but it was usurped by a noun with blank tonality and lacking any magisterial presence, used indifferently to describe an economic decline or a rut in the ground, a true wimp of a word for such a major illness. It may be that the scientist generally held responsible for its currency in modern times, a John Hopkins Medical School faculty member justly venerated - the Swiss born psychiatrist Adolf Meyer - had a tin ear for the finer rhythms of English…As one who has suffered from the malady in extremis yet returned to tell the tale, I would lobby for a truly arresting designation… Told that someone has evolved a storm - a veritable howling tempest in the brain, which is indeed what clinical depression resembles like nothing else - even the uniformed layman might display sympathy rather than the standard reaction that “depression” evokes something akin to “So what” or “You’ll pull out of it” or “We all have had bad days” (12).

**Professor Kay Redfield Jamison, manic-depressive, John Hopkins scholar and world authority on bipolar disorder**

Kay Redfield Jamison is the Professor of Psychiatry at the Johns Hopkins University School of Medicine and co-director of the Johns Hopkins Mood Disorders Center. She is also Honorary Professor of English at the University of St. Andrews in Scotland. Kay is a prolific publisher of peer-reviewed manuscripts and best-selling books. Her magnum opus on manic-depressive (bipolar) illness was chosen in 1990 as the most outstanding book in biomedical sciences by the American Association of Publishers. She is also the author of Touched with Fire (this was the text that manic-depressive Stephen Fry was perusing whilst reclined on a bench in his award-winning documentary The Secret Life of the Manic-Depressive), An Unquiet Mind, Night Falls Fast, and Exuberance.

An Unquiet Mind, which chronicles Professor Jamison’s own experience with manic-depressive illness, was cited by several major publications as one of the best books of 1995. Dr Jamison is the recipient of numerous national and international scientific awards, including a MacArthur Award. Indeed, naysayers ought to take heed of Professor Jamison’s accomplishments and disabuse themselves of the illusion that those with psychopathology cannot be high achievers. The case of Professor Jamison should sound the death knell of associating psychiatric illness with poor performance and under-achievement.

All of this renders her autobiographical account especially illuminating, for she is able to adopt the dual perspective of objectivity and subjectivity, of repudiating the perception that service-user and service-provider are ostensibly dichotomous and of reconciling healed with healer. Her mastery of the English language gives a voice to the voiceless; it is an efficacious adjunct to pharmacotherapy, particularly for those who derive solace from shared experience.

It is our contention that any individual who wishes to be informed in bipolar disorder must be, at the very least, familiar with her works. The paragraphs below are extracted from her autobiographical narrative An Unquiet Mind and, in our opinion, far surpass present day psychiatric nomenclature in conveying the essence of bipolar disorder.

**Bipolar disorder and autobiographical narrative**

Depressive illness has recognizable effects on cognition and behaviour as depicted by Jamison in the following excerpt:

*Sleep deserted me. And, no longer able to stomach myself, I stopped eating. There was no revulsion but I didn’t want to eat anything* (13).

Those who suffer from bipolar disorder are all too familiar with these symptoms and will indeed identify with Professor Jamison. Such identification and the catharsis that can come from it is, in our opinion at least, a step towards convalescence.

Jamison goes on to describe how once she had decided to end her life:
‘I was cold-bloodedly determined not to give any indication of my plans or the state of my mind. I was successful. The only note made by my psychiatrist on the day before I attempted suicide was severely depressed. Very quiet’ (14).

This deliberate artifice in order to conceal one's intentions to commit suicide is instructive to psychiatrists. The compulsive nature of suicidal thinking and the tendency to deceive others once the decision to take one's life with one's own hand has been reached should be more broadly understood by all clinicians but perhaps more so by the nurses who are charged with a patient's day-to-day care. This supports our contention that autobiographical narratives should be read not only by psychiatrists but also by other mental health service providers.

Depression is situated at one pole of the spectrum of disturbed mood. At the other end of the continuum is mania. Jamison described the experience of manic exuberance and ebullience very vividly in her autobiographical narrative:

*My memories of the garden party were that I had had a fabulous, bubbly, seductive, assured time. My psychiatrist, however, in talking with me about it much later, recollected it very differently. I was, he said, dressed in a remarkably provocative way, totally unlike the conservative manner in which he had seen me dressed over the preceding year… [I] seemed to him, to be frenetic and far too talkative. He says that he remembers having thought to himself, Kay looks manic. I on the other hand, had thought I was splendid* (15).

This passage is especially revelatory. Whilst beholden to the spur, mania can cast a romantic hue on events and henceforth the lens that sufferers view the world through can contort reality. In extremis, insight is lost and so whilst those who have bipolar disorder may maintain that their behaviour was not unbecoming in any way, shape or form, the general consensus of observers countermands this assertion. This supports the necessity of requesting for a patient to bring a friend or significant other as part of a thorough psychiatric assessment to provide an alternative account on what prompted a service user to consult a service provider.

**The wide-ranging benefits of the health humanities**

“In short, to teach a student to read, in the fullest sense, is to help train him or her medically. To ask the medical student what is being said here… is to prepare him or her for the doctor-patient encounter.” (16).

“A reader reading well is simultaneously experiencing the text, responding to it emotionally, and at the same time analyzing that response, tracking it to its sources… Doing one without the other is not reading. And it is not doctoring either.” (17).

There is a growing perception that science alone (or science with glances towards ethics and the social sciences) provides insufficient overall foundation for holistic understandings of the interaction between health, illness and disease. A distinguished group of evidence-based researchers agrees (18):

‘... knowing the tools of evidence-based practice is necessary but not sufficient for delivering the highest quality patient care. In addition to clinical expertise, the clinician requires compassion, sensitive listening skills, and broad perspectives from the humanities and social sciences’ (19).

We contend that since autobiographical narratives of mental illness fall under the remit of health humanities, clinicians (particularly psychiatrists) who read them will be better able to deliver the highest quality patient care.

Moreover, autobiographical narratives can also be utilized by those in the medical profession; in a moving anonymous autobiographical narrative in the student BMJ, the author, a medical student who attempted to commit suicide, asserts:

“…we need to get better at accepting that things go wrong for medical students and doctors in the same way that they do for all people. In the US alone, 400 doctors are lost to suicide every year, a huge and needless toll. I was so nearly another casualty, and it is only through increasing the extent to which we make it more acceptable to share our experiences of difficulties with low mood that the number of suicides among medical students will fall… (20).”

Autobiographical narratives provide us with the means to “share our experiences of difficulties
Conclusion

Autobiographical narratives of mental illness are precious sources of information. They provide a window into the nature of psychiatric disorders in a way that is not possible from standard psychiatric texts. They allow psychiatrists, other mental health service providers, relatives of people with mental illness and the general public a rare qualitative insight into the richness and, as David Holloway so pertinently put it, the ‘colors’ of psychopathology as experienced firsthand rather than as drawn out and described by psychiatrists. It is abundantly evident that psychiatrists would derive immense benefit from perusing them.

Perhaps it is for these reasons that the editors of Cutting Edge Psychiatry in Practice have decided to include autobiographical narrative in their journal. For the GP or psychiatrist reading them, it can be insightful and instructive, for family and friends of loved ones who suffer from psychopathology informative and illuminating and for those who actually compose the articles therapeutic and cathartic. It allows those with mental illness to convey the essence of their condition and by doing so validates their suffering. This can then aid them to make headway with their convalescence. In this regard, Cutting Edge Psychiatry in Practice is a brilliant concept and I know I speak for all who engage in creative writing as a form of therapy when I say that we are truly indebted to Professor Besag and to Dr Agius for the inclusion of autobiographical narrative in Cutting Edge Psychiatry in Practice and we urge you to continue in doing so.

GP Comment

What have I learned from this paper?

It is difficult to read an account such as this without feeling deeply moved, not only by the content but also by the beauty of the writing. What have I learned? Above all that people with mental illness are human beings just like everyone else. They include some wonderfully creative people who can enrich our lives by the combination of their creative artistry and their extraordinary insight.

Mayruja Santhirakumar, GP Trainee.

Bibliography

Part 7. Comorbidities and Bipolar Disorder

Comorbidity of bipolar affective disorder and obsessive-compulsive disorder

Laura Darby3, Mark Agius1,2 & Rashid Zaman1,2
1 Department of Psychiatry, University of Cambridge, UK
2 South Essex Partnership University NHS Foundation Trust, UK
3 School of Clinical Medicine Cambridge University, UK

Abstract

The comorbidity of bipolar affective disorder and obsessive-compulsive disorder is an important, although relatively unusual in community mental health teams. Patients with comorbid bipolar condition affective and obsessive-compulsive disorders appear to require a greater number of outpatient appointments, have a greater number of hospital admissions and also to be more likely to require a care coordinator and to require psychological input than those with OCD alone. They also appear likely to be more difficult to treat and to carry more risk factors than patients with OCD alone.

Key words: obsessive compulsive disorder, OCD, bipolar affective disorder, comorbidity.

There is much recent evidence that there is a frequent comorbidity of OCD with bipolar affective disorder. A review of recent studies has demonstrated that 7-21% of patients with bipolar affective disorder also have an additional diagnosis of OCD (1-5). This link is said to be more prevalent in men. For example, one study showed 69% of those with comorbidity to be male (6). Studies endeavouring to identify bipolar disorder in patients with OCD have found a prevalence of 15-15.7% (1-2,7). It appears that OCD is most commonly associated with bipolar affective disorder II (3,8). The significance of this association lies in the possible effects of comorbidity on the phenotype of each condition and in the implications for treatment.

Research suggests that patients with bipolar affective disorder (BPD) tend to experience a more episodic course of OCD (4). The symptoms of OCD tend to be more severe during the depressive phase of BPD and tend usually to be less severe or absent during the manic/hypomanic phase (6). Patients with comorbid OCD appear to be more likely to have a history of rapid-cycling BPD (4). It has also been noted that there is an increased risk of suicidality and alcohol dependency in patients with this comorbidity (3-4,6,9-10).

Interestingly, olanzapine has been demonstrated to be less effective in treatment of bipolar affective disorder in patients with comorbid OCD (1).

Given the growing evidence of the high rates and complex needs patients with this comorbidity appear to have, we recently undertook a study to establish the additional burden placed on healthcare resources by this comorbidity. We focused on the prevalence of bipolar disorder in outpatients with OCD, and then we explored how the care needs of patients with bipolar-OCD comorbidity differed from those with OCD but without bipolar disorder. This was considered to be particularly important because the OCD-bipolar comorbidity is not frequently described in ordinary UK community psychiatry practice, and the need for increased resources for these patients is not usually taken into account by commissioners, nor is there an adequate provision for these increased resources in the HONOS PBR (payment by results) classification, which in the future is to determine funding for the treatment of mental health patients in the community.

In our study (11), we extracted data from a database of outpatient visits to a community mental health team from 2006-2011. Diagnoses were classified according to ICD-10 criteria. We identified all patients
recorded as having a diagnosis of OCD (N=58). We then assessed the proportion of these patients who were also recorded as having bipolar affective disorder I, bipolar affective disorder II or unspecified bipolar affective disorder (total N=9). We thus found that 16% of the patients with OCD were also diagnosed as having BPD. Of these 67% had bipolar affective disorder II.

In order to study the effect of BPD on patients with OCD, we compared the group of patients with this comorbidity to a control group of patients with OCD, without bipolar disorder who were randomly selected from the database (11). We compared the following measures of healthcare requirements: number of outpatient appointments required; number of home treatment episodes [by the crisis team]/hospital admissions required; whether or not a care coordinator was allocated; the number of risk factors listed, medications prescribed, and use of psychotherapy. We found that the group of patients with this dual diagnosis attended a greater number of outpatient appointments. Furthermore three patients in the dual diagnosis group required hospital/ home treatment admissions while no-one in the pure OCD group did (11). Only patients with more complex needs are assigned a care coordinator. In this sample 78% of patients with comorbid bipolar disorder either currently had or had previously had a care coordinator; in comparison with 55% of patients in the control group.

Regarding risk factors, including suicide and self-harm risk, there were more risk factors recorded in the comorbidity group than in the control group. Regarding medication, 44% of the patients with comorbid bipolar disorder were receiving the maximum dose of the antidepressant compared to 22% of those in the control group. However, the drugs used were different from case to case so direct comparison is of limited use. An atypical antipsychotic was prescribed to 78% of those with bipolar and 55% of the controls. Use of mood stabilisers was limited to the comorbid group (55%). Antipsychotics used in the comorbid group included risperidone, quetiapine and aripiprazole. Antidepressants included fluvoxamine, citalopram, paroxetine, sertraline and clomipramine. Anti-

We found that the proportion of patients that had received psychotherapy was greater in the group with the comorbidity (67% vs 44%).

It is important to note that when the study was performed, we only compared groups consisting of nine patients in each group. However the results were useful as a demonstration of the fact that this bipolar/OCD comorbid group had greater special needs compared to patients with OCD alone. Our finding that a substantial proportion of OCD patients seen by the team also had BPD is consistent with the literature. A new study of 605 patients with OCD (12), has reported that there are very high rates of comorbidity in OCD with both depressive disorders (50%) and bipolar disorder (10%). They further reported that there was a graded severity pattern among their patients, with the bipolar group being the most severe, followed by the depressive disorder group and finally the group which had OCD with no other comorbid disorder. As with our study, severity was reflected by the total number of Axis I disorders (P<.01), the number of psychiatric hospitalizations (P<.001), impairment measures (P<.05), and OCD symptoms (P<.01).

In another recent study (13), bipolar disorder was reported as often comorbid with obsessive-compulsive disorder. OCD with BPD was characterized by: (i) an episodic course; (ii) a higher number of depressive episodes, greater suicidality and a higher rate of hospitalization; (iii) fewer pathological doubts and more miscellaneous compulsions; and (iv) poorer insight into obsessive-compulsive symptoms. An episodic course appears to be typical of OCD with BPD. The authors suggested that bipolarity has a pathoplastic effect on OCD and that it is possible that some forms of OCD and bipolar disorder are pathophysiologically related. BPD with OCD was said to have a greater morbidity. Long-term prospective follow-up studies and studies addressing the pathophysiology and genetic basis are needed to understand the complexity of such comorbidity.

Since our study was conducted, we have become more alert to the possibility of the existence of this comorbidity, and hence we have continued to identify more patients with this combination of disorders. The total number of patients on our database is now 1172. Of these there are 23 patients with the bipolar-OCD comorbidity. Of these, 10 are bipolar I and 13 are bipolar II. What has been
important is that all of these patients have presented a challenge to treat, and the knowledge that they have the comorbidity has provided an important explanation of the treatment difficulties we have been experiencing. We have found that the patients with comorbid OCD and BPD have more complex needs and draw on more mental health care resources. This remains an important point to consider when planning resource allocation.

Treatment of comorbid patients presents an interesting challenge. One of the first line treatments for OCD is use of SSRIs (selective serotonin re-uptake inhibitors). These medications present a significant risk of inducing mania or rapid cycling in patients with BPD (9,14). Prescription of medications for relief of the symptoms of OCD must therefore be carefully balanced against their potential interaction with the treatment of BPD. Some suggest that one solution would be the preferential use of non-pharmacological treatments for OCD such as CBT. However, if drug therapy for the OCD is necessary, SSRIs are thought to be preferable to tricyclic antidepressants and cover with a mood stabiliser will be important (15). Another area to consider is the general rule in the treatment of bipolar disorder that one should only prescribe anti-depressants in the depressive/euthymic phase of bipolar if the OCD is asymptomatic in the hypomania/mania phase. Since bipolar affective disorder may not be overt at the time of diagnosis of OCD it is important to monitor all patients with OCD carefully for signs of development of mania/hypomania. This is vital if the patient is to be started on antidepressant medication. Further identification and understanding of the pattern of OCD in patients with BPD will allow more effective therapy. Potential warning signs that have been suggested include young age at presentation and the hoarding type of OCD (7,10). Given the evidence for increased morbidity in comorbid patients it is important to find methods for early identification in order to provide appropriate care and support.

In conclusion, comorbid OCD and bipolar disorder is a little recognised but important condition within community mental health teams, which requires identification because of the important treatment and risk issues. We suggest that long-term prospective follow-up studies as well as studies addressing the pathophysiology and genetic basis should be carried out to increase our understanding of this complex comorbidity.

GP Comment

What have I learned from this paper?

This articles increases awareness that obsessive compulsive disorder can be comorbid with bipolar disorder and that the presentation of both conditions can be different when they exist together. It is also clear that patients with both conditions draw on more mental health care resources and are more of a challenge to treat, requiring preferential use of non-pharmacological OCD treatments or an SSRI with a mood stabiliser if pharmacological OCD treatment is needed.

Dr Jenny Hopwood, GP Trainee.

References

5. Chen YW, Dilsaver SC. Comorbidity for obsessive compulsive disorder in bipolar and unipolar.
Migraine and bipolar disorder as comorbid disorders

J. Holland1., M. Agius2.
1. West Suffolk Hospital, Bury St. Edmunds, Suffolk, UK
2. South Essex Partnership University Foundation NHS Trust , University of Cambridge Department of Psychiatry, Clare College Cambridge UK

Abstract

There are several reports suggesting that patients with bipolar spectrum disorders experience migraines more frequently than the general population or those with other mood disorders. This could have implications for the treatment of bipolar disorders; untreated migraine could exacerbate their affective states. A previous study of comorbidity of these conditions in a regional hospital psychiatric outpatient department found a much lower comorbidity than expected. It was suggested this might have been attributable to under-diagnosis or under-recognition of the two conditions. Here we re-analyse data from the same outpatient department and find that with greater recognition of this comorbidity the reported prevalence has increased markedly to 33.3% of new referrals in the past year and 8.5% overall. We conclude that there may be considerable under-recognition of the co-existence of migraine and bipolar disorders.

Key words: migraine, bipolar disorder, prevalence, headache, depressive disorders.

Introduction

Identification of comorbid disorders – where multiple conditions exist in the same individual – is useful with respect to treatment as well as suggesting possible common aetiological factors. It is important to be aware of what other conditions are likely to exist in a patient with a given diagnosis; left unrecognised, a comorbid disorder may make treatment more difficult and lead to a lower overall quality of life. Bipolar affective disorders and migraine are two such conditions. Although estimates of comorbidity vary, for example, the rate of migraine found in people with bipolar disorder varies between 24.8% (1) and 39.8% (2), this rate is generally higher than the population prevalence of migraine, which ranges between 10% (1) and 25% (3).

A previous analysis of a UK regional hospital outpatient department found a much lower comorbidity of migraine in people with bipolar disorder, namely 4.7% (4). One possibility for this was under-recognition. Over the past year, new and continuing bipolar spectrum patients were assessed to determine whether they also suffered from migraine disorders.

Methods

A patient database recording age, gender, main diagnosis, other diagnoses and ethnicity of patients seen in the Bedford East Community Mental Health Team based at Weller Wing, Bedford Hospital, UK, in the previous 5 years was examined for patients with diagnoses of bipolar spectrum disorders and migraine. 1137 patients had recorded diagnoses and were suitable for analysis. Deceased patients were excluded. The 55 patients seen in the last year as new referrals were next studied for comorbidity using the same criteria; 3 had unclear diagnosis or no mental illness and were excluded. The new patients were assessed in a specific clinic known as ASPA, standing for ‘Assessment and Single Point of Access’.

Results

A total of 217 patients with bipolar disorder were found, 213 excluding 4 patients whose diagnosis included ‘query’ bipolar disorder. These 213 represented 18.7% of the total sample of 1137 patients. 58/1137 (5.1%) of the patients were recorded as having migraine, with 18/213 (8.5%) having both bipolar disorder and migraine.
Of the 52 new referrals, there were 15 individuals with bipolar spectrum disorder (28.9%) and 5 with migraine (9.62%). All the 5 patients with migraine had a primary diagnosis of bipolar disorder, giving a comorbidity of 33.3% (5/15) in this group.

The gender of the patients and bipolar subtype were also examined, as some previous studies have suggested increased comorbidity amongst female patients (1-2) as well as with bipolar II disorder as opposed to bipolar I (5).

Table 1: Analysis of 1137 patient database from 5 years prior to September 2012.

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Number</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar Disorder</td>
<td>213</td>
<td>18.7% of total (213/1137)</td>
</tr>
<tr>
<td>Migraine</td>
<td>58</td>
<td>5.1% of total (58/1137)</td>
</tr>
<tr>
<td>Bipolar Disorder + Migraine</td>
<td>18</td>
<td>8.5% of bipolar disorder (18/213)</td>
</tr>
<tr>
<td>Migraine ♀</td>
<td>40</td>
<td>69.0% of migraine (40/69)</td>
</tr>
<tr>
<td>Migraine ♂</td>
<td>18</td>
<td>31.0% of migraine (18/69)</td>
</tr>
<tr>
<td>Bipolar Disorder + Migraine♀</td>
<td>11</td>
<td>61.1% of comorbid patients (11/18)</td>
</tr>
<tr>
<td>Bipolar Disorder + Migraine♂</td>
<td>7</td>
<td>38.9% of comorbid patients (7/18)</td>
</tr>
<tr>
<td>Bipolar I + Migraine</td>
<td>7</td>
<td>60.0% of comorbid patients (7/18)</td>
</tr>
<tr>
<td>Bipolar II + Migraine</td>
<td>11</td>
<td>61.1% of comorbid patients (11/18)</td>
</tr>
</tbody>
</table>

Table 2: Analysis of 52 new Referrals over ~1 year prior to September 2012

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Number</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar Disorder</td>
<td>15</td>
<td>28.9% of total (15/52)</td>
</tr>
<tr>
<td>Migraine</td>
<td>5</td>
<td>9.6% of total (5/52)</td>
</tr>
<tr>
<td>Bipolar Disorder + Migraine</td>
<td>5</td>
<td>33.3% of bipolar disorder (5/15)</td>
</tr>
<tr>
<td>Migraine ♀</td>
<td>2</td>
<td>40.0% of migraine (2/5)</td>
</tr>
<tr>
<td>Migraine ♂</td>
<td>3</td>
<td>60.0% of migraine (3/5)</td>
</tr>
<tr>
<td>Bipolar Disorder + Migraine♀</td>
<td>2</td>
<td>40.0% of comorbid patients (2/5)</td>
</tr>
<tr>
<td>Bipolar Disorder + Migraine♂</td>
<td>3</td>
<td>60.0% of comorbid patients (3/5)</td>
</tr>
<tr>
<td>Bipolar I + Migraine</td>
<td>3</td>
<td>60.0% of comorbid patients (3/5)</td>
</tr>
<tr>
<td>Bipolar II + Migraine</td>
<td>2</td>
<td>40.0% of comorbid patients (2/5)</td>
</tr>
</tbody>
</table>
Discussion

It appears that, in contrast to the entire patient group, amongst whom comorbidity of migraine in patients with bipolar disorders was relatively lower than previously reported in the general literature at 8.5%, the new referrals with bipolar disorders, in whom active enquiry was made about migraine, had a much greater comorbidity of 33.3% which is closer to reports from previous studies.

Interestingly, although the prevalence of migraine overall amongst the new patients (9.6%, 5/52) was almost double that found over the past 5 years, it is still lower than the general population prevalence. Figure 1 compares the comorbidity prevalence together with the results of the previous analysis described in Holland et al. 2011.

![Figure 1](image.png)

**Figure 1**: Comparison of analysis of present data with Holland et al. 2011. The comorbidity prevalence is shown as the percentage of patients with bipolar and migraine amongst those patients in their respective samples with bipolar disorder.

From the larger patient sample, migraine was more frequent amongst females and accordingly comorbidity was increased amongst females. Comorbidity was also greater for patients with bipolar II disorder. However, these findings were not replicated amongst the new patients seen in the ASPA Clinic, in whom there was no clear difference between gender and bipolar subtype. This is probably attributable to the much smaller sample size.

Recognition of comorbid migraine in patients with bipolar disorder is important for several reasons. First, the stress of experiencing a migraine may act as a triggering factor for a manic or depressive episode; altered sleeping patterns resulting from migraine may also be contributory. Furthermore, patients already restricted in their active participation in society due to episodes of mania or depression may suffer additional or prolonged restrictions through suffering severe migraine, which in turn, could exacerbate their affective symptoms.
Treatment should also be modified in these patients to cover both conditions. For example, sodium valproate and lamotrigine are effective in the treatment of both migraine and bipolar disorder (6). In contrast, tricyclic antidepressants are routinely used for migraine prophylaxis but can induce manic episodes in patients with bipolar disorders (7). One case report describes effective control of both conditions using lithium with topiramate (8).

A final point is in reference to the ‘kindling’ phenomenon, whereby risk of recurrence of bipolar episodes increases with the number of previous episodes (9). If untreated migraine were to lead to more bipolar episodes, it could indirectly worsen the primary condition. Much as we might aim to achieve a better blood lipid profile in diabetic patients, we should attempt to optimise the treatment of both conditions in patients who suffer with comorbid bipolar disorder and migraine. In addition to this, untreated migraine may evolve into a form of chronic daily headache known as ‘transformed migraine’ which is generally resistant to treatment (10), emphasising the importance of effective early treatment.

The underlying reasons for the apparent increased frequency of migraine in people with bipolar disorder remain unclear but there are several hypotheses relating to the underlying neurobiology that are currently under investigation.

It appears that multiple pathways may be dysfunctional in these disorders, and that their combined effects produce the phenotype characteristic of each condition. There is some overlap in these processes. It is feasible that a shared pathology could lead to each condition.

A family history of bipolar or migraine disorders increases an individual's likelihood of developing each condition, which suggests that genetic factors may be important. As high as 60% heritability in bipolar disorder and 40-65% for migraine have been reported, with attempts to find responsible genes identifying possible overlapping ‘susceptibility zones’ encoding various ion channels (11).

One of the more significant effects of these genetic changes may be how they affect levels of neurotrophic factors such as BDNF. There appears to be less BDNF in patients affected with bipolar disorder (12) and more in chronic migraine (13). Altered levels of neurotrophic factor support for neurons may produce altered neural network function, perhaps one manifestation of which is the abnormal EEG recordings observed in migraine and bipolar disorders. For both, decreased inhibitory alpha with increased theta band activity has been seen (14-15).

It is increasingly suggested that chronic inflammation plays a part in development of neuropsychiatric conditions. A study of migraine patients identified the presence of auto-antibodies associated with white matter hyperintensities (16). In bipolar disorder, levels of pro-inflammatory compounds in circulating monocytes have been reported, apparently as a result of environmental influence upon individuals with genetically-determined susceptibility (17). Of interest with regard to the general practice setting, the involvement of inflammation has implications for cardiovascular disease risk. Many antipsychotic agents have adverse effects on lipid profiles and, together with an inherent pro-inflammatory disease state, this could accelerate atherosclerotic plaque development. Furthermore, some groups advocate essential fatty acid supplementation as an adjunct to symptom control in bipolar disorder (18). A few studies suggest eicosapentaenoic acid supplementation may benefit headache disorders (19).

Prior to the recognition of the increased prevalence of migraine amongst patients with bipolar disorder in our community mental health team, it appears that comorbid migraine may have been under-treated. It remains to be seen whether, in the longer term, treatment of the comorbid migraine actually will lead to better quality of life outcomes for these patients.

The population analysed here is relatively small, which could account for the observed difference from our previous data. Nonetheless, we would still suggest that clinicians assessing patients with bipolar
disorder routinely enquire about symptoms of migraine. Migraine encompasses a broad range of conditions and ideally requires a neurologist diagnosis. However, in the majority of cases patient self-reporting of the characteristic symptoms is probably enough for the wise practitioner to attempt to treat comorbid migraine in conjunction with bipolar disorder.

GP Comment

What have I learned from this paper?
Migraine appears to be more common in patients with bipolar disorders. Specific enquiry for migraine should be made in these patients so that early treatment can be provided.

Dr Mayruja Santhirakumar, GP Trainee.

References

15. Sand T. Electroencephalography in migraine: a review with focus on quantitative electroencephalography and the migraine vs. epilepsy relationship. Cephalalgia 2003; 23 (S1): 5-11.
17. Padmos RC, Van Baal CM, Vonk R et al. Genetic and Environmental Influences on Pro-Inflammatory...
Bipolar affective disorder and substance abuse

Dr Anton Grech MD PhD (Maas) MSc (Psychiatry) (Lond) FRCPsych. (UK)
(Mount Carmel Hospital, Attard, Malta. University of Malta, Msida, Malta
e.mail: anton.grech@gov.mt)

Abstract

Epidemiological studies show that substance abuse and bipolar disorder are strongly associated. The reasons include of self-treatment and poor self-control during hypomanic/manic periods. Substance abuse influences the outcome of bipolar disorder and makes diagnosis more difficult. Patients with bipolar disorder who abuse substances tend to have a worse outcome and greater suicidal risk. If good outcomes are to be achieved, substance abuse in these patients cannot be ignored. An integrated treatment approach of both conditions together probably gives the best results.

Key words: substance abuse, alcohol, bipolar disorder, outcome, suicide, clinical implications.

Introduction

Both bipolar affective disorder and substance abuse are conditions that afflict many individuals with potentially disastrous consequences. These two conditions co-exist more than is expected by chance and influence each other.

Epidemiology

Studies have repeatedly shown that the rate of substance abuse in bipolar patients is higher than that in the general population (1). The Epidemiological Catchment Area (ECA) study (2) was a survey of 20,000 individuals in five U.S. communities. It showed a particularly high association between substance abuse and bipolar disorder. 60.7% of those with bipolar 1 disorder had a diagnosis of alcohol or other substance abuse at some point in their life, while in bipolar 2 disorder 48% had such a diagnosis. This was roughly six times that found in the general population. Similar trends were found in the National Comorbidity Survey (3) that was conducted on individuals aged between 15 and 54. This study showed that bipolar patients were nearly 10 times as likely to have alcohol dependence than the general population. These patients also had a rate of 8 times as much as that in the general population of dependence on a psychoactive substance other than alcohol.

The reasons for the association between substance abuse and bipolar disorder

One of the principal reasons put forward for such a strong association between substance abuse and bipolar disorder is what is known as ‘the self-treatment hypothesis’. This means that patients who have bipolar disorder use substances to alleviate their symptoms. For example, sedatives (such as alcohol or opiates) can be used to decrease the hyperactivity of hypomania or mania, or to decrease the anxiety and distressing symptoms of a depressive state. An alternative explanation is that during manic or hypomanic episodes the associated lack of self-control can lead to more alcohol or substance abuse (4, 5). It appears that the hypomanic/manic phase plays a key role in this association because the association between substance abuse and bipolar disorder is stronger than that between substance abuse and unipolar depression (3). Further studies need to clarify if use of substances can trigger the onset of bipolar illness.

The impact of substance abuse on bipolar disorder

The abuse of alcohol and substances has a strong impact on the manifestation, course and outcome of
bipolar disorder. It particularly causes instability of the illness, results in worse outcome and causes a higher suicidal risk. It also poses diagnostic difficulties.

a. **Instability in the manifestation of the illness**

Substance abuse in patients with bipolar disorder may increase the acceleration of the manifestation of the condition, and hasten the transition from hypomanic to manic state. Also when there is presence of substance abuse during an active episode of bipolar illness this episode tends to be longer (6). An important component in the prognosis of bipolar disorder is compliance with treatment. The erratic behaviour associated with substance abuse makes such compliance with treatment more problematic than usual.

b. **Worse Outcome**

Bipolar disorder in general has a better prognosis than schizophrenia. In a study conducted by Kaworski et al. (7), 40 subjects with schizophrenia were compared with 40 subjects with bipolar disorder. Both sets of patients were in the stable phase of the disorder. Patients with bipolar disorder who did not have substance abuse had better social adjustment and better outcome of their illness than those patients with bipolar disorder who did abuse substances. Also, the patients with bipolar disorder who abused substances had poor social adjustment and poor outcome, comparable to that of patients with schizophrenia.

c. **Suicidal Risk**

Hawton et al. (8) in a meta-analysis of 36 studies conducted between 1966 and 2003 identified abuse of alcohol and drugs as one of the main risk factors for nonfatal suicidal behaviour. In the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (9), 1,643 individuals with a DSM-IV lifetime diagnosis of bipolar disorder were studied. More than half of these (54%) also reported alcohol use disorder, and they were at greater risk for suicide attempt than those individuals without alcohol use disorder (adjusted odds ratio=2.25; 95% CI, 1.61-3.14).

d. **Diagnostic Difficulties**

Agitation and hyperactive behaviour associated with intoxication by substances or withdrawal states from these substances can mimic the behaviour associated with hypomania or mania. Such an example is stimulants causing hyperactivity or psychotic symptoms. On the other hand, substances can suppress the manifestations of bipolar illness, making it difficult to reach a diagnosis. For example, in a patient with bipolar disorder and heavy alcohol abuse, the manifestations of the bipolar illness tend to be suppressed by the effects of the alcohol.

**Clinical implications**

Considering the negative impact of substance abuse on the outcome of bipolar disorder, when the two conditions are present together it does not make sense to try to achieve mood stability without aiming to reach abstinence as well. With the trend towards the specialisation of services, treatment for affective disorders and substance misuse tends to be provided by different services in different settings. However, the best outcome occurs when an integrated treatment approach for both these conditions together is provided (10). In Malta we have a 9 year experience of offering services for dual diagnosis patients jointly by the Psychiatric Services and the services catering for substance abuse (11). These services are for both inpatient and outpatient settings. The outcomes since these services were set up seem to be better. It is very important that, in their assessment, all patients with bipolar disorder are screened for the presence of substance abuse. Research is underway to establish if there are particular approaches of pharmacotherapy and psychotherapy that are mostly effective in these circumstances. The conventional wisdom so far is to use the same approaches used when one of the two conditions manifests on its own, but in an integrated way.
GP Comment

What have I learned from this paper?

This article highlights the significant correlation between bipolar disorder and substance misuse. Not only does it accelerate transition from a hypomanic to manic state but can also increase risk of suicide. Substance misuse increases the possibility of non-compliance and thereby affects prognosis. Diagnosing bipolar can be more challenging in those who also misuse substances, as they may present with symptoms disguising bipolar traits. Therefore a combined, integrated approach to treating both bipolar mood disorder and substance misuse will achieve a better outcome for patients.

Dr Snehal Khajuria, BSc (hons), MBBS, GP trainee.

References

Bipolar disorders and borderline personality disorders: two sides, one coin

Sandro Elisei, Norma Verdolini, Serena Anastasi
Division of Psychiatry, Clinical Psychology and Rehabilitation
Department of Clinical and Experimental Medicine - University of Perugia
Santa Maria della Misericordia Hospital - Perugia, Italy
School of Specialization in Psychiatry - University of Perugia

Abstract

Because of their pervasiveness and comorbidity, bipolar disorder and borderline personality disorder represent a broad field of interest for scientific research. Several studies have pointed out that there are positive correlations: affective instability and impulsive behaviour could represent shared characteristics. To understand the relationship between the two disorders fully, the authors underline the importance of recovering the concept of affective temperament and the psychodynamic approach. Finally, we consider the effects of early traumatic experience.

Key words: bipolar disorder; borderline personality disorder; continuum; abuse, trauma.

Introduction

There is currently a heated international debate about the relationship between mood disorders, especially bipolar disorder, and borderline personality disorder (1-8). In fact, much clinical evidence shows that often borderline personality disorder may be clinically difficult to distinguish from bipolar disorder and that patients with bipolar disorder are frequently misdiagnosed with borderline personality disorder (9).

Discussion

It is now more than twenty years since Akiskal first suggested that borderline personality disorder could be better understood as an Axis I disorder within a bipolar affective spectrum (10-11). Akiskal used the concept of spectrum to indicate mild, subclinical and atypical bipolar disorders, including forms of depression with hypomanic episodes, both short-term and long-term, temperamental traits of hyperthymia and cyclothymia and subjects with a family history of bipolar disorder. In a schematic revision of the several forms within the bipolar spectrum Akiskal described at least 7 different clinical subtypes, shown in Table 1 on next page (12).
Table 1. Bipolar spectrum (12)

<table>
<thead>
<tr>
<th>Spectrum Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar I</td>
<td>Depression plus mania</td>
</tr>
<tr>
<td>Bipolar I and 1/2</td>
<td>Depression plus prolonged Hypomania</td>
</tr>
<tr>
<td>Bipolar II</td>
<td>Depression plus hypomania</td>
</tr>
<tr>
<td>Bipolar II and 1/2</td>
<td>Depression plus cyclothymia</td>
</tr>
<tr>
<td>Bipolar III</td>
<td>Depression plus hypomania occurring solely in association with antidepressants</td>
</tr>
<tr>
<td>Bipolar III and 1/2</td>
<td>Bipolarity associated with stimulants</td>
</tr>
<tr>
<td>Bipolar IV</td>
<td>Depression and hyperthymic temperament</td>
</tr>
</tbody>
</table>

The concept of spectrum points out the existence of a quantitative continuum between phenomena which apparently differ in quality, considering a wide range of psychopathological phenomena including typical, atypical and subclinical symptoms as well as groups of symptoms and behavioural disorders related to the core symptoms. These phenomena may either represent prodromes, precursors or residual symptoms of a disorder with complete clinical expression, or they can be present without meeting the criteria for an Axis I disorder, usually interfering with the subject’s social-occupational adaptation and quality of life (13).

However, it is worth noting that the definition of “soft” bipolar spectrum also includes temperaments and personality traits, since, according to the concept of spectrum, personality is considered a mosaic of complex dimensions, simpler or elementary, with different psychological and psychopathological features, constantly changing according to the environment (14).

Almost a century before Akiskal, Kraepelin detected the existence of a considerable quantitative and qualitative variability among patients with manic-depressive psychosis and about this issue he wrote: “We include here (in manic-depressive insanity) certain slight and slightest colourings of mood, some of them periodic, some of them continuously morbid, which on the one hand are to be regarded as the rudiment of more severe disorders; on the other hand, pass without sharp boundary into the domain of personal predisposition. In the course of years I have become more and more convinced that all the above mentioned states only represent manifestations of a single morbid process” (15). Several studies have since shown a high frequency of comorbidity between borderline personality disorder and mood disorders (bipolar disorder and major depression) and reported that 12-23% of patients with bipolar II meet criteria for borderline personality disorder as well (16-17,5,18). Table 2 shows the frequency of mood disorders in subjects with borderline personality disorder in a 6-year follow-up period (19).

Table 2 Frequency of mood disorders in subjects with borderline personality disorder in a 6-year follow-up period (Modified from (19)).
Patients with Borderline Personality Disorder: Follow up

<table>
<thead>
<tr>
<th>Axis I Disorder</th>
<th>Baseline (N=290)</th>
<th>2 Years (N=275)</th>
<th>4 Years (N=269)</th>
<th>6 Years (N=264)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mood Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood Disorders</td>
<td>281 96.9</td>
<td>233 84.7</td>
<td>199 74.0</td>
<td>198 75.0</td>
</tr>
<tr>
<td>Major Depression</td>
<td>251 86.6</td>
<td>189 68.7</td>
<td>166 61.7</td>
<td>162 61.4</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>130 44.8</td>
<td>93 33.8</td>
<td>78 29.0</td>
<td>107 40.5</td>
</tr>
<tr>
<td>Bipolar I</td>
<td>0 0.0</td>
<td>2 0.7</td>
<td>4 1.5</td>
<td>3 1.1</td>
</tr>
<tr>
<td>Bipolar II</td>
<td>16 5.5</td>
<td>19 6.9</td>
<td>18 6.7</td>
<td>12 4.6</td>
</tr>
</tbody>
</table>

However, in the literature we also found studies coming to different conclusions. For example, Berrocal claimed that the coexistence of the two disorders is quite uncommon (20), while other authors underlined the specific distinction between them (21-22).

Regarding the likely common elements shared by these two complex psychopathological entities, Benazzi highlighted that the Work Group on borderline personality disorder for DSM-IV concluded that the possible overlap between borderline personality disorder and mood disorders was caused by the item “affective instability” and that “impulsivity” could be its “essential feature” (6).

Concerning this, numerous studies agreed that affective instability and impulsivity themselves are the common basic clinical characteristics (18,22,23,24), which, however, can manifest themselves in qualitatively different ways in the two disorders (25,18,8).

With regard to impulsivity, Benazzi detected that the only significant association is between the episodic impulsivity of hypomania and the impulsivity characterizing borderline patients (6); in borderline personality disorder, impulsivity can also be present in the form of lack of concentration, loss of ideas, disorientation, difficulty in organizing and planning actions and considering their consequences (18).

MacKinnon suggested that affective instability could be referable to a common genotype that manifests itself with different phenotypes, depending on the influence of environmental and psycho-social factors, such as, for example, an experience of abuse. This author underlined that affective instability in borderline personality disorder is related to environmental stimuli, contrary to what happens in bipolar patients; he considered the affective instability of borderline personality disorder as a form of prolonged ultra-rapid cycling with extreme rapid mood switching (7), closely resembling the classic description of cyclothymia (10).

Henry showed that affective instability in borderline personality disorder is mainly present as oscillations between anger and euthymia, while in bipolar disorder II it is more often expressed as oscillations between depression and/or elation and euthymia (26).

Other studies detected that borderline patients show greater fluctuations towards anger and anxiety, often as a reaction to stressful environmental stimuli, especially in the field of personal relationships; oscillations between depression and anxiety have been also described in patients without
comorbidity with bipolar disorder II, but without episodes of elation (27,18).

Recently, in line with previous literature, Bradford Reich observed that lability involving anxiety, anger, intense discomfort and irritability is more characteristic of borderline patients (24), as well as being of a more episodic nature (18), whereas lability involving elation is more characteristic of bipolar patients (24).

These authors thus concluded that the recognition of the different characteristics of the oscillations in the item “affective instability” may represent a useful element for differential diagnosis between borderline personality disorder and bipolar disorder.

With reference to lowered mood, borderline personality disorder patients may use the term “depression” to describe chronic feelings of boredom, loneliness and emptiness, without showing the classic signs and symptoms of major depression (28). Authentically depressed patients, in fact, do not feel empty but, on the contrary, feel full of several negative mental states, affective and cognitive, described as sadness, lack of interest in life, feelings of unworthiness and of guilt; in the case of “negative” experiences, such as the loss of interests, there is always a reference to the world of objects: the concept of loss itself implies the fact that once there was something, something that then loses its value. In borderline cases, on the other hand, the void refers to the absence of objecthood and relations (29), probably because such experiences refer more to identity than to tone of mood (30,29). The continuous oscillation of transitory representations, positive and negative, divided, makes borderline subjects incapable of defining themselves in their own real identity, which remains inconsistent, indefinite or empty (29).

MacKinnon agreed with those who consider borderline personality disorder a mood disorder within the bipolar spectrum and thus suggested that the clinician has to decide whether symptoms are best attributed to an acute mood disorder or whether they are merely the latest manifestation of a more chronic and pervasive problem. He also suggested that borderline personality disorder should be transferred to Axis I and be integrated into BP II as one of its clinical subtypes (7).

Concerning this, Benazzi claimed that bipolar disorder II can be divided into two subtypes: one stable and functional between episodes and one unstable between episodes, which is related to borderline personality disorder (5).

Affective instability seems to be related to a cyclothymic temperament. Another wide field of research is currently dealing with the recovery of the concept of affective temperament, to try to overcome the difficulties deriving from the attempt to link Axis I Bipolar Disorders to Axis II Personality Disorders. In line with this idea, several studies highlighted that bipolar disorder and borderline personality disorder may share a cyclothymic temperament, involving affective reactivity and lability, interpersonal sensitivity, hostility and anxious-avoidant traits (23-24,31-32).

Ehrt described affective temperament as a biological disposition involving different levels of energy and mood quality which determine a particular reactivity to external stimuli (33).

According to Akiskal, temperamental characteristics of the cyclothymic and hyperthymic types may represent the phenotypic expressions of the underlying bipolar genotype and determine the extreme sensitivity to external events; at the same time several features such as stability over time, early onset and long duration make the concept of temperament similar to the concept of personality (3).

Regarding personality, Cloninger’s psycho-social theory offers interesting clues: this author considers the concept of personality a complex hierarchic system, expressing itself through the synthesis of two psychobiological dimensions: temperament and character. Character refers to the part of personality, scarcely inheritable, primarily influenced by learning, culture and unique events for every individual; regarding character, he distinguishes 3 different dimensions: self-directedness (SD), cooperativeness, and self-transcendence (34).

In a clinical population survey, in comparison with a population of students, Svrakic observed that subjects with a personality disorder showing low scores on SD (significantly related to borderline
personality disorder), also showed frequent comorbidity with dysthymia and depression (35-36).

In this way it seems that the SD dimension of character may represent a common factor between mood disorder and personality.

Patients with low scores on SD are described as immature, weak and poorly integrated; they seem to be lacking an internal organizing principle and this makes them fragile and influenced by external stimuli and circumstances (37).

To understand the complex relationships between personality, temperament and mood disorders fully, it is also necessary to take a psychodynamic approach (38-40), which has not been adequately considered in recent years, mainly because of the popularity of evidence-based medicine (41). The internal world of subjects and all those deeper aspects of individual personality which concur in determining the pathological impact of biological, environmental and interpersonal factors, are further aspects requiring consideration in this context. (39,42).

Theoretical and clinical investigations of manic-depressive illness have followed each other over the years; the earliest concepts developed by Freud (43-44) were fundamental to the research of many other authors, including Abraham, Klein, Winnicot, Jacobson and Bibring, who further analysed and improved the understanding of the deep dynamics behind the development of manias and melancholia (45).

To understand the profound affinities between bipolar disorder and borderline personality disorder better, it is necessary to trace the stages of child psychological development described by Margaret Mahler (46).

In the separation/individuation process (6-24 months) the infant ceases to be ignorant of the differentiation between itself and the mother, becoming progressively aware that she is a separate person. In this way it begins to explore the surrounding world with a euphoric feeling of greatness and omnipotence, becoming more distant from its mother. In doing this, the infant reaches the awareness that it is separated from its mother and experiences a feeling of vulnerability related to the loss of the loved object which gave it confidence. This is why it now tries to regain it (46).

In this phase, euphoric advancing movements alternate with depressive return, which leads to the achievement and consolidation of the object constancy (interiorisation of a whole and constant image) comforting and supporting it during the separation process (47).

It is possible to consider the sense of inadequacy and the opposite pseudo-omnipotent part of the bipolar subject as the expression of the failed attempt to overcome the separation/individuation phase. In fact the subject gets stuck in the oscillation between the attempts to obtain a grandiose independence and the return to the emptiness, without ever reaching the structural stabilisation of the Self (45).

This kind of developmental failure is the same as can be observed in the Borderline Personality Organisation, where the founding element is the failed achievement of an integrated identity and of object constancy, with the anguished feeling of abandonment which determines the development of primitive defences like splitting, denial and projection (47).

In this phase of psychosexual development the occurrence of traumas and suffering violence, often repeated, at an early stage, have been considered for some time factors of recognized importance in the causal chain at the core of borderline pathology (48).

Indeed, a trauma generates an extremely intense frustration in fragile Egos that have just overcome, without too many hitches, the first months of life and are continuing on their path towards Oedipus. Such a trauma has to be understood in the affective sense of the term; it corresponds first of all to an intense drive-related anxiety, the occurrence of which has taken place during a scarcely organized and
still too immature stage as far as the instruments, ability to adapt and defences to be able to deal with it in conditions of safety are concerned; attempts at sexual seduction on behalf of an adult, often quite real and not merely illusory, can prevent entrance into the Oedipus (49).

In such patients the trauma seems to be linked to an “original turbulence” (50) and it emerges with a diffusive mode; it tends to flood other constructions (51).

The initial effects of sexual abuse include fear, anxiety, depression, guilt, anger, hostility and inappropriate sexual behaviour. Long-term results are represented by impulsivity, self-guilt, suicidal behaviour, anxiety, isolation, low self-esteem, substance abuse, sexual problems and lack of trust in interpersonal relationships. Abuse trauma can contribute to the borderline patient’s difficulties in expressing affection.

The literature suggests that individuals who have undergone traumatic events are unable to develop the ability to deal with emotional arousal, to the point that they respond to it with a severe coercion of affection or in a way inappropriate to the situation, engaging in impulsive behaviours (52). This is even more true if we consider impulsivity as a predisposition implying the tendency of subjects to act quickly, without planning their behaviour, and without the opportunity of elaborating a rational and aware assessment of the consequences (53). As a result, borderline experience consists in an original instability of relations with others and the world, in an “emotional invalidation”; it is as if the borderline subject grew up with no stable indicators, always in an uncertain balance. In this case the traumatic element is not so much an event (or a series of events), but rather an environment as a whole; “an earthquake swarm consisting of small but continuous and unpredictable shocks that develop on an ever vacillating floor surface: in a state of “stable instability” and “alarmed dysphoria” (54). People with borderline personality are characterized by this absolute pervasive precariousness (51). They are constantly oscillating between challenge and dependence, between a desire for trust and deep disillusionment (48). As a result, their only intention is to test the solidity of every possible relationship: with things, with the ‘other’, with their own bodies (51).

The psychodynamic and phenomenological assessment underlines the common root of the presumed elation/depression antinomy: melancholic suffering and racing thoughts which are opposite on a descriptive point of view then become the result of a “common despair” deriving from an unsuccessful fulfilling of the Ego (55).

Those who support the hypothesis of a common matrix for borderline personality disorder and bipolar disorder consider affective instability the common starting point. The interaction with frustrating environmental factors, mainly early dysfunctional relationships and traumatic experiences which exacerbate the basic affective instability, represent key moments in which the two disorders may diverge and the primary mood disorder may evolve into borderline personality disorder. In the case of subjects with a predisposition to affective instability, who grow up in an adequate and supporting environment, object relations are better and it is thus more likely for such subjects to develop a bipolar disorder rather than a borderline personality disorder (7).

The central thread of this report is the awareness that the clinician always remains the essential tool, thanks to her/his ability to explore different situations in an integrated way and from different points of view. The enhancement of knowledge, empathy and patience give the clinician the possibility to understand psychic suffering in the evolution of human existence (56-57).

GP Comment

What have I learned from this paper?

1. The relationship between bipolar disorder and borderline personality disorder is interesting and remains controversial (although it has been shown in the BRIDGE study: Angst et al. Arch Gen Psychiatry. 2011; 68 (8): 791-799, that Borderline Personality disorder may be a ‘specifier’ for a Bipolar Diagnosis).
2. Affective instability and childhood developmental issues are important themes

3. GPs should consider a Bipolar Disorder diagnosis in a patient with ‘Borderline Personality Disorder’ if there are clear features of hypomania/mania and depression. In practice this would warrant referral for expert Psychiatric review

4. From a GP perspective, it remains unclear how we should treat patients with Borderline Personality Disorder, especially as the evidence base for pharmacological treatment is limited and adverse effects may be significant. Psychological approaches may play a key role.

Dr Daniel Dietch, GP, Lonsdale Medical Centre, London.

References

21. Wilson ST, Stanley B, Oquendo MA, Goldberg P, Zalsman G, Mann JJ. Comparing impulsiveness,
hostility and depression in Borderline personality disorder and Bipolar II disorder. Journal of Clinical Psychiatry 2007 68; 1533-1539.


51. Ferro FM. Psychopathological considerations on borderline personality disorder XIII. Perugia Meeting of Medicine and Psychiatry Psychopathology personality and personality disorders. Perugia; 23th June 2012. Associazione per la Ricerca in Psichiatria (ARP) Perugia.

Sandro Elisei
Division of Psychiatry, Clinical Psychology and Rehabilitation,
Department of Clinical and Experimental Medicine - University of Perugia
Santa Maria della Misericordia Hospital - Perugia, Italy
sandro.elisei@unipg.it
The overlap of pervasive developmental disorders and bipolar disorder in young people

Mai Uchida, MD1,2, Emily Gray, MD1,2, and Gagan Joshi, MD1,2
1 Pediatric Psychopharmacology Program, Massachusetts General Hospital
2 Department of Psychiatry, Harvard Medical School
Boston, Massachusetts

Address of Corresponding Author
Gagan Joshi, MD. Clinical & Research Programs in Pediatric Psychopharmacology, Massachusetts General Hospital, 55 Fruit Street, YAW 6900, Boston MA 02114
Email: Joshi.Gagan@MGH.Harvard.edu

Abstract

Recent research has proved the bidirectional relationship between pervasive developmental disorders (PDD) and bipolar disorder (BPD). Young people with BPD comorbid with PDD present with earlier onset and higher severity of mood disturbance, and young people with PDD with family history of BPD present with mood disturbance characterized by a severe cycling pattern and agitation along with neurovegetative disturbances. Treatment approaches include similar comprehensive psychosocial interventions targeting PDD symptomatology with the addition of psychopharmacological interventions to target comorbid mood symptoms. This population is more prone to adverse effects and can have an atypical response to psychoactive medications; it is recommended that medication be initiated at a low dose and titrated in small increments. Second-generation antipsychotics are effective with both the consequences of the PDD (aggression and irritability) and the comorbid mania but also carry the concerning adverse effects of weight gain and impaired glucose metabolism.

Key words: pervasive developmental disorder, bipolar disorder, comorbidity, young people, clinical correlates.

Pervasive Developmental Disorders

Pervasive developmental disorders (PDD) are characterized by delays in development of socialization and communication, and include diagnoses such as autism, Asperger Syndrome and Pervasive Developmental Disorder not otherwise specified. Children with PDD present with symptoms such as difficulty relating to people (lack of eye contact, unresponsive to social cues such as smiles and body language), difficulty communicating with or without language, limited range of interests which may involve unusual play, difficulty with change in routine, and repetitive behaviour patterns. Autism spectrum disorders (ASD) are estimated to affect more than 1% of children and adolescents in the general population (1). Since these children often have excessive anxiety and mood lability, the co-occurrence of mood disorders and other psychiatric disorders must be carefully investigated.

Bipolar disorder in children

Both autism spectrum disorders (ASD) and pediatric bipolar disorder (BPD) are severely impairing chronic conditions. Each disorder affects at least 1% of the pediatric population (2). It is reported that mood disturbance in children with BPD is often characterized by mixed features of depression and mania. These children commonly present with extreme irritability, explosiveness, abrupt changes in mood states from angry to giddy, and occasional periods of low energy and withdrawal.

Comorbid pervasive developmental disorders and bipolar disorder

The existence of an overlap of BPD and PDD has been suggested by clinicians prior to the recent growth of literature in this topic, since children with PDD presented with high rates of aggressive...
behaviours and labile mood. The high incidence of BPD in family members of children with PDD had also been noticed.

An accumulating body of literature has demonstrated that there are high rates of aggressive behaviours and mood disturbances in children with PDD that indeed qualify for diagnoses of affective disorders including BPD (3-12). Conversely, high rates of PDD or PDD traits have been reported in children and adolescents with BPD. One study reported that in children with mood and anxiety disorders, PDD traits can be found in as many as 62% (8).

**A bidirectional relationship**

In our study, we assessed children and adolescents using a comprehensive diagnostic battery and structured diagnostic interview. We found a bidirectional relationship: BPD occurred in 21% of PDD, and PDD occurred in 11% of BPD young people (8). In another study, we administered a structured diagnostic interview to children with PDD in our clinic, and we were able to diagnose one-third of them with also BPD (11). Similarly, we found 15% comorbidity of PDD in the research population of children with BPD (11,12).

**Characteristics of children with comorbid PDD and BPD**

The clinical characteristics of PDD and BPD were strikingly similar irrespective of the comorbidity (11). On CBCL profile reported by parents, significantly worse behavioural difficulties were found in BPD young people in the presence of PDD (13). Furthermore, when comorbid with PDD, children and adolescents with BPD present with an earlier onset, increased severity of mood disturbance and poorer level of functioning (11-13). Young people with a PDD diagnosis with family history of BPD often present with mood disturbance characterized by a severe cycling pattern and agitation, along with neurovegetative disturbances (14). There is also a growing body of literature from family genetic studies suggesting higher incidence of BPD in first-degree relatives in PDD population (14–16).

**Treatment**

Treatment of children with PDD is complex and involves coordinating care through multiple domains of services including: psychotherapy, social skills training, speech and language intervention, occupational and physical therapy, vocational training, and psychopharmacologic interventions to target impairing symptoms of comorbid psychiatric disorders. The remainder of the discussion will focus on the treatment of the comorbid bipolar disorder through pharmacological means.

**Pharmacological treatment considerations**

An important concern, with regard to the PDD population, is that treatment response to psychotropic medication is noted to be less robust and with higher rates of adverse effects to both medication and placebo (17-19). Therefore, due to an atypical response and higher susceptibility to adverse effects, it is advisable to “start low and go slow,” initiating psychotropics at a lower dose and titrating upward in smaller increments in this population. Despite substantial evidence documenting the role of pharmacotherapy for the management of extreme mood difficulties, there is a paucity of published literature, with limited controlled trials regarding psychoactive medications for the treatment of comorbid BPD in this population and, therefore, psychopharmacological treatment approaches should be made judiciously with patients being closely monitored for treatment effects (adverse effects and symptom improvement).

The limited literature on the treatment of comorbid BPD in children with PDD suggests that first-generation antipsychotics (haloperidol, chlorpromazine, thioridazine) and traditional mood stabilizers (lithium, carbamazepine) are minimally effective as monotherapy for the treatment of mania (20). Although there are few studies of lithium within the PDD population, case reports indicate that lithium may be helpful in combination with neuroleptics or other antimanic medications (20). In a
recent secondary analysis of acute second-generation antipsychotic monotherapy trials in BPD young people, we reported acceptable tolerability and robust antimanic response to atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, or aripiprazole) in the presence of PDD comorbidity (10). There were no differences observed in the rate of antimanic response and tolerability, with the exception that PDD young people were more susceptible to the adverse effect of slurred speech and teary eyes. Furthermore, compared with other atypical antipsychotics, risperidone produced a superior antimanic response in BPD young people with comorbid PDD. However, this study was limited by the retrospective nature of post hoc analysis and lack of direct measures of PDD symptomatology.

There is evidence from the treatment trials of risperidone, aripiprazole, and ziprasidone that second-generation neuroleptics are also well tolerated and effective in treating symptoms of irritability and aggression in young people with PDD, a spectrum of symptoms suggestive of BPD. Controlled trials of risperidone consistently report favourable safety, tolerability and efficacy profiles for treating symptoms of irritability and aggression in young people with PDD (21-23). Although risperidone is the only atypical antipsychotic that the United States Food and Drug Administration has approved for the treatment of irritability and aggression in autistic children, weight gain associated with risperidone is a significant adverse effect that often limits continuation of treatment in this population. In contrast, results from recent short-term open trials with the newer atypical antipsychotics aripiprazole and ziprasidone show promise as a treatment for irritability in children with PDD and are associated with negligible weight gain (24,25). Contrary to the encouraging response observed with the aforementioned atypical antipsychotics, the atypical antipsychotics quetiapine and olanzapine are noted to be ineffective in treating symptoms of irritability and aggression in this population (26-28).

Therefore, when selecting a thymoleptic agent for the treatment of BPD in young people with comorbid PDD, attention should be given to those atypical antipsychotics that are also shown to be effective in treating associated and core features of PDD. Furthermore, in this population, due to higher susceptibility to adverse effects, as mentioned above, it is advisable to initiate and titrate psychotropics at a lower dose. As the aforementioned empiric evidence suggests, risperidone appears to be effective in treating both core and associated features of PDD and may be superior to other atypical antipsychotics as an atypical antipsychotic agent in young people with PDD. Young people should be monitored closely for adverse effects, especially weight gain, as this remains a concern in short-term and long-term therapy with risperidone. Recent studies have investigated the use of metformin to mitigate weight gain and abnormal glucose metabolism secondary to the use of second-generation antipsychotics. These studies have shown a positive effect for metformin use in children, but failed to produce similar results in adults (29, 30). With regard to evidence for the effect of metformin on mitigating weight gain secondary to antipsychotic use in the PDD population, there are only case reports (31).

Conclusion

Within the PDD population, there is a high prevalence of comorbid psychiatric conditions. There is an overlap in symptomatology between PDD and BPD that presents diagnostic challenges; a growing literature demonstrates that there is a bidirectional relationship between the two conditions. Severe behavioural disturbance and poor level of functioning are found in the young people with comorbid PDD and BPD. Identifying comorbid BPD in individuals with PDD is crucial so that these children can receive appropriate treatment. Within the limited studies, second-generation antipsychotics as monotherapy show promising responses. However, the success of these medications is diminished with the concerns about the adverse-effect profile of weight gain and impaired glucose metabolism; these appear to be more common in children. Additional studies have investigated the use of metformin to mitigate the metabolic adverse effects of antipsychotics with conflicting results. With the paucity of literature that has systematically evaluated psychopharmacological treatment of comorbid BPD and PDD, there continues to be a gap in our understanding of the full risks and benefits of treatment. There is a need for further rigorous investigation.
GP Comment

What have I learned from this paper?

1. There is an overlap of symptoms between bipolar disorder and autism spectrum disorder; there appears to be a bidirectional relationship between the two diagnoses.

2. The limited evidence seems to suggest that risperidone could be useful for treating both conditions but concerns about weight gain and the risk of diabetes imply that close monitoring is required.

3. Because of the complexities around both diagnosis and treatment, if I suspected that an individual had both bipolar disorder and autism spectrum disorder, I would refer to a specialist psychiatrist for management.

Dr Mayruja Santhirakumar, GP Trainee.

References


ADHD and bipolar disorder among adolescents: Diagnostic traps for the unwary.

S. Rozencweig MD, N. Zdanowicz MD PhD, A. Myslinski MD, Ch. Reynaert MD PhD, D. Jacques MD

Université Catholique de Louvain, Universitary Hospital Center of Mont-Godinne, Psychosomatic Unit, 5530 Yvoir Belgium

Abstract

Since we have effective medication for adolescents with ADHD, it has become important for it to be diagnosed. However, diagnosing ADHD has been complicated by the fact that bipolar disorder may also be present at this age. Although these entities can be distinguished from each other they may also overlap. This paper sets out to review the clinical pictures of both conditions and highlights the conceptual and symptomatic separating lines.

Key words: bipolar disorder, ADHD.

Introduction

In the majority of cases, it is easy to distinguish a child with ADHD from one with a bipolar disorder. However, in certain situations, these disorders may not be so easily differentiated. Hence, when faced with a restless, elated, or even depressed child, both diagnoses are possible. The dividing lines between these two entities are clear in theory but sometimes less so in practice. Such imprecision results chiefly from three causes:

1. Although ADHD is relatively well-known and identified, this does not alter the fact that the rate of prevalence may vary from 1 to 20% from one continent to another, from one country to another, or even from one region to another. There is, as yet, no single or full explanation for this peculiarity. Even though a recent meta-analysis (1) stresses the methodological differences (diagnostic criteria, information sources, exclusion criteria, etc.) as causes of the disparities between Europe and the USA, other studies point to the nosological and cultural differences between practitioners, differences in young people's academic requirements, and so on.

2. It is not new knowledge that bipolar disorder (BPD) may be present in a child or an adolescent but, practically speaking, this possibility is always ruled out in the DSM IV-TR (2). The diagnostic criteria for BPD are thus particularly vague at these ages. Some writers support strict respect of the adult criteria applied to young people; others recognise the same criteria but applied in a less strict fashion; yet others talk about atypical clinical pictures.

3. Epidemiological studies into the co-occurrence of the two diagnoses in the same young person show that double diagnoses are more frequent than a single diagnosis! Whilst one may often observe in psychiatry that one disorder is accompanied by other psychiatric comorbidities, this is never seen with such frequency. For the double diagnosis of ADHD-BPD, the figures most often reported are 85% of ADHD-BPD diagnosed among patients affected by BPD and 22% of BPD identified among children with ADHD (3).

The difficulty in distinguishing the two entities is obviously a major problem when choosing the appropriate treatment. We shall attempt to go back over each of the two entities, both from the standpoint of conceptual as well as diagnostic dividing lines; we shall demonstrate how some symptoms may overlap and lead to errors in diagnosis. Finally, we shall discuss the implications of the high rate of double diagnosis.
Results

Attention Deficit Hyperactivity Disorder

The History of ADHD

Attention Deficit/Hyperactivity Disorder has been known since the Nineteenth Century. In 1845, H. Hoffmann in Germany, and in 1897, Bourneville in France, were the first to describe cases of motor instability, initially amongst children and then in adults. This concept of “neuromotor instability” was later expanded upon by Wallon's contributions which included it in a broader nosological classification: Children's Instability Syndrome. In Europe in the fifties, the influence of the psychoanalytic current and psychodynamic approaches grew in psychiatry. This development changed “neuromotor instability” into “affective-emotional” disorders. On the other hand, in the USA, the prevailing focus was on a non-psychological approach and the study of the cortex and mesencephalic regions. Neuro-anatomical observations of restless children gave rise to various publications at the beginning of the Twentieth Century. The work of Still and von Economo resulted in the concept of “Brain Damage Syndrome,” and then hyperkinesia. Subsequently, the work of Bradley and Lauffer helped refine the hyperkinetic syndrome, which appeared in DSM II in 1974. Until that time, hyperkinesia was the major diagnostic criterion. In subsequent versions of DSM (III and III R), diagnostic criteria evolved into other dimensions, resulting in a disorder with three characteristics: inattention, hyperactivity and impulsivity. However, in the later version (DSM IV), following longitudinal studies showing the significance of hyperactivity, the disorder became based on two dimensional diagnostic characteristics: attention deficit on the one hand and hyperactivity-impulsivity on the other.

The Symptomatology of ADHD

The prevalence of ADHD ranges from 3% to 5%; the sex ratio is 3 to 5 boys to one girl (4). ADHD is one of the behavioural disorders most frequently diagnosed in children and adolescents. The three principal symptoms of ADHD are hyperactivity (disorganisation and an excessively high level of activity), inattention (difficulty in concentration, distractibility), and impulsive behaviour (little patience). According to the DSM IV classification (2), ADHD is comprised of three subtypes:

- ADHD Predominantly Inattentive Type
- ADHD Predominantly Hyperactive-Impulsive Type
- ADHD Combined Type. The most severe forms of the combined type, is also referred to as “hyperkinetic syndrome” (HKS).

To make a diagnosis, assessments must be carried out in at least two different situations (for example at school and at home) and the symptoms must have been present for at least six months. Although parents are more likely to identify the symptoms of hyperactivity and teachers the attention symptoms, the concordance rate with the criteria set out in the DSM IV, taking information from parents and teachers, is satisfactory. Teachers are more likely to make the diagnosis in primary rather than secondary school. This is because the academic requirements are more standard and because, in secondary school, the academic curriculum of the “more noisy and distracted children” has already been re-orientated.

More clinically speaking, we may hypothesise the presence of the disorder when a young person has difficulty in any of the following.

- Controlling motor activity, especially if it is complex.
- Controlling chattering.
- Utilising internalised language in behavioural self-control.
- Expressing him/herself or organising his/her thoughts.
- Controlling negative emotions.
- Memorising a task.
- Thinking up and applying a strategy, especially if it is sequential.
- Resisting temptation and delaying gratification.

Bipolar disorder in adolescents

The History of Bipolar Disorder

Mania and melancholy have been identified since antiquity. However, the close links which bring them together into one illness were not recognised until the second half of the Nineteenth Century (4). In 1854, Baillarger described a “dual-form insanity” and J-P Falret identified a “circular insanity,” while German writers gave descriptions of periodic mood disorders. In 1899, Kraepelin identified what he called “manic depressive illness,” to which he assigned predispositional (constitutional, hereditary) propensities and a favourable prognosis despite the tendency to relapses. It has long been acknowledged that the illness (manic-depressive psychosis) constitutes but one distinct disorder. However, in the fifties, clinical and family studies suggested the existence of sub-groups with different characteristics of transmission and progression. This led Léonhard (1959), Angst, Perris and Winokur to propose the first sub-divisions based on “polarity”, as follows.

- Bipolar psychoses, characterised by the occurrence of manic crises and melancholic attacks in the same subject.
- Unipolar psychoses, characterised by the recurrence of melancholic attacks.

Subsequently, Dunner and Fieve (1974), identified a sub-group of rapid cycling manic-depressive psychoses, characterised by the occurrence of at least four dysthymic episodes per year.

The symptomatology of bipolar disorder in adolescents

Even though it was acknowledged in DSM II that adolescents may present a bipolar disorder, with the publication of DSM III at the end of the seventies, this diagnosis was no longer recognised, except in adults. Consequently, until the nineties, the disorder became under-diagnosed amongst adolescents. In 1986, Professor Weller highlighted that many adolescents suffering from a bipolar disorder were being erroneously diagnosed with schizoaffective disorder (Weller and Weller, 1986). Between 1994 and 2003, we saw an “epidemic” of bipolar disorder diagnoses in young people. The reason for this “epidemic,” apart from the under diagnosis in previous years, stems undoubtedly from the great variability of diagnostic criteria utilised by the researchers. Indeed, they must have gone beyond the strict framework of the DSM because “officially speaking” this disorder does not require a description different from that of the adult (5). The only observation specific to this cohort which one finds in the DSM is that mixed disorders seem to be more frequent in adolescents and young adults. However, the clinical expression of bipolar disorder in adolescents differs from that in adults on many levels, principally in terms of duration of episodes and mood variations. In adolescents and young adults, we find much more rapid cycling (6), less distinction between episodes and less inter-critical periods with a return to more or less neutral moods.

The clinical picture of a manic or hypomanic phase in adolescents or young adults, mainly displays the following features.

- A “joyful” mood, uncontrollable laughing, a desire to transgress, feelings of invincibility, increased self-confidence.
- Increased talkativeness with hard-to-follow reasoning, and a need to attract attention.
- Decreased need for sleep with persistent high levels of energy throughout the day.
- The need to carry out many activities, and seek pleasure.

During a manic phase, it is not unusual to observe a psychotic dimension, characterised by auditory and visual hallucinations, usually in relation to mood-congruent delusions of grandiosity. After this rather “high” phase, adolescents displaying this clinical picture swiftly find themselves overwhelmed...
and their mood may quickly switch from a state of excitation to one of anxiety and distress. A depressive phase may set in very rapidly and is characterised by the following features.

- Irritability, fatigue. Parents describe their child as grumpy, mournful and crotchety.
- Loss of interest, boredom.
- Loss of appetite or bulimia.
- Difficulty concentrating, especially at school.
- Bouts of crying for no apparent reason.
- Feelings of rejection and failure.

In order to diagnose a bipolar disorder in an adolescent, it is important to carry out a full heteroanamnesis which takes into account the adolescent’s behaviour at school, in interaction with his/her peers, and his/her family’s functioning. Indeed, the family environment influences, and is strongly influenced by, the symptoms of its bipolar adolescent member. A study analysing the functioning of families of bipolar adolescents was able to demonstrate a faster resolution of manic symptoms in adolescents living in families in which conflicts are rare (7).

**Comparison of Entities**

The main symptoms can often be clearly distinguished. However, some symptoms can overlap between the two entities.

A bipolar disorder in the manic phase is characterised by the following (8, 4).

- Mood elevation.
- Megalomania ideas, a flight of ideas, psychotic characteristics or seeking pleasurable activities.

In hyperactive children, these characteristics are not clearly found. The focus is more on dysphoria. It is unusual to observe megalomaniac ideas, a flight of ideas or psychotic characteristics.

However, it can be difficult to differentiate the following.

- Psychomotor agitation in mania from hyperactivity in ADHD.
- Distractibility and irritability in BPD from inattention and excitability in ADHD.
- Sleep disorders may be present in the two entities but tend to be viewed more as concomitants to mood elevation in BPD, whereas they are more persistent in ADHD (9).

A bipolar disorder in the depressive phase is characterised by the following.

- Low mood function, insomnia, anhedonia, abulia.
- Body weight alterations, most frequently following a loss of appetite.
- Fatigue, loss of energy, hypersomnia and suicidal ideations are specific to this kind of mood disorder.

In a child with ADHD, the focus is chiefly on dysphoria, even depression associated to the disorder, without real fatigue, loss of energy or suicidal ideations.

However, it may be difficult to differentiate the following.

- The difficulties in concentration of the depressive syndrome from the inattention of ADHD.
- Some psychomotor agitation may be manifest in the depressive syndrome following, for example, an episode of increased anxiety. This may correspond to what is referred to as hyperactivity in ADHD, although it is more overt and constant in that disorder.

Tables I and II below propose an evaluation of the level of symptom overlap between the two entities.
### Table I: comparison of the symptomatology of Bipolar Disorder (BPD) in the manic phase and Attention Deficit/hyperactivity Disorder/Hyperactivity (ADHD) (according to Scheffer, 8).

<table>
<thead>
<tr>
<th>BPD</th>
<th>ADHD</th>
<th>Level of symptomatic overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor agitation</td>
<td>Hyperactivity</td>
<td>High</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>Impulsivity</td>
<td>High</td>
</tr>
<tr>
<td>Distractibility</td>
<td>Inattention</td>
<td>High</td>
</tr>
<tr>
<td>Irritability</td>
<td>Excitability</td>
<td>High</td>
</tr>
<tr>
<td>Garrulousness</td>
<td>Logorrhea</td>
<td>Moderate</td>
</tr>
<tr>
<td>Exaltation</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Delusions of grandeur</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Flight of ideas or the</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>sensation of racing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>thoughts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased need for sleep</td>
<td>Difficulty going to bed</td>
<td>Low</td>
</tr>
<tr>
<td>Increase in goal oriented</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive involvement in</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>pleasurable activities</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table II: comparison of the symptomatology of Bipolar Disorder (BPD) in the depressive phase and Attention Deficit/hyperactivity Disorder (ADHD) (according to Scheffer, 8).

<table>
<thead>
<tr>
<th>BPD</th>
<th>ADHD</th>
<th>Level of symptomatic overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive mood</td>
<td>Dysphoria</td>
<td>High</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Difficulty to calm down</td>
<td>High</td>
</tr>
<tr>
<td>Irritability</td>
<td>Irritability</td>
<td>High</td>
</tr>
<tr>
<td>Diminished aptitude to</td>
<td>Inattention</td>
<td>High</td>
</tr>
<tr>
<td>concentrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychomotor Agitation</td>
<td>Hyperactivity</td>
<td>Moderate</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>Impulsivity</td>
<td>Moderate</td>
</tr>
<tr>
<td>Weight loss or gain</td>
<td>Weight loss under</td>
<td>Moderate (after treatment</td>
</tr>
<tr>
<td></td>
<td>stimulating drugs</td>
<td>with stimulating drugs)</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Fatigue or loss of energy</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Diminished interest or</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>pleasure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BPD and ADHD may also be distinguished by the following.

- Their sex ratio (3 to 5 boys for 1 girl in ADHD and 2 girls for 1 boy in BPD).
- The age of diagnosis (before 7 years old for ADHD and during adolescence or adulthood for BPD).
- The evolution (more episodic for BPD and more constant over time for ADHD).
- The hetero-anamnesis, mainly familial and scholastic, which may be contributory to one or the other of the disorders.
- Prevalence (1% for BPD and 3-5% for ADHD)
- Therapeutic responses to various therapeutic agents.
- Simultaneous use of diagnostic scales (10, 3). The main rating scales are the Young Mania Rating Scale (YMRS) for mania, the Hamilton scale for depression and the ADHD-RS-IV (11) for hyperactivity. Few
studies propose establishing a differential diagnosis using one single scale. For example, the YMRS has been used (12) on the assumption of overstated scoring in mania in relation to hyperactivity. However, this scale is not a diagnostic instrument and its only purpose is to gauge the intensity of symptoms (10, 3).

Discussion

Although, in theory, the entities are very distinct, in day-to-day practice the distinction may be less straightforward. This observation has led researchers to question the links between the two entities. Three possible relationships have been discussed (13, 14).

1. The symptoms of ADHD are prodromal to the development of a bipolar disorder in children or adolescents. Three observations support this hypothesis. First, individuals reporting a BPD earlier in childhood have significantly more ADHD than adolescents reporting a BPD (15). Second, double-diagnosed patients start their BPD earlier as compared with patients with bipolar disorder alone (16). Finally, we find more ADHD in the descendents of bipolar patients (17, 18).

2. BPD and ADHD are two separate disorders but each present common emotional difficulties in childhood and adolescence.

3. Perhaps a BPD-ADHD entity does exist. In retrospective family studies, we observe a greater risk of developing ADHD when a first-degree relative has had the same diagnosis. Bipolar disorder is more frequent when the person has a close relative with BD or BD-ADHD but not ADHD alone (19). These data thus suggest the existence of a particular pattern of a mixed bipolarity and hyperactivity disorder with its own evolution, an earlier onset, predominance in Caucasian males, a specific clinical presentation (more mixed states, irritability as a main feature, more severe manic symptoms with increased psychosocial difficulties), and a continuous rather than cyclical evolution (20), requiring sequential treatment (21).

Conclusion

The relationship between bipolar disorder and ADHD in adolescents raises questions because of clinical similarities between the two conditions. Extensive research is underway in order to rethink the manner in which these two pathologies coexist. The therapeutic challenge is considerable in view of the poor prognosis resulting from this double diagnosis. The research is all the more difficult as the current nosology for bipolar disorder is not adapted to adolescents. It is important to reconceptualise a symptomatological classification (22) focused on the very complicated, complex, and unique period of adolescence.

GP Comment

What have I learned from this paper?

There is a frequent difficulty in assessing a clinical differential diagnosis in adolescents between bipolar disorder and ADHD because of common similarities at that age. This implies a possible way of seeing those two entities in a different manner, as the consequences of a misdiagnosis is crucial to the evolution of the illness due to a different pharmacological approach. It is important to consider that research at this age is very poor due to the lack of adapted nosology of bipolar disorder.

Dr Juan Mendive, Family Physician, Barcelona.

References

How to manage a patient with bipolar who is starting to develop cognitive decline as a result of dementia

Krzysztof Krysta1, Anna Sobieraj1, Leontyna Wyleżek1, Mariusz S. Wiglus2, Wiesław J. Cubała2

1 Department of Psychiatry and Psychotherapy, Medical University of Silesia, Katowice, Poland
2 Department of Psychiatry, Medical University of Gdańsk, Poland

*Corresponding Author: Krzysztof Krysta
krysta@mp.pl

Abstract

Bipolar disorder may coexist with cognitive deficits, which may be one of the core symptoms of the disease. Additional, independent organic changes in the brain may appear, which cause further deterioration in the cognitive and social functioning of patients. The existence of such comorbidity raises many diagnostic and therapeutic questions. It is necessary to use the existing tools carefully to diagnose bipolar dementia, with a special focus on neuropsychological assessment. Regarding pharmacological treatment, it is very important to avoid medication which could compromise the state of the patient additionally, due to toxicity and adverse effects. Pharmacotherapy should be accompanied by other methods of cognitive and social rehabilitation.

Key words: bipolar disorder, cognition, dementia, deterioration.

Introduction

Bipolar disorder (BPD) has been known for a long time to be associated with cognitive deficits. The persistent and trait-related deficits of this disease refer to verbal memory and sustained attention and, to some extent, executive function and visual memory (1). However, lately there have been an increasing number of reports on the comorbidity of bipolar disorder and serious cognitive deterioration typical for dementia. In the literature there are more and more case reports of patients with this dual problem (2, 3, 4). There is an ongoing discussion as to whether this condition is only a problem of simple co-existence of two different disorders or whether there is a separate type of BPD closely related to the dementia process. Some authors postulate the existence of a BPD subtype, referred to as late onset bipolar illness, dementia specific to BPD or Bipolar VI (5, 6). It is hypothesized that there is a link between the number of subsequent affective episodes and the risk of developing the dementing process (3). There are also reports of early-onset BPD with features of dementia, related to genetic vulnerability (7). This comorbidity has serious implications for the patients because of the impairment of social cognition followed by impairment of social functioning. We present the diagnostic and therapeutic challenges which the clinician may encounter in the treatment of this group of patients.

Diagnostic and therapeutic problems

Bipolar disorder itself can impair cognitive function and, as has already been stated, the course of the disorder may increase the vulnerability to further loss of cognitive function leading to symptoms typical of dementia. Dementia may also be an independent process (4). However, for the practicing clinician, encountering a patient with comorbid bipolar disorder and dementia in the treatment setting, the question that arises is how to manage the dual conditions effectively. As no special diagnostic guidelines for such comorbid patients have been developed as yet, we need to follow the criteria we already have to diagnose dementia and BPD according to ICD-10, DSM-IV/5 and, in the case of dementia, also the criteria used by neurologists. The basic elements of the dementia diagnosis...
include: structural neuroimaging with non-contrast CT or MRI, screening for hypothyroidism, syphilis screening in patients at risk and routine laboratory tests, including complete blood count, serum electrolytes, glucose, blood urea, nitrogen/creatinine, folate and B12 (8). This should be followed by a neuropsychological examination. The most popular screening tool is the Mini Mental State Examination (MMSE). However, more detailed diagnostic tests are usually needed, including the California Verbal Learning Test, the Trail Making Test A and B, and the Category Fluency Test (9, 10). Further recommendations include: the Clock Drawing Test, Complex Figure Copying to diagnose, for example, apraxia, and other tests such as Judgment of Line Orientation or the Money Road Map Test (11, 12). So far no particular standard to diagnose cognitive functioning in BPD has been accessible, so similar batteries of tests could be proposed (6).

It is more difficult to find guidelines for the pharmacological treatment of such patients. Until recently there have been many interesting reports about the beneficial influence of treatment with lithium on cognitive functioning (13,14,15). Other interesting observations referred to memantine, which is a drug approved for Alzheimer disease. It may also show antimanic and mood-stabilizing effects in treatment-resistant bipolar disorder (16). Other recommendations for the treatment of patients with comorbid BPD and dementia include being cautious with the use of procholinergic drugs such as donepezil and rivastigmine, which can increase the risk of mania, avoiding antidepressants, which may precipitate elevated affective episodes and also avoiding benzodiazepines, which can decrease cognitive function. With regard to mood stabilisers, sodium valproate appears to be better tolerated than carbamazepine. Antipsychotics can be used very cautiously in cases of agitation (6). In our practice we have treated a patient, whose main complaint for many years was only recurrent affective episodes. However, there was a decline in cognitive and social functioning. On neuroimaging, subcortical cerebral atrophy was found and it was revealed that the ventricular system was enlarged symmetrically, with no shift. (Figure 1).

The battery of neuropsychological tests showed deficits in recent memory, attention and concentration. Affective episodes were effectively controlled by carbamazepine, so no change in mood stabilising treatment was proposed. No pro-cognitive treatment was administered initially. However, it was decided that the neuropsychological assessment should be repeated every 6 months (17). We also paid attention and encouraged the patient to control his diabetes, which could be an additional factor having an influence on cognitive functioning. A very important element in our therapeutic strategy was to improve the patient’s social function through his participation in group psychotherapy and other activities, such as dance therapy, music therapy and art therapy. We also focused on the psychoeducation of his family.
Conclusions

Research analysis and our own example demonstrate that a practicing clinician may often face the specific comorbidity of BPD and dementia, especially when dealing with older patients. Discussion of this comorbidity is ongoing; there are currently no specific diagnostic and therapeutic guidelines for this group of patients. However, careful implementation of the diagnostic tools for BPD and dementia, which are already accessible, can be very valuable. When administering pharmacotherapy it is especially important to avoid toxicity and negative iatrogenic effects on the course of the two disorders. Further research in this field is needed. In addition to pharmacotherapy, treatment should also include the forms of interaction that improve cognitive functions. Cognitive rehabilitation may improve social functioning of these patients. It should be supported by group therapy, art therapy, music therapy, and dance therapy, as appropriate.

GP Comment

What have I learned from this paper?

It is increasingly recognised that bipolar disorder can be associated with cognitive impairment, even in younger people.

Cognitive issues are more complex in the elderly with pre-existing bipolar disorder and possible superimposed dementia.

Management strategies in this situation are unclear and there are risks from polypharmacy.

Non-pharmacological strategies are important and should be emphasized

Dr Daniel Dietch, GP, Lonsdale Medical Centre, London.

References

Bipolar Disorder and Epilepsy

Mariusz S. Wiglusz1, Mark Agius2, Krzysztof Krysta3, Wiesław J. Cubała1

1 Department of Psychiatry, Medical University of Gdańsk, Poland
2 South Essex Partnership University Foundation NHS Trust, UK, Department of Psychiatry
University of Cambridge, Clare College Cambridge.
3 Department of Psychiatry and Psychotherapy, Medical University of Silesia, Katowice, Poland

*Corresponding Author:
mwiglusz@gumed.edu.pl

Abstract

The comorbidity of epilepsy and mood disorders has been a subject of interest and of many studies for decades. Although the data on the prevalence of bipolar disorder in epilepsy is still limited, there is growing evidence that these disorders are frequently comorbid. Bipolar disorder and epilepsy have a number of clinical, biochemical and pathophysiological features in common.

Mood disorders in epilepsy often have atypical symptomatology and fail to meet DSM-IV-TR criteria. They can be classified according to the temporal relationship between the onset of psychiatric symptoms and seizure occurrence into ictal (as a clinical manifestation of the seizure), peri-ictal (symptoms precede [pre-ictal] and/or follow [postictal] the seizure), and interictal (symptoms occur independently of the seizure occurrence).

A pleomorphic affective syndrome in patients with epilepsy has been named interictal dysphoric disorder (IDD). Recent data suggest that some symptoms of IDD can be related rather to bipolar spectrum disorder than to unipolar depression, which has implications for treatment and prognosis.

Key Words: epilepsy, bipolar disorder, interictal dysphoric disorder, kindling.

Introduction

Epilepsy is a common and diverse set of chronic neurological disorders characterized by seizures (1). It is the most common serious neurological disorder (2). The lifetime prevalence of true epilepsy is 2-5%. Mood disorders represent a frequent psychiatric comorbidity in epilepsy and often go unrecognized, underdiagnosed and untreated with adverse consequences for health-related quality of life, costs and utilization of epilepsy healthcare, and an increased risk of suicide (3, 4). Most studies on mood disorder have focused on major depressive disorder (MDD) as it is the most frequent psychiatric comorbidity in people with epilepsy (PWE), with a lifetime prevalence of 11-62 % (5, 6). The symptomatology of mood disorders in epilepsy is often atypical, intermittent and pleomorphic. Because the clinical picture can be so diverse it is often difficult to classify mood disorders in epilepsy according to DSM-IV-TR (7) categories, with symptoms overlapping, especially between unipolar and bipolar spectrum disorders. Bipolar disorder features include manic and hypomanic episodes as well as major depressive episodes. Combined mixed episodes also exist (7). The lifetime prevalence of bipolar spectrum disorders may be as high as 2.6 % in the general population (8).

Studies and data on prevalence, recognition and clinical features of bipolar disorder in epilepsy remain limited. Nevertheless, there is growing evidence of bipolar disorders and epilepsy being frequent comorbid conditions. There are features that are common to both conditions, suggesting that there might be a shared mechanism of pathogenesis.

DSM-IV-TR criteria and bipolar disorder recognition

Bipolar Disorder until recently has been classified according to Diagnostic and Statistical Manual
of Mental Disorders, Fourth Edition, Text Revised (DSM-IV-TR). There are two main types of bipolar disorder, depending on the occurrence of manic/mixed (type I) or hypomanic (type II) episodes in addition to major depressive episodes. Bipolar disorder not otherwise specified (NOS), is the category that includes bipolar spectrum disorders that do not fulfil type I or type II criteria. Cyclothymic disorder represents a more chronic and less severe, clinical form of bipolar disorder with periods of hypomanic symptoms alternating with periods of mild or moderate depression. Lifetime prevalence of bipolar disorder type I has generally been estimated at 2% (9). However, including bipolar II type, cyclothymic disorder and sub-threshold diagnostic criteria for BPD, 6.4% of the general population has been classified as having bipolar spectrum disorder (8). There is evidence that BPD is often not recognized and is misdiagnosed. In an attempt to improve recognition of BPD, self-report instruments such as the Mood Disorder Questionnaire (MDQ) (10) or the Hypomania Checklist (HCL-32) (11) have been developed.

**Recognition of bipolar disorder in epilepsy**

When reviewing the literature on mood disorders in epilepsy it is important to note that there are significant methodological differences among the studies, including variable, often non-standardized diagnostic instruments, small sample size, lack of control groups, variability in study populations (inpatients, outpatients, neurosurgical patients, refractory epilepsy) (12). There are only limited studies on bipolar disorder in epilepsy and most of the studies are based on clinical examination but without the use of standardized diagnostic criteria such as DSM-IV-TR or ICD-10. This probably explains, at least partially, why bipolar disorder was rarely reported in epilepsy in the older literature (13,14). Recent studies have pointed out that manic or hypomanic symptoms are not rare in epilepsy. A large U.S. survey revealed that bipolar symptoms occurred in 12.2% of community-based epilepsy patients, screened with MDQ, and were 1.6 to 2.2 times more common in subjects with epilepsy than with migraine, asthma, or diabetes mellitus, and 6.6 times more likely to occur than in the healthy control group. A total of 49.7% of the patients with epilepsy who screened positive for bipolar symptoms were diagnosed with bipolar disorder by a physician (15). In another study a group of consecutive patients with epilepsy (PWE) or migraine (M) have been established using the MINI for DSM-IV Axis I disorders. All subjects were also screened with the MDQ. Patients with epilepsy were more likely than those with migraine to screen positively with the MDQ (PWE = 17% vs. M = 5.3% p = 0.006) and to have a diagnosis of bipolar disorder (PWE = 14.5% vs. M = 4.5% p = 0.013) (16).

**The Kindling model**

Bipolar disorder and epilepsy share some similarities, such as a chronic, episodic course, often with increasing disability and drug resistance if not treated, and the fact that some of the antiepileptic drugs are also used as a first-line or second-line treatment in bipolar disorder. Unipolar depression may evolve into bipolar disorder, (17) more mood episodes can lead to a more chronic course of illness whilst in epilepsy it had been suggested (although not subsequently confirmed) that each epileptic event might increase the risk of future seizures. The idea that “seizures beget seizures” is sometimes confused with the experimental model seizure kindling in animals (see later). These observations led to a proposed kindling model as a common mechanism of pathogenesis of both disorders. The kindling phenomenon in epilepsy was discovered in 1967 by Graham Goddard (18) and was previously used as a model for the development of seizures in epilepsy in which the duration and behavioural involvement of induced seizures increases after seizures are induced repeatedly (19). The true model of kindling in epilepsy is somewhat different from what is usually envisaged. The amygdala is a key structure for the development of spontaneous epileptic activity (20). The type of kindling that has been confirmed in epilepsy refers to the experimental observation that repetitive subthreshold stimulation in animals can eventually induce seizures until seizures occur spontaneously without any stimuli. In unipolar and bipolar disorder life events trigger affective episodes, but finally relapse occurs in the absence of any obvious stress factor. It has been also postulated that each new mood episode contributes to the progression of the mood disorder in a similar manner to that of the experimental kindling model in epilepsy (21). These hypotheses were made partly on the observation that antiepileptic drugs (AEDs) such as carbamazepine, valproate and lamotrigine have a high antikindling
effect (20, 22, 23) and are also are broadly used in BPD due to their strong mood-stabilising properties (24, 25).

**Treatment with antiepileptic drugs**

There is considerable overlap in the pharmacological agents used in epilepsy and BPD. Controlled studies have shown that a number of antiepileptic drugs are effective in bipolar disorder in the treatment of acute mania (carbamazepine, valproate), as well as depression (lamotrigine) and for long-term mood stabilization (24, 25).

There are practically no controlled studies on the efficacy of AEDs on bipolar symptoms in epilepsy. Given the lack of data and guidelines for treatment of BPD in epilepsy, probably the primary strategy would be to optimize AED therapy to improve seizure control, preferably using an AED that also has mood-stabilising properties.

Valproate has similar actions to lithium (used in bipolar disorder) in that it manipulates inositol metabolism and extracellular signal-regulated kinase (ERK) pathways. These may lead to altered synaptic plasticity and anti-apoptotic effects. Lamotrigine can also be useful across these conditions, having inhibitory actions upon sodium channels. Its optimal effect is achieved long-term, as with lithium and valproate; thus these agents may act by a combination of acute actions on neurotransmission (reducing excitability) and longer-term genomic effects (26).

**Molecular biology, neurotrophic factors and network remodelling**

All major antiepileptic drugs that are also mood stabilisers, are known to inhibit sodium and calcium currents. The efficacy of AEDs in both conditions, suggests the existence of similar changes in neurotransmitters and voltage-dependent ion channels in epilepsy and bipolar disorder (26). Electrolyte regulation is considered important in the pathogenesis of bipolar disorder and epilepsy, given the suggestion that they involve a hyper-excitatable state. Calcium is of further interest in that one hypothesis of bipolar disorder features underlying mitochondrial dysfunction (27). Disturbance of neurotrophic factors may be involved. BDNF levels are reduced in bipolar disorder and can modify cellular excitability, whilst treatment can alter its expression (28). Conversely, levels are sometimes raised in epilepsy. The end result could be aberrant network changes, including microstructural abnormalities and sensitisation – in particular the above described kindling phenomenon (29). Cell death may also be a feature, given observations of larger-scale brain changes. Limbic structures are frequently affected in bipolar disorder and epilepsy. One theory of bipolar disorder postulates loss of function of ‘mood-stabilising neurons’ (27) regulating affective circuits, in keeping with the idea that the disorders may share altered inhibition.

**Epilepsy-specific mood disorders**

Mood disorders in epilepsy often have atypical symptomatology and fail to meet DSM-IV-TR criteria. As already stated, they can be classified according to the temporal relationship between the onset of psychiatric symptoms and seizure occurrence into ictal (as a clinical manifestation of the seizure), peri-ictal (symptoms precede [pre-ictal] and/or follow [postictal] the seizure), and interictal (symptoms occur independently of the seizure occurrence).

Ictal psychiatric symptoms are manifestations of the seizure itself. However, since most seizures are brief, with a few exceptions, it might be difficult to establish whether any ongoing psychiatric symptoms were truly ictal. Some of the older publications suggested that depression of sudden onset in people with epilepsy might be precipitated by the mood changes associated with a simple partial seizure, although it should be noted that simple partial seizures are usually very brief. This phenomenon was said to appear to be more common in patients with temporal lobe epilepsy, in whom rates of about 15 % were reported (30,31). The severity of symptoms could range from mild feelings of sadness to profound helplessness and despair, guilty feelings and anhedonia.

Prodrome is a well-recognised epilepsy-associated phenomenon, typically lasting for perhaps half
an hour to two or more days before a seizure. Mood and consequently behaviour can be disturbed during this period. Preictal dysphoria can manifest as prodromal depressive mood or irritability. The prodrome is resolved when the seizure occurs. (30, 31, 32). Preictal unstable mood with euphoria and paroxysmal irritability has also been observed (33). It has also been reported that in children, these dysphoric moods can take the form of irritability, frustration intolerance, and aggressive behaviour (34).

Postictal symptoms typically last up to 48 hours after ictus with median duration from 6 to 24 hours (34, 35). Some studies indicate that postictal depression can last up to 2 weeks after the ictus and may lead to suicide (32, 36, 37). The most frequent symptoms are anhedonia, irritability, frustration, poor tolerance, feelings of hopelessness and helplessness, suicidal ideation, feelings of guilt and self-deprecation, and crying bouts (32). Postictal manic/hypomanic symptoms, usually lasting up to 2 hours, have also been reported. These symptoms could represent a part of postictal psychosis or more often a mixed episode with psychotic features. (38,39,50).

### Interictal Dysphoric Disorder

The Interictal recurrent syndrome of periodic dysphoria is the most common form of mood disorder in epilepsy. Frequently, it does not fulfil any of the DSM-IV criteria and has an atypical clinical presentation of depressive symptoms with paroxysmal irritability and also euphoric mood. It is commonly described as a chronic depression or dysthymic disorder but without fulfilling time criteria for these DSM-based diagnoses. However, it can also be a part of the bipolar disorder spectrum. These episodes have symptomatic periods ranging from hours to days interrupted by symptom-free periods of similar duration.

Blumer et al. (51) drew attention to these forms of mood disorder commonly seen in patients with epilepsy and coined the term interictal dysphoric disorder (IDD). A long time before Blumer, similar clinical observations had been made by Kraepelin, who provided a similar clinical description of such a form of mood disturbances in epilepsy (52). IDD is characterized by a constellation of eight symptoms and requires the presence of any three: depressive mood, anergia, pain, paroxysmal irritability, euphoric moods, fear/anxiety and insomnia. Interictal dysphoric disorder is typically of short duration; symptoms occur at various intervals and tend to last from hours to two or three days. In women, these symptoms can become accentuated in the premenstrual period. Blumer et al. considered that almost one-third to one-half of patients with epilepsy suffer from IDD and require pharmacological treatment (51). Unfortunately there are only limited data on comparisons in the literature evaluating this form of mood disorder in epilepsy using standardized DSM-IV based diagnostic techniques with IDD criteria. Recently Mula et al. (16) investigated whether IDD occurs only in patients with epilepsy and validated IDD features against DSM-IV criteria. Consecutive patients with a diagnosis of epilepsy (E) or migraine (M) have been assessed using the BDI, MDQ, and the Interictal Dysphoric Disorder Inventory (IDDI). Diagnosis of current and lifetime DSM-IV Axis I disorders was established using the MINI. Validation of IDD against DSM-IV categories showed current major depression being the foremost diagnostic category correlated with IDD in both epilepsy and migraine. They concluded that IDD was not typical only of epilepsy, occurring also in other central nervous system disorders such as migraine (16). Interestingly, in the study sample PWE were more likely to have a diagnosis of bipolar disorder as compared to migraine patients.

In another study, Mula et al. (53) examined a group of 143 adult outpatients with epilepsy and revealed that 11.8% had the DSM-based diagnosis of bipolar disorder but only 1.4% of whom could be considered having “pure” bipolar disorder. In all other cases, BPD symptoms were related to symptoms of interictal dysphoric disorder, postictal manic or hypomanic states, and preictal dysphoria.

Based on these observations, it was suggested that perhaps interictal dysphoric disorder with its specific features and labile-angry-irritable states represents a more unstable form of bipolar spectrum disorder (53, 54). IDD could be a form of cyclothymic disorders that sometimes exacerbate and meet criteria of major depression episode. Mula et al. speculated that there is enough evidence suggesting that IDD may be closer to bipolar than unipolar mood disorders (53).
Conclusion

The comorbidity of epilepsy and mood disorders has been a subject of interest of many studies over many decades. Although data on the prevalence of bipolar disorder in epilepsy are still limited, there is growing evidence of bipolar disorder and epilepsy being frequent comorbid conditions. Bipolar disorder and epilepsy have a number of clinical, biochemical and pathophysiological features in common.

Bipolar disorder in epilepsy, excluding the ictal or peri-ictal symptoms, can be categorized using standardized measures. Standardized psychiatric interview procedures based on DSM criteria like SCID-I or MINI provide a comprehensive way to diagnose mood disorders in patients with epilepsy.

Different authors have suggested the occurrence of a pleomorphic affective syndrome in patients with epilepsy named interictal dysphoric disorder (IDD). There are only limited data on comparisons in the literature using standard diagnostic techniques with IDD criteria. Recent data suggest that some symptoms of IDD can be related rather to bipolar spectrum disorder than to a unipolar disorder, which has implications for the treatment and course of the illness. Standardised measures that include these unique aspects of symptomatology in epilepsy need to be developed and more direct comparisons with other populations should be evaluated (34).

GP Comment

What have I learned from this paper?

I found the molecular biology, network remodelling and kindling models made for interesting reading; however, perhaps more relevant to specialist physicians as compared general practitioners. I imagine more research could be directed towards this overlap in diagnoses, so as to obtain larger participant numbers.

Dr Vishal Naidoo, GP.

References


26. Jonathon Holland, Dr Richard Doughty, Dr Mark Agius, Dr Rashid Zaman Bipolar Disorder, Migraine, Epilepsy – a shared pathogenesis? e-poster EPA 2012


35. Kanner AM, Rabinovich A, Soto A. The prevalence of postictal symptoms of depression in patients
Bipolar Affective Disorder and Anxiety

Sophie Butler
Melbourne Health, NorthWest Area Mental Health.

Abstract

Bipolar affective disorder (BPD) frequently occurs with comorbid mental health problems. It has been shown that the prevalence of comorbid BPD and anxiety symptoms is especially high. This is important because, for a person affected by both BPD and anxiety, there is a negative impact on the symptoms, treatment response and recovery. A clinician faces particular treatment challenges when managing these comorbid conditions due to a limited evidence base for effective interventions. The frequent occurrence of anxiety symptoms and BPD together has informed theories of the shared aetiology of these conditions.

Keywords: bipolar, anxiety

BPD and Anxiety

Psychiatric comorbidity is a well recognised phenomenon; up to 14% of those with a psychiatric disorder will actually have three or more psychiatric comorbidities (1). Anxiety disorders are frequently seen as comorbid conditions (2). For those with BPD this is a specific concern because there is up to 93% lifetime risk (3) and 32% current risk (4) of comorbid anxiety. Those individuals with BPD who are more at risk of a comorbid anxiety disorder are those with depressive tendencies (5, 6) and those for whom a depressive episode was the initial mood disturbance of their illness (7). Those with comorbid generalised anxiety disorder or social phobia more likely to have worse outcomes than those with other anxiety disorders (8).

Although comorbid anxiety with BPD is highly prevalent and the clinical sub-population most at risk is recognised, these anxiety symptoms are under-reported and, more important, under-treated (9). This is especially concerning given the negative impact that this will have on the individual.

Effect of comorbid BPD and anxiety on a patient’s experience

Having comorbid BPD and anxiety can adversely affect the patient’s experience of BPD. It is related to a more challenging illness course, with an earlier age of onset of symptoms of both the BPD and anxiety disorder (10, 11), a higher number of mood episodes (7) and with rapid mood switching (12). It is also associated with a longer time to remission of BPD (13) and more severe psychopathology (14). Generally a person with both BPD and anxiety will have lower functioning as scored on the Global Assessment of Functioning Scale (GAF) (15) and diminished role functioning (4).

It is particularly important that the risk of suicidality is recognised; there are higher levels of suicidal ideation in this population (16-18) and there is a “dose-response” relationship between the comorbid anxiety symptoms and suicide attempts (19). There is a specific need for improved clinical monitoring in this population (20).

The treatment of these conditions together is challenging; patients are more likely to be on a greater number of medications and will therefore also be exposed to a higher risk of more severe adverse effects (21). There is some evidence that comorbid anxiety reduces the response of BPD symptoms to antiepileptic therapies (5). Treatment is further complicated by the fact that additional comorbidities are often found in those already with a comorbid anxiety disorder e.g. substance abuse (11, 14), alcohol abuse (16, 22) and eating disorders (7).

Treatment

The difficulties of choosing effective treatment options for BPD when an anxiety disorder is also
present are compounded by the fact that effective medications for anxiety (e.g. antidepressants) often have a negative effect on BPD symptoms (23). To avoid the need for antidepressants a good choice would be an antimanic agent that also has anxiolytic properties e.g. sodium valproate, antipsychotics or anxiolytics that do not induce mania e.g. gabapentin and benzodiazepines (except alprazolam) (24). Specific antipsychotics that have some evidence for benefit in BPD are quetiapine, aripiprazole, risperidone and ziprasidone (25).

There is a wealth of evidence for psychological interventions successfully alleviating anxiety symptoms (26) and there is evidence that psychological therapy can be a useful adjunct to medications for bipolar treatment (27). These management strategies reduce the need for pharmacological input and there is an association between improved awareness of symptoms (28) and better insight (29) for this population (those who have both BPD and anxiety), suggesting that they would be good targets for psychological interventions (30). Although there is not very much evidence specifically for BPD and anxiety, the addition of mindfulness-based cognitive therapy to treatment as usual in BPD has been shown to help the anxiety symptoms (31); further research in this area is warranted and feasible (32).

Aetiology

A number of observations have led to the postulation that BPD and anxiety may have an overlapping aetiology. First, that they occur so frequently together. Second, that treatment of anxiety disorders (panic disorder or social anxiety) can trigger a hypomanic or manic episode (33, 34). Third, that adolescents with anxiety are more likely to develop BPD and those with BPD are more likely to develop anxiety (35).

Familial studies have also supported this relationship. There is an inherited risk of BPD and anxiety symptoms which could reveal a shared genetic aetiology (36, 37). There is also a low prevalence of panic attacks (anxiety symptoms) in families with no affective disorders (38). Linkage studies have previously implicated chromosome 18 as a particular focus of this shared aetiology, with highest linkages of loci in families of probands (those with BPD) with panic disorder and lowest for those without panic attacks (39). Other genetic studies have added weight to suggestions that some anxiety symptoms (e.g. panic disorder) may be a subtype of BPD with COMT and 5–HTT polymorphisms having a particular role (40).

BPD and anxiety disorders could be seen as symptoms on the same affective continuum (32). For example, those with social phobia could be a subset of bipolar patients who sit on the scale of inhibitory restraint vs. disinhibited mania (33) or those with panic disorder a subset of patients whom exhibit symptoms that could be described as dysphoric manic/mixed hypomanic states (41).

Conclusion

The combination of comorbid BPD and anxiety poses difficulties for both the patient and clinician. Because it is a common comorbidity, patients with BPD should be routinely screened for anxiety; indeed, conversely when treating a person with anxiety, the possibility of comorbid BPD should be considered. There is limited evidence on how best to manage these conditions together. Options include choosing a mood stabiliser with anxiolytic effects, using an anxiolytic antipsychotic with a mood-stabilising effect and avoiding SSRIs when possible. Although effective psychological interventions are likely to yield improvement of symptoms, further research into this is warranted. An improved understanding of the reasons for the overlapping or shared aetiology might lead to improved treatment choices for the individual.
**GP Comment**

**What have I learned from this paper?**

This article highlights the high prevalence of anxiety symptoms amongst patients with bipolar affective disorder and their association with a more challenging illness course and increased suicidality. It is recommended that we screen for symptoms of anxiety amongst patients with bipolar disorder and that these patients are managed with a mood stabiliser with anxiolytic effects, thereby avoiding SSRI’s when possible. More investigation is needed into the impact of psychological interventions in this patient group.

**Dr Jenny Hopwood, GP Trainee.**

**References**


Relationship between postpartum mood disorders and bipolar disorder, based on a case report of a patient with postpartum psychosis.

Agnieszka Bratek 1, Julia Beil2, Krzysztof Krysta3, Anna Bocheńska4
1 Central Clinical Hospital, Katowice, Poland
2 Medical University of Silesia, Students` Scientific Association, Katowice, Poland
3 Department of Psychiatry and Psychotherapy, Medical University of Silesia, Katowice, Poland
4 General Hospital No. 1, Bielsko-Biała, Poland

Corresponding Author: agnieszka-bratek@o2.pl

Abstract

Data from the literature indicate the existence of a close relationship between some postpartum mood disorders and bipolar disorder. Women with a diagnosed bipolar disorder are at very high risk for affective psychosis in the weeks following delivery. We describe a case of a 28 year old woman, who developed the first symptoms of the disorder a few days after the delivery. Her first episode was successfully controlled with pharmacological treatment; however, she subsequently had relapses requiring hospitalisation. This case emphasises the importance of early psychiatric intervention, effective pharmacological treatment and co-operation with the family to control and treat the disorder successfully from the onset and through following recurring episodes.

Key words: postpartum mood disorders, bipolar disorder, risk factors, treatment

Introduction

The perinatal period is a particularly difficult time for women. Females are at an approximately 22 times higher risk of having onset of a manic or psychotic episode in the first month after giving birth than at any other time in their lives (1). That special time is not only associated with major lifestyle and economic changes, together with possible fear about childbirth complications, but on a physiological level it is also linked with significant changes in hormone levels. At the time of labour the level of oestrogen and progesterone is 200 times higher than during pregnancy and shortly after labour this level immediately decreases (2). The decrease in the level of estradiol seems to be most relevant, due to the major role that oestrogens perform in neurotransmission (3,4,5). Many authors have emphasised the role of the neurobiological changes after delivery in the occurrence of disorders with immediate postpartum onset (6). The spectrum of postpartum mood disorders includes postpartum depression, postpartum psychosis, postpartum hypomania, and maternal blues. These disorders will be described in the order of decreasing frequency.

The most frequent disorder - maternal blues, also called “baby blues” is the mildest among childbirth-related disorders and is so common (40-60 % (7) ) that some authors describe it as a physiological reaction to labour-related stress (8). The onset of maternal blues takes place 3-5 days postpartum and is manifested by dysphoria, emotional lability, irritability, anxiety and mood swings. It is self-restricting and resolves spontaneously after a few hours to a few days. Although the condition of maternal blues might seem to be irrelevant it is a proven risk factor for developing more serious postpartum depression or postpartum anxiety disorders (9).

Postpartum hypomania is the hardest postpartum disorder to diagnose since it seems difficult
to establish the border between the “normal” joy that a newborn baby brings to the mother and pathologically elevated mood (10). Occurrence within the first 3 days postpartum ranges from 9.6 to 20.4% (11). The main symptoms are irritability, psychomotor agitation, a sense of racing thoughts, distractibility and decreased need for sleep (12).

A clinical screening tool for postpartum hypomania is The ‘Highs’Questionnaire which currently is the only screening test validated for diagnosing the postpartum disorders on the bipolar spectrum (12). Postpartum depression is defined as an episode of major depressive disorder that occurs within the first four (according to DSM-IV-TR) or six (according to ICD-10) weeks after labour (13). It affects approximately 10% of women. Patients develop typical depressive symptoms: low mood, feelings of guilt, misery, apathy, irritability, social isolation, anxiety and dys-somnia.

Postpartum psychosis is a rare disorder: 1-2/1000 women are affected (14). Postpartum psychosis is currently not considered to be a distinctive disease entity. Its nosological status is not unambiguously classified - neither DSM-IV nor ICD-10 has a specific category for postpartum psychosis. It is a heterogeneous group of disorders. The patient can develop various mood disorders: depression, mania or switch from mania to depression within the same episode (15). Affective phenomenology coexisting with positive symptoms seems to be a hallmark of the disease and this combination is more often present in postpartum psychosis compared to non-postpartum psychosis (16). There is also a relatively low occurrence of symptoms specifically associated with schizophrenia, such as “Schneiderian first-rank symptoms” (17). Aside from mood disorders that represent a distinctive change from the patient’s previous functioning, the other typical symptoms are: disorganized thinking, insomnia, mood fluctuation, cognitive impairment (disorientation, derealisation, and depersonalization) and positive symptoms – hallucinations (auditory, olfactory or tactile) and delusions (persecutory, of reference or bizarre, often involving the child). The common denominator of these heterogeneous disorders is their temporal relationship with the labour. The timescale within which the symptoms manifest varies between reports, usually occurring within the first weeks after delivery, mostly up to three days after giving birth (18-25). Postpartum psychosis is the most severe postpartum disorder as it can potentially endanger the life of both mother and child. The risk of suicide in affected women increases 70 times and there is a 4% risk of infanticide (26). There is also a high risk of recurrence (20-50% (27)). The overwhelming majority of patients experience a complete remission of psychotic symptoms within 3 months postpartum after treatment.

Case history
M.S. is a 28 year old woman who delivered a healthy baby girl in June 2008. She has been happily married since 2004 and has no prior psychiatric history. Her childhood was happy; she was raised in a full family and felt taken care of by her parents and older brother. She has a Master’s Degree in Management and prior to this and to the onset of the disorder she was working as a store manager. She lives with her husband and mother-in-law. Her relatives describe her as sociable, quick-witted, well organized and full of energy.

The onset of her psychotic symptoms was 3 days after the delivery. Her family (husband and mother-in-law) noticed alarming symptoms: disorganized behaviour (e.g. in the middle of the night she was ironing with her iron unplugged), delusions of the child’s death (she was celebrating mass over her baby’s bed), she neglected the child and became irritable, timid and insomniac. Two weeks after the delivery she was admitted to the Psychiatric Center in Katowice-Szopienice. The diagnosis was F23.0 - Acute Polymorphic Psychotic Disorder without Symptoms of Schizophrenia. Treatment with risperidone and perazine resulted in full remission of the psychotic symptoms. Since July 2008 she was treated as an outpatient with a suspicion of bipolar disorder. In that period there were 8 exacerbations at monthly intervals in constant sequence: first insomnia, then anxiety, strange inadequate speech, disorganized behaviour and tearfulness. Between these exacerbations she had symptoms of hopelessness, apathy, anergy, and difficulty in thinking and planning. After the introduction of valproic acid, the exacerbations were less severe but between them significant somnolence occurred.

On admission it was difficult to establish verbal contact with her, due to lack of spontaneity and excessively concrete speech. Her affect was poorly modulated and not matched to verbal content. She also had auditory hallucinations (baby crying), thought blocking, difficulty in abstract thinking and a sense of emptiness in her head. She did not have any of Schneider's first-rank symptoms. She denied delusions or suicidal thoughts/attempt. Neuroimaging and psychological evaluation were performed. Her treatment was modified. Quetiapine 200 mg was added to valproic acid 800 mg. The therapy resulted in partial improvement of her mental state activity, emotional reactivity and concentration.


On admission she was fully orientated. Her mood and affect were normal but she had vivid emotional reactions. There were no psychotic symptoms, nor suicidal thoughts/attempt. On 2.07.2009 she accidentally took another patient’s medications: clozapine 100 mg and diosminum (a naturally-occurring agent used for vascular protection). She also took her own medication: valproic acid 300 mg and Sertraline 50 mg. She lost consciousness and was immediately transferred for close observation and therapy to a closed ward. The patient was re-transferred to the daycare ward the next day, in a stable condition. Psychotherapeutic interventions (occupational therapy, music therapy, group therapy) and increasing dosage of medications (valproic acid 800 mg->1000 mg, sertraline 50 mg->100 mg, quetiapine 200 mg -> 400 mg) resulted in a slight improvement in her social functioning and mental condition.


She was admitted for modification of therapy. On admission: full orientation, mood and affect within normal limits, she denied hallucinations, delusions, or suicidal thoughts/attempt. Properly administered medications (quetiapine 400 mg, sertraline 100 mg, valproic acid 1000 mg) and psychotherapeutic interventions (occupational therapy, music therapy, group therapy) resulted in an improvement of her mental and social functioning.


The reason for admission was distressing peri-menstrual swings. Her husband stated that she tended to become extremely irritable and anxious, then hypoactive and somnolent. The patient stated that her mood made her unable to take good care of her child. She was still not working but she did not miss her job. Her treatment was modified. The valproic acid was increased from 800 mg to 1300 mg. Quetiapine was discontinued and fluoxetine 20 mg was introduced. She actively and eagerly participated in psychotherapeutic activities and motivated other patients. By the end of January she stated that she did not experience the mood swings to be as disturbing as usual, which was confirmed by her husband. Stabilization of her mood had been achieved and she was discharged earlier than planned due to the improvement.

Postpartum psychosis and bipolar disorder

Bipolar disorder is a heterogeneous disorder, very often coexisting with other disorders. Most (95%) of the respondents with bipolar disorder in the National Comorbidity Survey met criteria for 3 or more lifetime psychiatric disorders. In a Stanley Foundation Bipolar Treatment Outcome Network study of almost 300 patients, 65% met DSM-IV criteria for at least one comorbid Axis I disorder (28). There are data indicating the existence of a close relationship between some postpartum mood disorders and bipolar disorder. Women with a diagnosed bipolar disorder are at very high risk (25-50%) for affective psychosis in the weeks following delivery (29). When, in addition, a first-degree relative has a history of postpartum psychosis, the risk rises to 75% (30).

For many women (40-80%) with no prior history of psychiatric disease, postpartum psychosis is the incipient onset of a bipolar mood disorder (31). 72-80% of postpartum psychosis cases are due to
bipolar disorder or schizoaffective disorder (32). The studies have confirmed the strong connection between severe postpartum episodes and susceptibility for bipolar disorder on a genetic level (33). There is a hypothesis that bipolar disorder in the postpartum period is associated with immune activation postpartum (34).

In the present case report there were no serious negative consequences of the disorder, thanks to an almost immediate response from the family. It should be emphasized that single mothers and women that are unsupported by relatives are particularly at risk. Obstetricians, midwives and general practitioners should pay close attention to women with risk factors for developing the most serious of childbirth related disorders – postpartum psychosis. Furthermore, psychiatrists should be aware of the relationship when diagnosing women with psychiatric problems unrelated to childbirth with bipolar disorder.

GP Comment

What have I learned from this paper?

The postpartum period is a time of increased vulnerability to a number of medical conditions, especially those affecting mental health and it is important to support women and their families at this time. Postpartum problems like wound infections, mastitis, insomnia and feeding problems may have adverse effect on the mother and infant. Preconception and antenatal planning are essential in women with known mental health problems, but serious mental illness, including postpartum psychosis may occur de novo at this time and GPs, Midwives, Health Visitors and the Primary Healthcare team should be alert for women who do not appear to be coping or who appear unwell. Women who do not have effective family support may be at particular risk, because presentation to medical services and treatment are likely to be delayed. Hypomania can be difficult to differentiate from the normal joys of motherhood and mixed states can occur.

The Edinburgh Postnatal Depression Score is now routinely assessed at the 6 weeks postnatal GP check, and earlier by the Midwife and Health Visitor but there is a potential gap of medical assessment between the time of birth and the 6 week check, and calls for help during this time – often to the on-call or out of hours GP - must be taken seriously, but with care not to over-medicalise normality. Postpartum psychiatric disorder, particularly postpartum psychosis, increases the risk for subsequent psychiatric disorders, particularly bipolar disorder and if a woman develops postnatal depression and subsequent recurrent depression, bipolar disorder should be considered and further evaluation arranged.

Dr Daniel Dietch, Lonsdale Medical Centre, London.

References

Childhood bipolar disorder: diagnostic and treatment challenges

Bernadka Dubicka BSc, MBBs, MRCPsych, MD
Affiliation:
Honorary Senior Lecturer, University of Manchester and consultant in adolescent psychiatry, Lancashire Care Foundation Trust
Address for correspondence:
The Junction Adolescent Unit, Scotforth, Piccadilly, Lancaster LA1 4PW
Email: Bernadka.Dubicka@manchester.ac.uk
Conflicts of interest: none.

Abstract

Since the peak onset of bipolar disorder occurs in late adolescence, there is great interest in identifying and treating this disorder early in young people. However, the diagnosis of bipolar disorder in children and adolescence can be challenging and this paper outlines some of these diagnostic difficulties. Treatment is similarly challenging, since the evidence base in this age group remains limited and medication can be associated with significant adverse effects. The available treatment options are discussed, together with the role of the GP in recognising and managing this condition.

Key words: bipolar, mania, depression, child, adolescent, diagnosis, treatment

Introduction

There has been much publicity in recent years regarding an ‘epidemic’ of childhood bipolar disorder (BPD). In the US, clinical studies have reported a sharp increase in prevalence, with a 40-fold increase in clinic visits over recent years (1). However, there is no evidence from international epidemiological studies to suggest that the true rate is increasing in the community (2). This indicates that there is a marked discrepancy between recognition by clinicians and diagnoses made by researchers, and this has been the subject of much controversy.

BPD is generally considered to be an uncommon condition in children that becomes more frequent in the teenage years (2, 3), with the peak onset of the disorder occurring in late adolescence (4). Since many adults with BPD also report early symptoms in childhood (5), there has been much interest in the recognition of bipolar disorder in children and adolescents, in the hope that early diagnosis and treatment might improve longer-term outcomes.

BPD is associated with significant levels of morbidity and a high risk of both suicide and suicide attempts, particularly in young people (6). Children and adolescents with BPD have greater levels of severity and complications than adult-onset cases (7); the course of the illness is more protracted, making these younger-onset bipolar cases appear more like treatment-refractory adult-onset cases (8). For example, in the COBY study, adolescents continued to have symptoms for 60% of the time during a four-year period and, in comparison to adult cases, were more likely to have repeated changes in polarity and a mixed presentation (9, 10). Only 20% experienced complete recovery after admission, with most continuing to suffer from a significant degree of impairment (11). Despite the evidence regarding the severity of this condition, diagnostic delay is greater in these early-onset cases (5). The COBY study reported that the length of time to diagnosis was around 10yrs, and for each year of illness, there was a corresponding 10% less chance of recovery (12).

Although there is clearly a need to recognise this disorder in young people, early diagnosis is challenging and there are concerns about both inappropriate over-diagnosis and under-diagnosis of BPD. This paper will outline some of the developmental challenges in early diagnosis, together with some of the diagnostic controversies. The paper will also outline treatment strategies, the risks and
benefits of medication, and the role of the GP in management.

**Diagnostic Challenges**

**Developmental context**

a) Distinguishing normal behaviour

Some of the key features of BPD may be seen commonly in children and adolescents, and need to be distinguished from normal behaviour. For example, mood swings are common and need to be considered in a developmental context when assessing for BPD. Brief periods of elation and excitability are normal in response to positive life events; in order to diagnose (hypo)mania, the episode will need to be prolonged with a clear onset and offset, and be accompanied by other symptoms of mania. Functioning also needs to be impaired but, in cases of mild hypomania, functioning may temporarily improve with a greater sense of wellbeing, increased confidence and productive activity; recurrent symptoms are, however, associated with numerous difficulties. Grandiosity is an example of another symptom which needs to be considered within a developmental context. Younger children may make grandiose statements which are in keeping with their developmental age and would not necessarily indicate a symptom of mania. Children may state that they are the best in the world at sport, that they are the strongest, the fastest and brightest, or may believe that their behaviour may be beyond consequences ('I'll fight the police so they can't get me'); these types of statements may not be unusual for their developmental age.

b) Comorbidity

Comorbidity is common, complicating both diagnosis and treatment; it is associated with poorer outcomes (13). In younger children, attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), speech and language disorders and autistic spectrum disorders (ASDs) with accompanying mood lability can make diagnosis difficult. ADHD and behaviour disorders are frequently comorbid with mania in children (14, 15). In adolescents, diagnosis can be complicated by comorbid substance abuse and emerging personality disorder (16, 17). Greater comorbidity also increases the risk of self-harm and attempted suicide (6). Even in the presence of a history of any of these disorders, there needs to be evidence that there has been a marked change of usual behaviour for that child in order to make the additional diagnosis of a (hypo)manic episode.

c) Symptom overlap

Diagnosis is also made difficult by the degree of symptom overlap with a number of disorders, particularly with regard to irritability. For example, ADHD symptoms in children can resemble mania, since these children can talk excessively, are overactive and impulsive, can be giddy and irritable, and often have little need for sleep. ODD children can also behave in an impulsive, irritable and grandiose manner. However, the key factor which separates these behaviours from (hypo)mania, is the presence of a change in behaviour or personality in (hypo)mania; ADHD and ODD symptoms are chronic, but manic episodes have clear onsets and offsets.

**Diagnostic criteria**

Opinions differ on the developmental appropriateness of applying adult criteria. Classical mania meeting DSM-IV-TR criteria (acute and clear onset and offset of symptoms, lasting at least 1 week for mania) appears to be rare in young people (18, 19). Mania in adolescents is often complicated, with rapid cycling and mixed manic/depressive features (20). Atypical presentations are controversial in terms of their true relationship to BPD, and also in terms of diagnostic agreement (21). Varying diagnostic approaches have been proposed, but the implications of these approaches for treatment and prognosis remain unclear (22). The key issues under investigation are whether brief periods of hypomania (less than 4 days) are a subtype of bipolar disorder and whether irritability should be a...
Duration

US researchers have described ultrarapid cycling in children (brief, frequent manic symptoms lasting hours to days, but less than the 4-day prerequisite for hypomania) and ‘ultradian cycling’: repeated brief (minutes to hours) daily cycles (23). The concept of ‘ultradian’ cycling is controversial and may be confused with brief periods of mood lability which are environmentally driven or brief mood variations within an episode (9). For example, during an episode of depression, a child’s mood can fluctuate from sad to irritable and even cheerful, if distracted.

Although the concept of ultradian cycling is controversial, there is evidence, however, that episodes of less than the prerequisite 4 days for hypomania may be of significance. Data in young people with only a 2-3 day symptom duration have shown that the outcomes for these individuals are similar to those with a 4-day duration of symptoms (24). Research suggests that about half of these cases will progress to bipolar I/II over 5 years and that they have similar levels and types of difficulties (24, 25). The diagnosis of bipolar disorder not otherwise specified (NOS) is used for cases that do not meet the current minimum duration criteria, however bipolar disorder-NOS is not well-defined. In order to avoid over-diagnosis, researchers have suggested that a minimum number of days, symptoms and episodes, together with impairment, should be present to diagnose bipolar disorder-NOS (24, 25).

Irritability

Irritability is a symptom that is a core feature not only of BPD but also of a number of childhood disorders, including both the emotional and behavioural disorders (26). The UK NICE guidelines view on irritability is that it should not be used as a core criterion in BPD, except in older adolescents, since it is such a non-specific symptom (27). Very few young people with BPD will present with irritability without elation but they do appear similar to those with elation (28); in these cases mania should only be diagnosed if accompanied by other manic symptoms and there are clear episodes.

One line of investigation has been whether chronic irritability in young children might be a precursor of future rapid-cycling adult BPD. A condition called severe mood dysregulation (SMD) has been studied, which describes children with chronic irritability, hyperarousal and ADHD. Although SMD has been shown to be associated with significant difficulties, it does not appear to increase the risk for future bipolar disorder (29). Temper dysregulation disorder with dysphoria (TDDD) is a new category, based on SMD, that has been proposed for inclusion in DSM-V. This category has been devised for children with chronic irritability and temper outbursts who do not meet criteria for BPD in order to avoid the problem of over-diagnosis of bipolar disorder in young people in the US. However, numerous concerns exist regarding this proposal. In particular, this category may pathologise many children unnecessarily and create new additional problems with inappropriate over-diagnosis of TDDD (30).

The problem of under-recognition or over-recognition

There is a wide variability in reported rates of BPD between international clinical samples. For example, high clinic rates of mania (16%) have been reported in specialist US ADHD centres (31), in contrast to UK clinical data where prepubertal mania appears to be very rare (32). In a survey of 200 UK children and adolescents with ADHD only one case of bipolar disorder-NOS was reported (33). Since epidemiological studies indicate that the rates of bipolar-I are similar internationally (2), there is no evidence to suggest that there is a true epidemic of BPD and differences between clinical studies are likely to be a result of cultural influences as well as differing approaches to diagnostic ascertainment in young people. A recent meta-analysis of community diagnostic studies found that the greatest variability in rates between the US and other countries was for subsyndromal BPD. Hence these differences may be partly attributed to the lack of clarity regarding the diagnosis of bipolar disorder-NOS where it is recognised more frequently in the US, and potentially overlooked elsewhere (2). An
additional factor is that there is also ambiguity around the interpretation of mania symptoms in DSM-IV-TR (34), resulting in variation in diagnostic instruments based on this (35).

A study of UK and US clinicians investigated views on diagnosis in a range of case vignettes (21). Although there was agreement regarding a classical presentation of BPD, there was less agreement for more complex cases, with US clinicians being more likely to diagnose mania. There appear to be differing interpretations of symptom presentations by clinicians. It is possible that the recent high level of media exposure regarding BPD in the US, together with differences in health organisation and delivery may be contributory factors to these findings. In contrast, the UK NICE guidelines advocate a conservative view to diagnosis in children and adolescents, whereby the adult criteria for a manic episode need to be met, and with less emphasis on irritability; NICE also states that bipolar-II should not be diagnosed in children and younger adolescents, in view of the uncertainties regarding the diagnostic criteria. It is likely that this more conservative view on diagnosis has also contributed to the differing cross-national perspectives on this condition.

The issue of over-diagnosis and underdiagnosis is vitally important, as it has significant implications for the child. Over-diagnosis brings a potentially stigmatising diagnostic label with possible lifelong implications and potentially inappropriate treatment that could have serious adverse effects; the danger of under-diagnosis is that a serious mental illness may be missed and not treated appropriately, with significant risks of suicidality and impaired quality of life. Therefore the issue of diagnosis remains an important area for research, in order to improve agreement on diagnostic criteria and aid the reliability of clinical detection.

The search for a prodrome

We do not yet have reliable markers confidently to identify those cases at high risk of converting to BPD (36). Young people with a family history and recurrent depression (37) are at a higher risk but studies of prodromal features have not identified symptoms that are specific to BPD (36, 38, 39). In those cases with a familial risk, the conversion rate to BPD is still relatively low. For example, a 10 year follow-up study of Amish offspring of bipolar parents did not identify any cases of BPD in late adolescence (40).

Although more specific markers are not yet available, there is evidence that young people who are at risk and who go on to develop major mood and psychotic disorders, often develop non-specific symptoms over time and development prior to the onset of the recognised disorder (41, 42). Current cross-sectional diagnostic symptoms which do not take familial risk and clinical course into consideration fail to recognise these stages. There is emerging evidence of identifiable clinical stages in the development of these disorders and clinical staging models have been proposed which may improve early identification and help to develop stage-specific treatments (41, 42). Anxiety and sleep problems often precede bipolar disorder, followed by adjustment and minor mood problems. The Amish study described symptom progression during development from anxiety to high levels of energy, sleep disturbance, excessive talking and problems with thinking and concentration; these symptoms also occurred in mini-clusters rather than being chronic, reflective of the episodic nature of BPD (40). The first diagnosable mood episode tends to occur by the age of 12, mostly bipolar disorder-NOS or major depression (37), prior to the peak onset of BPD, around late-adolescence. Thus the available evidence emphasises the importance of a developmental approach to the early identification of young people who may be at risk of developing bipolar disorder and an awareness of the early stages in the course of this disorder. Further work is, however, needed on describing these stages more accurately and developing treatments.

Pharmacological treatment

There have been relatively few studies of pharmacological treatment of BPD in young people (43). Published studies are problematic, as they include a limited number of RCTs, most of which have been small and in which treatment response rates have varied, partly as a result of inconsistent definitions of BPD and differing methodology. Existing guidelines are therefore largely extrapolated from adult data; the more classical a presentation, the more likely it is that adult guidelines will be applicable.
Medication remains the first-line treatment for cases of that meet diagnostic criteria (27), although caution should be used with pre-pubertal mania as the effectiveness and safety of medication has not yet been established in children (43). Medication should be prescribed by a specialist in child and adolescent psychiatry and, as this is a rapidly changing area, clinicians need to be aware of recent developments in prescribing and changes in licensing indications (www.medicines.org.uk/EMC/default.aspx). We have little data on the management of cases at high risk of developing BPD; psychosocial approaches remain first-line management in these young people.

Randomised controlled trials (RCTs)

Although lithium is generally considered to be the ‘gold standard’ treatment for bipolar disorder in adults and is an option for adolescent classical mania, more recent placebo-controlled trials for lithium in young people have had mixed findings (44, 45). A large lithium trial is currently underway (46). Placebo-controlled RCTs for divalproex have been negative in young people for both BPD and BPD spectrum (47, 48).

With regard to the second-generation antipsychotics (SGAs), one large placebo-controlled trial has been conducted involving adolescents with mania. This study demonstrated that olanzapine was effective but weight gain and metabolic adverse effects were a problem (49). There is some evidence from two small studies for the efficacy of quetiapine and risperidone in relation to divalproex (50, 51). In a large trial of children and adolescents with BPD-I, risperidone was superior to either lithium or divalproex; response rates between lithium and divalproex did not differ (52). Therefore, current evidence suggests that the SGAs are more effective than lithium or divalproex in acute mania, in contrast to adult data (53). Little data is available on bipolar depression in young people, so treatment decisions are therefore made on a case-by-case basis. One small placebo-controlled study of quetiapine in bipolar depression has been negative in adolescents (54).

Guidelines

The NICE National Collaborating Centre for Mental Health guidelines recommend SGAs, rather than mood stabilisers, as a first-line treatment for acute mania, in cases meeting adult criteria (27). This recommendation is supported by the more recent trial data and Food and Drugs Administration (FDA) indications in the US (55).

In the UK, lithium carbonate remains the only medication licensed for BPD in young people from 12 years of age. Therefore, off-licence prescribing will need to be discussed with families for the majority of medications used. Lithium is generally not recommended for acute mania if symptoms are severe, in view of its slower onset of action. Regular blood monitoring is required, which is often not popular with young people. NICE advises against prescribing valproate in girls, owing to its possible association with polycystic ovarian syndrome. If an antipsychotic alone is ineffective, lithium or valproate are suggested as an augmentation strategy, and a benzodiazepine such as lorazepam can be used to manage agitation, if required. In the US, risperidone, quetiapine and aripiprazole have also been approved by the FDA from the age of 10, and olanzapine from age 13.

BPD may require lifelong treatment, although results from an 8 year longitudinal study of childhood BP-I (definitions adapted) would suggest that the majority of childhood cases will not meet criteria for manic episodes by age 18 and above (56). For those young people requiring longer-term treatment, there is little evidence to guide clinicians and consequently adult guidelines are used. One small study of lithium versus divalproex in maintenance treatment did not find a difference in relapse rates (57). NICE suggests the use of lithium, olanzapine or valproate, and either switching medications or using a second agent in the event of an inadequate response. Carbamazepine or lamotrigine are suggested if a trial of combined agents proves ineffective. However, there is minimal available data on their use in young people with BPD and their use is also not licensed in the US in this age group.

In practice, the choice of medication will be governed not only by guidelines but also the most recent evidence base, treatment response, willingness to comply with blood testing and adverse effect profile.
In view of the paucity of the evidence and concerns regarding potentially serious adverse effects, the risks and benefits of medication need to be considered carefully with the family. If medication is commenced, the principle is to ‘start low, go slow,’ with closer monitoring than in adults.

**Adverse effects**

Children and adolescents appear to be at higher risk than adults for a number of adverse effects, such as extrapyramidal symptoms, metabolic effects and endocrine abnormalities. Although the SGAs carry a lower risk for extra-pyramidal side effects (EPS) than the first-generation antipsychotics, case reports exist for all of the SGAs. SGAs are associated with weight gain, type 2 diabetes, and dyslipidemias. The risk appears to be greatest with olanzapine, intermediate with quetiapine and risperidone, and low for aripiprazole. Young people are more susceptible to weight gain than adults. Risperidone is associated with the greatest risk for hyperprolactinemia, followed by olanzapine; aripiprazole is associated with reduced prolactin levels. Long-term anti-psychotic use in adults has been associated with brain tissue loss over time, suggesting the importance of a careful risk-benefit review of dosage and duration of treatment, particularly since the longer-term effects in young people are unclear. Although adverse events have usually been minor in the randomised studies of SGAs, longer-term open-label studies have indicated that some adverse events, such as the metabolic effects, may be severe and potentially life-threatening in the long term.

Lithium needs to be carefully monitored for renal adverse effects and hypothyroidism, as well as for lithium intoxication. Valproate is highly teratogenic and increases the risk of polycystic ovary syndrome, with its associated symptoms of menstrual dysfunction, hirsutism and acne.

**Psychosocial treatment**

All medication prescribing should occur within a psychosocial therapeutic framework. Because academic, social and family functioning may all be affected, treatment needs to be multimodal; it should include liaison with other professionals and advice on relapse prevention. Components of psychosocial interventions should include advice on managing overactivity, sleep, diet, structured activities and psychoeducation, as well as increasing parental collaboration. Other components include helping parents distinguish between normal developmental behaviour and manic symptoms, managing emotional arousal, improving family communication and providing problem-solving strategies. Multi-family psychoeducation produces improvements over routine care and functional family therapy is associated with more favourable outcomes for depressive symptoms.

**The Role of the GP**

Risk factors for longer episode duration include rapid cycling, psychotic symptoms, earlier age of onset, low socioeconomic status, comorbid anxiety, ADHD, and/or disruptive behaviour disorders and a negative parenting style, as well as nonadherence with pharmacological treatment.

GPs have an important role throughout the longitudinal course of this illness with regard to the following.

1. Early detection of young people at high risk of BPD (family history, recurrent low mood, non-specific impairing symptoms) and referral to CAMHS.

2. Early referral of young people to CAMHS with possible manic symptoms, particularly in those with a family history and recurrent depression. Psychotic symptoms would indicate an urgent need for specialist assessment.

3. Risk assessment and prompt referral to CAMHS of young people with suicidal thinking/behaviour.

4. Managing parents with BPD or other psychiatric disorders.

5. Awareness of safeguarding issues. One in five young people with BPD have experienced physical or...
sexual abuse (66); child maltreatment and neglect is associated with suicidality and poorer outcomes (67).

6. Assessment for concurrent drug and alcohol use (17). Refer to appropriate agencies.

7. Family support and relapse prevention: psychoeducation, particularly regarding safe medication management, and need for medication adherence, since this is a major factor associated with relapse (11).

8. Need for physical monitoring with medication (in conjunction with specialist): healthy eating and exercise habits should be encouraged, with monitoring of weight, cardiac, renal, liver and thyroid function, and blood monitoring of glucose and lipids (68).

Conclusion

Although bipolar disorder is a relatively rare disorder in young people, it is a complex, high-risk condition which requires careful specialist management. The GP has a vital role throughout the course of this disorder, with regard to early detection, the management of physical health, risk identification and awareness of the psychosocial factors which may be contributing to the disorder.

GP Comment

What have I learned from this paper?

This an interesting article. However, there are unrealistic expectations of how much can be achieved within the 7-10 minute GP consultation period. Perhaps a GP with special interest in psychiatry with 30 minute appointment slots might be an option but this could impact negatively on the other partners at the practice.

This makes good reading for difficult implementation

Dr Vishal Naidoo, GP.

References


29. Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar


68. Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in
Bipolar Disorders in Adolescents

Zdanowicz N. MD, PhD. Université Catholique de Louvain. Cliniques de Mont-Godinne, service de psychosomatique
Jacques D. MD, MSc. Université Catholique de Louvain. Cliniques de Mont-Godinne, service de psychosomatique
Tordeurs D. PhD. Université Catholique de Louvain. Cliniques de Mont-Godinne, service de psychosomatique
Reynaert Ch. MD, PhD. Université Catholique de Louvain. Cliniques de Mont-Godinne, service de psychosomatique

Corresponding Author: Zdanowicz N. MD, PhD. Université Catholique de Louvain. Cliniques de Mont-Godinne, service de psychosomatique, 5530 Yvoir, Belgium. Phone: 003281423752, fax 003281423753, nicolas.zdanowicz@uclouvain.be

Abstract

In the 1980s, with the transition from the DSM II to the DSM III, the possibility for an adolescent to present a bipolar disorder became close to non-existent. Adolescent psychodynamic psychiatrists did not agree with this change and stayed with the old classification. Nevertheless, DSM III led to a decrease of bipolar diagnosis in adolescents especially in Anglo-Saxon countries, even becoming a rarity in the 2000s. Now, the evolution of current criteria for adolescents tends to bring these two approaches closer together. Despite the differences, there is a consensus regarding the poor prognosis of type I bipolar disorder, particularly when psychotic traits are observed. Early diagnosis and treatment are therefore important, yet they both remain a challenge, with each having limitations inherent to their respective approaches. In “classical psychiatry”, if the criteria are met for bipolar disorder, treatment is started right away amid the risks of over-diagnosis and the stigmatization of false positives. For psychodynamic psychiatrists, even if the criteria for bipolar disorder are met, it is still necessary that the psychopathological analysis of the disorder in the developmental framework of adolescence confirms that the disorder is stable, at the risk of delayed treatment and increased or insufficiently treated false negatives.

Key words: mood disorder, bipolar disorder, adolescence, nosology.

Introduction

A number of adolescent psychiatrists have always had difficulty with the DSM classification system since the publication of its third version. This is true in general, and particularly for mood disorders, including bipolar disorder. These psychiatrists continued to rely on the DSM II system because of its psychodynamic-like dimension. According to their most salient criticism, in the revision of DSM-II, under the influence of R. L. Spitzer (1968), toward a Kraepelinian nosology, the notion of “adolescent crisis” had disappeared. The Kraepelinian system of DSM III differs from the more normothetic psychodynamically influenced system of DSM II, by putting more emphasis on objective rather than subjective symptoms. Therefore, the highly subjective concept of “crisis” could not subsist in the revised nosology. Although “adolescent crisis” does not appear as such in DSM II, it is always present in the coding system that requires the clinician to determine the reactive nature of the observed disorders. If the definition of DSM II provides the clinician with the flexibility to include clinical pictures that can be found in the adult age range, this is excluded from the DSM III nosology, which only allows for specific disorders to be coded. If the symptoms correspond to an adult disorder, they must be coded in the adult nosology. This change in the diagnostic system led to the relative disappearance of some disorders. Indeed, the new requirement to meet the entire diagnostic criteria of the adult nosology reduced the incidence of certain disorders such as bipolar disorders. Conversely, in the Francophone countries where there were more psychodynamic psychiatrists (PP), the diagnostic criteria have not changed and bipolar disorder has maintained, as in adults, an approximate prevalence of 1%. Realizing the impact of this underestimation, the Anglo-Saxon psychiatrists are...
currently re-addressing the diagnostic criteria for children and adolescents. In this respect, Professor E. Weller has contributed to reconciling these trends while arguing in 1986 against the undervaluation of these disorders in adolescents in the US.

In this article, we propose the following.
(a) To familiarize the readers with the nosological concepts of mood disorders, particularly bipolar disorder in the psychiatry of adolescents.
(b) To highlight the major issues in the field of adolescent bipolar disorders.

**Mood disorders among adolescents**

For PP the diagnosis of a mood disorder in adolescence requires two prerequisites. On the one hand, the adolescent person is conceived as a subject who is wholly psychically unstable, and on the other hand, adolescence is perceived as a depressive developmental stage (Zdanowicz et al., 1996). Because of the psychic reorganization related to adolescence, PP believe that teens can display a number of different clinical pictures, including those of adult disorders. In most cases, clinicians consider that these disorders are not stable and hence they are neither as serious nor require the same treatment or suggest similar prognosis as those of adults. What determines the stability of the disorder (therefore, its seriousness) are psychodynamic criteria, i.e. data on the adolescent's subjectivity. In this conception, normality and pathology are not defined by a ratio of exclusion but by a ratio of continuity. Being considered the essence of being a human, “Pathos” is one of the possible modes of the human psyche's functioning. The criteria of normality in this case are “stuck” on the one hand in the subject's inner world (subjectivity) comprising instinctual life and coping mechanisms, and on the other hand, in the external reality, i.e. the objective symptoms (Bergeret, 1974). For PP, the presence of objective symptoms is not enough to establish that a teenager displays a psychiatric disorder in the full sense of its definition for adults; internal criteria are still required. These internal criteria for adolescents mainly include the existence of psychological distress and stereotyped coping mechanisms, but also a blockade in the subjective process of the acquisition of autonomy (Diatkine 1972). Furthermore adolescence is also conceived as a depressive episode, not only because it includes a process of separation from childhood, but also because this forsaking is necessary for the child to redefine him/herself as a future adult. Unlike depression and grief in adults that result in loss, grief-depression in adolescents has a good prognosis, mainly because it opens the way to the adult world, richer in potential than that of childhood. Hence, depression in adolescence would be frequent and even necessary. For PP one must distinguish normal adolescent “depressive mood” from major depressive disorder. In this perspective, depressive symptoms among adolescents are common and mundane. The diagnosis of major depressive episode is made even more complex as the number of depressive symptoms increases between 12 and 17 years, and in the range 17-18 years they are so frequent that the boundary between “depressive mood” and major depression becomes tenuous. This conception of depression in adolescence has led some authors to hypothesise a normal dysthymia of adolescence (Marcelli and Braconnier, 2008).

Since DSM III, bipolar disorders belong to the category of mood disorders. The former classification insisted much more on the psychotic dimension of these disorders, therefore, in DSM II, they were classified as “affective psychoses”. Today, this above psychotic dimension is only present in schizoaffective disorder. PP, have remained much attached to the old conception of manic-depressive psychosis that covers two distinct phenomena: those that occur in the context of a normal personality, and those occurring in the context of psychotic traits. Faced with a teenager who displays bipolar symptoms, PP must answer several questions pertaining to their diagnostic process, assessment of severity of the disorder, and treatment options:

1 / Is the disorder stable or is it just a temporary state (see above)?
2 / If the disorder is stable are there reasons to believe that the adolescent patient is psychotic? If yes (as is more frequently the case with type 1 bipolar patients), the diagnosis is of manic-depressive disorder. This diagnosis requires a more intense treatment in terms of neuroleptics.
3 / Is the adolescent patient displaying traits of psychotic functioning? If not (as often in hypomania BPD II), then the diagnosis is rather conceived in terms of a counter-depressive reaction, and
antidepressant treatment is more important than antipsychotic treatment. 

4 / Is the delusional aspect of the symptoms the most salient of the clinical picture? If so, the diagnosis is that of a schizoaffective disorder.

Current Issues in bipolar disorder

Notwithstanding these differences between psychiatrists, the issues that arise in relation to bipolar disorder are almost identical in the two trends of adolescent psychiatry. They include:

3.1 Prevalence
3.2 Diagnostic criteria
3.3 Comorbidities, particularly in relation to ADHD
3.4 Therapeutic strategies

3.1 Prevalence

Professor Weller has shown in 1986, that many U.S. adolescents suffering from a bipolar disorder were wrongly diagnosed with schizoaffective disorder (Weller and Weller, 1986). Although bipolar disorder was under-diagnosed at that time, between the years 1994 and 2003, we observed an “epidemic” of bipolar disorder diagnoses in the same cohort. In 10 years, in the U.S., the estimated annual number of youth below 20 with a diagnosis of bipolar disorder increased from 25 (1994-1995) to 1003 (2002-2003) office-based visits per 100,000 population (Moreno et al, 2007).

3.2 Diagnostic criteria

Beyond the under-diagnosis in previous years, one reason for this “epidemic” undoubtedly lies in the great variability of diagnostic criteria used by researchers. They indeed had to leave the strict confines of DSM as “officially” this condition does not require a description different from that of adults (the only specific remark regarding age found in the DSM is that mixed disorders seem more common among adolescents and young adults). In 2001 the National Institute of Mental Health Research Roundtable on prepubertal bipolar disorder “is considering a new classification for youth offering a subdivision of the disease in terms of “narrow”, “broad” and “mixed” phenotypes.

• The “narrow” entity refers to the DSM-IV-TR bipolar disorders I and II.
• The “broad” entity includes bipolar disorder not otherwise specified (NOS) with two phenotypes: the intermediate and broad.
  - Intermediate: the symptoms that are necessary to the diagnosis are present but either do not meet duration criteria, or conversely, duration criteria are met, but all the necessary symptoms for the diagnosis could not be observed.
  - Broad: the disorders identified with the broad entity show a phenotype of severe irritability, without episodic nature of the condition, ideas of grandeur, or high mood.
• The mixed states fall into a continuum between manic symptoms and concomitant depression, forming either a homogeneous episode, or a more heterogeneous pattern whereby mania and depression are present simultaneously, with at each moment, the predominance of one over the other. This classification and the creation of a scale of prodromes (Bechdolf et al. 2010) obviously represent a significant advance for early diagnosis. However, PP are left wanting in two areas: 1/ they still have not recovered the old concept of crisis (formerly the old Transient Situational Disturbances of the DSM II) even if the concept of the bipolar spectrum of Akiskal (Akiskal, 2007) is closest to it, and 2/ Van Os’s hypothesis (Van Os, 2009) of bridges between bipolar disorder, schizophrenia and schizoaffective disorder, does not appear in this classification.

3.3 Comorbidities, particularly in relation to ADHD

The co morbidities are many, and include:

• Anxiety disorders, and ADHD among younger adolescents;
• Drug Use and Antisocial Behaviours among older adolescents.
Comorbidity with ADHD presented a particular interest among Francophone psychiatrists, since 85% of young people with ADHD also meet the criteria for bipolar disorder. This is strange because the dual diagnosis is more common than the diagnosis of the single entity. Various explanations have been proposed to account for that peculiarity (Zdanowicz and Myslinski, 2010) in the international literature.

1. A partial overlap of symptoms between ADHD and bipolar disorders causes diagnostic errors
2. Treating ADHD with psychostimulants can induce a bipolar disorder.
3. ADHD may be a prodrome of bipolar disorder.

3.4 Therapeutic strategies

What are the secure and effective therapeutic strategies? Regardless of these differences, there is unanimity on the poor prognosis of bipolar disorder I in adolescence, and especially, according to PP, if the disorder is accompanied by psychotic features. Indeed, the return to euthymia is slower, the rate of remission is lower, and relapse is more frequent than in the adult form of the disorder. The disorder seems even more deleterious in that it hampers a crucial stage of the adolescent’s development toward becoming an adult. Dawn (Dawn et al. 2004) argues that the evolution of bipolar disorder in early life is characterized by a greater number of mixed episodes or rapid cycling, and greater symptomatic periods. The first episode is often manic, with a time of remission of five weeks to six months, and a relapse twenty-three months later. Regarding treatment, one must obviously take into account the fact that studies of safety and effectiveness are rarer than in adults.

The current consensus among psychiatrists in relation to bipolar disorders in adolescents is as follows:

**Acute manic or mixed phase**

- Without psychotic symptoms, the first choice is monotherapy. Several treatments are more or less well documented: lithium, valproate, carbamazepine, olanzapine, risperidone, quetiapine. Only in the case of successive failures of three monotherapies will a combination of a mood-regulator with an atypical neuroleptic be attempted.
- In the case of psychotic symptoms, the first choice is the combination of a mood-regulator with an atypical antipsychotic. If no therapeutic effect can be observed, another association of two treatments of the same family must be attempted. The lack of response causes the transition to another association where the mood-regulator is maintained, but the antipsychotic is changed.

**Depressive phase**

The treatment of this phase does not benefit from clear guidelines. It often involves lithium in combination with an SSRI. Lamotrigine gives encouraging results during adolescence, especially when combined with an antidepressant, especially venlafaxine.

**Maintenance treatment**

It is believed that the medication that helped control the manic phase should be continued for 12 to 24 months. The relapse rate decreases if, in addition to lithium, atypical antipsychotics are associated. In the absence of clear consensus and safety studies, the risk/benefit ratio should be investigated each time before deciding on the maintenance of long-term medication. If interruption is decided, it must occur at a time when the risk of an unfavourable change seems small, in a stable environment, and under close supervision.

**Bipolar disorder NOS**

There is no consensus on Bipolar disorders NOS, mainly because of their many forms. The intervention focuses on the predominant symptoms in the clinical picture, comorbidities, and issues of concern for the social environment.
Psychotherapeutic intervention

Apart from the interest in psychoeducation, the authors point out that bipolar disorder in adolescence affects a highly strategic period in the development of the individual, and of the development of both the patients’ functioning and his social network. The consequences are therefore very harmful to patients by hampering the process of their personal evolutionary process, as well as by disconnecting them from the outside world. Individual psychotherapy can help patients develop individual abilities, provide support, and accompany their development. Psychosocial intervention is often recommended to maintain or restore the patients’ relationship with the outside world.

Discussion

The evolution of the diagnostic criteria in the DSM system seems to allow some level of reconciliation between different conceptions of psychopathology in adolescence. It is certain that a prompt diagnosis and early treatment are an asset in the treatment of young bipolar I patients. Even though the two psychiatric paradigms agree on this point, their respective attitudes toward young people with bipolar disorder are different. It is at this level that the above two systems of thought reach their limits. For the “classical psychiatrist”, if the criteria for bipolar disorder are met, the treatment is decided upon at the risk of over-diagnosis and of stigmatization of false positives. For PP, even if the criteria are met, it is still necessary that psychotic features should be present and that the psychopathological analysis of the disorder in the developmental framework of adolescence confirms that the disorder is stable at the risk of beginning treatment later and an increase in insufficiently-treated false negatives. If these two psychiatric trends could be brought together, we could increase the sensitivity and specificity of diagnostic criteria.

GP Comment

What have I learned from this paper?

Although the busy GP is unlikely consider the complexities of the underlying psychodynamic theory, it is important to understand the psychiatric assessment of teenagers against the background of what is often a time of great change and instability in their lives.

Teenagers with bipolar I disorder are likely to require prompt and expert treatment.

Dr. Juan Mendive, Family Physician, Barcelona.

References


Correlates of disability in depressed older adults with bipolar disorder

Ariel Gildengers, M.D., Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic
Curtis Tatsuoka, Ph.D., Department of Neurology, Case Western Reserve University School of Medicine, University Hospitals Case Medical Center
Christopher Bialko, M.A., Department of Psychiatry, Case Western Reserve University School of Medicine, University Hospitals Case Medical Center
Kristin A. Cassidy, M.A., Department of Psychiatry, Case Western Reserve University School of Medicine, University Hospitals Case Medical Center
Philipp Dines, M.D, Department of Psychiatry, Case Western Reserve University School of Medicine, University Hospitals Case Medical Center
James Emanuel, B.S., Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic
Rayan K. Al Jurdi, M.D., Mental Health Care Line, Michael E. DeBakey, VA medical Center, Baylor College of Medicine
Laszlo Gyulai, M.D., University of Pennsylvania Medical Center and School of Medicine
Benoit H. Mulsant, M.D., Centre for Addiction and Mental Health, University of Toronto
Robert C. Young, M.D., Department of Psychiatry, Weill Cornell Medical College
Martha Sajatovic, M.D., Department of Psychiatry, Case Western Reserve University School of Medicine, University Hospitals Case Medical Center

Address Correspondence to: Dr. Ariel Gildengers, 3811 O’Hara Street, Pittsburgh, PA 15213, telephone 412-246-6002, email: gildengersag@upmc.edu

This study was supported by an investigator-initiated research grant from GlaxoSmithKline, Research Triangle Park, North Carolina, USA, and grant UL1RR024989 from Case Western Reserve University Clinical and Translational Science Awards (CTSA). The CTSA is a component of the National Institute of Health (NIH) and NIH Roadmap for Medical Research. The contents are solely the responsibility of the authors and do not necessarily represent the official view of the National Center for Research Resources or the NIH.

Abstract

Aims To identify clinical factors associated with disability in depressed older adults with bipolar disorder (BPD) receiving lamotrigine.
Methods Secondary analysis of a multi-site, 12-week, open-label, uncontrolled study of add-on lamotrigine in 57 adults 60 years and older with BD I or II depression. Measures included the Montgomery Asberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Cumulative Illness Rating Scale for Geriatrics (CIRS-G), Dementia Rating Scale (DRS), and WHO-Disability Assessment Scale II (WHO-DAS II).
Results Medical comorbidity in this group of elders was substantial, with roughly 60% of subjects having disorders of the vascular, musculoskeletal/integument, and endocrine/metabolic/breast systems. We found significant relationships among mood (MADRS), medical comorbidity (CIRS-G), cognition (DRS), and disability (WHO-DAS II). More severe BPD depression, more medical comorbidity and more impaired cognition were all associated with lower functioning in BPD elders.
Conclusions Our findings fit the paradigm shift that has been occurring in BPD, supporting the notion that BPD is not solely an illness of mood but that it affects multiple domains impacting overall functioning.

Key words: bipolar disorder, elderly, geriatric, lamotrigine, mood stabilizer, anticonvulsant, depression.
Introduction

In the past several years, in the field of psychiatry there has been a paradigm shift in the understanding of bipolar disorder (BPD). Among researchers, BPD is no longer being seen as a disorder solely of cyclical mood episodes interspersed with normal euthymic periods, but rather as a multi-system disease that is chronic and progressive (1, 2). Numerous studies in the past 10-15 years have shown that across the life-span BPD is associated with increased medical comorbidity, cognitive dysfunction, and substantial impairment in everyday function (3-5). Additionally, while suicide contributes to premature mortality in BPD, evidence now reveals that medical comorbidity (cardiovascular and cerebrovascular disease) predominantly contributes to excess mortality, ranging from 35% to 2-fold higher than the general population and higher than major depressive disorder (6). Hence, the paradigm shift in understanding extent and severity of the effects of BPD on an individual has led to broadening of treatment to encompass medical comorbidity, cognitive dysfunction, and everyday function.

The paradigm shift in BPD is relevant to patients across the lifespan and perhaps most acutely to older adults with BPD where the medical comorbidity and cognitive dysfunction are most pronounced. However, older adults with BPD have been a segment of the population of individuals with BPD that have been least studied with this paradigm shift in mind. The reasons for this include longstanding misconceptions that BPD burns out with age, that patients with BPD do not make it into older age because of premature mortality, and funding priorities of national governments and the pharmaceutical industry (7). There is a growing need to understand the healthcare needs of elders with BPD better because this segment of the population is growing and is among the most expensive utilizers of healthcare (8).

We have previously reported on a multi-site open-label, prospective trial of lamotrigine for geriatric bipolar depression (9). In our previous study of lamotrigine in older people with bipolar depression, lamotrigine was associated with improvements in depression, psychopathology and functional status. In a follow-up analysis of the patients enrolled in the trial, we found that lamotrigine appeared to work well in depressed BPD older adults with high levels of cardiometabolic risk and low levels of mania (10).

To understand the relationships among medical comorbidity, cognitive dysfunction, and mood on everyday function better, we carried out secondary analyses of the baseline data collected in our open-label trial of lamotrigine for geriatric BPD depression (9). Our interest was in examining to what extent medical comorbidity, cognitive dysfunction and mood impacted on everyday function and to what extent these domains might be synergistic. While it is well understood that these domains impact on everyday function individually (11), we were interested in exploring whether, when acting together, these domains would have greater than expected impact on an individual with BPD.

Methods

We conducted a multi-site, 12-week, open-label, uncontrolled trial of add-on lamotrigine in 57 adults 60 years and older with BPD I or II depression. Detailed methods of the trial are described elsewhere (9). All subjects met depressive symptom severity criteria of 18 or greater on the GRID version of the 24-item Hamilton Depression Ratings Scale (GRID HAM-D) (12, 13). Individuals with dementia were excluded from the study.

Measures

Mood. We assessed mood with the MADRS (14), GRID HAM-D, and Young Mania Rating Scale (YMRS) (15).

Medical Comorbidity. Medical illness burden was evaluated at baseline with the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (16). The CIRS-G organises acute and chronic medical burden across
different systems (heart, vascular, etc.), rating burden within each system from “0” (“no problem”) to “4” (“extremely severe/immediate treatment required/severe impairment in function”). Past significant problems that are not currently active are rated as “1.”

Cognition. Cognitive function was assessed with the Dementia Rating Scale (DRS) (17). This instrument has demonstrated sensitivity and specificity in elderly individuals, including those with mood disorders (18). It assesses cognitive function in several domains, including attention, executive function (Initiation/Perseveration), visuospatial ability (construction), abstraction (conceptualization), and memory.

General health/disability status was evaluated with the WHO-Disability Assessment Schedule II (WHO-DAS II) (19). The WHO-DAS II assesses the following domains of function: understanding and communicating, getting around, self-care, getting along with others, household and work activities, and participation in society. The WHO-DAS II is cross-cultural and treats all disorders at parity when determining level of function. The following items from the WHO-DAS II that had a cognitive component were aggregated together: Getting around (s1, s7), life activities (s2), understand/communicates (s3, s6), self-care (s8, s9). These items were used to form a subscale, to focus on everyday function that could be impacted by cognitive impairment.

Statistical Methods. Multiple linear regression models were fitted with WHO-DAS II (or a cognitively-oriented subscale of WHO-DAS II) considered as the outcome measure. Models included adjustment for age and education. A first model considered the full WHO-DAS II scale score, regressed with CIRS-G and MADRS as explanatory variables. This model used all data from 53 subjects. Since the DRS cognitive test data were not collected for all subjects in the sample, this model did not consider DRS. A second model considered a WHO-DAS II subscale involving the items thought to engage cognitive functioning as measured by DRS. As explanatory variables, we also considered subscales of DRS, specifically those associated with I/P and memory. This allowed for the association of everyday function as measured by the WHO-DAS II items with specific cognitive domains. This second analysis involved 29 subjects.

Results

Baseline characteristics of the subjects (n=57) have been reported previously. In brief, subjects were mean (SD; range) age of 66.5 years (6.7; 60-90), 40% female, 86% Caucasian, mean education of 14.5 years (2.7; 8-23), 77.2% bipolar I and 22.8% bipolar II. Mean CIRS-G was 9.5 (4.7; 2-21), which is consistent with medical severity noted in geriatric samples in mood disorder treatment studies (16). As illustrated in Figure 1, medical comorbidity in this group of elders was substantial, with roughly 60% of the subjects endorsing disorders of the vascular, musculoskeletal/integument, and endocrine/metabolic/breast systems. Individuals were moderately depressed with a mean (SD) MADRS score of 25.3 (8.3) and moderately functionally impaired with a WHO-DAS II subscale scores: Getting around=5.1 (3.0), Self-care=3.5 (2.0), Life activities=2.9 (1.2), Understand/communicate=4.7 (1.9), Participation in society=6.0 (2.0), and Getting Along with people=4.1 (2.1). Married subjects comprised 45% (n=26) of the group, while 45% (n=26) were living alone. Among those with DRS data, there were little differences with the sample as a whole. For instance, for this subgroup, mean (SD; range) age was 66.4 years (6.4; 60-85) and mean (SD; range) education of 14.9 years (2.8; 8-21).

We found significant relationships between everyday function (WHO-DAS II) and medical comorbidity (CIRS-G), cognitive function (DRS memory), and mood (MADRS). See Tables 1 and 2. In the model, a 10 point increase on the MADRS resulted in a 2.3 point increase in the WHO-DAS II, while a 10 point increase in CIRS-G resulted in an 8.1 increase in the WHO-DAS II. We found no interactive (synergistic) effects among the domains on everyday function.

There was little discrepancy in age and education between those with DRS data versus those without. For the second model, MADRS was initially included in this model, but was found not to be significant and subsequently removed. R-square and adjusted R-square for the first model were: 0.382, 0.330; for
the second model the values were 0.577, 0.507 (the difference in the R-squares suggests that cognition can help explain variability in certain items of the WHO-DAS II).

Discussion

In this secondary analysis of the baseline data acquired in an open-label trial of lamotrigine for BPD depression, we found significant relationships between everyday function and medical comorbidity, cognitive function, and mood. More severe BPD depression, more medical comorbidity and more impaired cognition were all associated with lower functioning in BPD elders. A recent review of the literature on comorbidity in older adults with BPD comorbidity concluded that medical comorbidity is common, affecting multiple organ systems with a mean of 3-4 medical conditions (20). The most frequently seen comorbidities in this sample were disorders of the vascular, musculoskeletal, and endocrine/metabolic systems. It appears that the relationships between BPD and medical illnesses are multifactorial, related to shared genetic risk, iatrogenic medication effects, lifestyle and other factors (21-24). With some medical conditions, such as diabetes, there may be a bidirectional relationship between psychiatric and medical illnesses (23, 25).

We found no greater than expected impairment in everyday function among BPD individuals when these domains were looked at together. It appears that multiple factors and not one particular factor impacts functional outcomes. Our findings support the notion that BPD is not solely an illness of mood, but that it affects multiple domains impacting patients overall functioning (1, 2).

While our findings fit the paradigm shift that has been occurring in BPD, some limitations of the findings need to be considered. First, the WHO-DAS II is a self-report and has been criticized for failing to identify relationships between observed cognitive dysfunction and identified functional impairments in schizophrenia (4). Hence, the measure is subject to bias and may underreport deficits in everyday function. Second, the sample studied is a sample of convenience and is biased to patients eligible and willing to undergo a trial of lamotrigine. By design, individuals with dementia were excluded from our study. Consequently, the patients reported may not reflect the larger pool of older adults with BPD. Last, the small sample size resulted in limited power to look at interaction effects among the domains.

Noting the above limitations, our analysis supports the understanding that BPD impacts an individual beyond mood and that treatments need to be directed to address all aspects of the illness for patients to enjoy full and sustained recovery. Our findings emphasize the need to look beyond BPD symptoms in assessment and treatment planning. Given the significant presence of medical and cognitive comorbidities among BPD elders, it is critical that clinicians providing care to these individuals carefully assess for concurrent conditions, use treatments that do not worsen these comorbidities, and coordinate care with other providers to minimize treatment burden and avoid conflicting information or advice (20). Considering the global demographic trends in community and healthcare settings, clinicians in both primary and specialty care will be likely to see and need to provide services to geriatric patients with mood disorders (26, 27). Integrated care that addresses medical illness, mood and cognitive function together are needed to optimize health outcomes for this vulnerable group of patients.
Table 1. Parameter estimates for the regression model incorporating medical burden (CIRS-G) and depression (MADRS) scores on everyday function (WHO-DAS II) among 53 older adults with bipolar disorder

<table>
<thead>
<tr>
<th></th>
<th>$\beta$</th>
<th>Std. Error</th>
<th>t</th>
<th>Sig.</th>
<th>95% Confidence Interval (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>Intercept</td>
<td>30.726</td>
<td>12.147</td>
<td>2.530</td>
<td>.015</td>
<td>6.303</td>
</tr>
<tr>
<td>Cumulative Illness Rating Scale-Geriatric (CIRS-G)</td>
<td>.808</td>
<td>.206</td>
<td>3.921</td>
<td>&lt;.001</td>
<td>.394</td>
</tr>
<tr>
<td>Montgomery-Asberg Depression Rating Scale (MADRS)</td>
<td>.230</td>
<td>.109</td>
<td>2.111</td>
<td>.040</td>
<td>.011</td>
</tr>
<tr>
<td>Education</td>
<td>-1.033</td>
<td>.333</td>
<td>-3.103</td>
<td>.003</td>
<td>-1.703</td>
</tr>
<tr>
<td>Age</td>
<td>.001</td>
<td>.134</td>
<td>.011</td>
<td>.992</td>
<td>-2.67</td>
</tr>
</tbody>
</table>

Table 2. Parameter estimates for the regression model incorporating cognition (DRS I/P and DRS Memory) and medical burden (CIRS-G) scores on everyday function (WHO-DAS II cognitively-oriented subscale) among 29 older adults with bipolar disorder

<table>
<thead>
<tr>
<th></th>
<th>$\beta$</th>
<th>Std. Error</th>
<th>t</th>
<th>Sig.</th>
<th>95% Confidence Interval (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>Intercept</td>
<td>75.658</td>
<td>17.949</td>
<td>4.215</td>
<td>&lt;.001</td>
<td>38.528</td>
</tr>
<tr>
<td>Cumulative Illness Rating Scale-Geriatric (CIRS-G)</td>
<td>.490</td>
<td>.223</td>
<td>2.198</td>
<td>.038</td>
<td>.029</td>
</tr>
<tr>
<td>DRS Initiation/Perseveration Subscale</td>
<td>- .097</td>
<td>.209</td>
<td>- .461</td>
<td>.649</td>
<td>- .529</td>
</tr>
<tr>
<td>DRS Memory Subscale</td>
<td>-2.014</td>
<td>.664</td>
<td>-3.035</td>
<td>.006</td>
<td>-3.388</td>
</tr>
<tr>
<td>Education</td>
<td>- .531</td>
<td>.282</td>
<td>-1.886</td>
<td>.072</td>
<td>-1.114</td>
</tr>
<tr>
<td>Age</td>
<td>- .054</td>
<td>.108</td>
<td>- .504</td>
<td>.619</td>
<td>- .277</td>
</tr>
</tbody>
</table>
Figure 1. Cumulative Illness Rating Scale-Geriatric (CIRS-G) scores in 57 older adults with bipolar disorder

References

Treatment of bipolar disorder in pregnancy and post partum

Marjeta Blinc Pesek
Psihiatrična ordinacija Rudnik
Rudnik II/4
Ljubljana

Abstract

Bipolar disorder tends to occur during reproductive years in women. It is a source of distress, disability, burden to relatives and caregivers, and death through suicide. Prevention and treatment is especially important for women in the reproductive age. Close psychiatric follow up and coordinated care with the obstetrician is needed.

Key words: bipolar disorder, pregnancy, postpartum period.

Introduction

Is pharmacotherapy in pregnancy ethical?

We should always weigh the benefit against potential risk or harm to the fetus. There is now much evidence that untreated bipolar disorder presents many risks for the fetus and newly born.

The amount of suffering that is caused by the symptoms of untreated bipolar disorder and the possible preventive role of early treatment must be considered. Treatment with medication, psychotherapy and psychoeducation may reduce the suffering of patients and their families, prevent potential harm to the fetus and newborn, enable better bonding between the mother and the newborn and influence the course of the bipolar disorder in the future.

Risk and course of bipolar disorder during pregnancy

There are a few studies that support the view that pregnancy has a protective effect on the course of bipolar disorder (1), but the sample may not have been representative for broader groups of women with BPD (2). Other research and growing clinical evidence suggest that pregnancy does not protect against recurrences but is a time of substantial risk of relapse. The risk is higher after discontinuation of mood-stabilizing maintenance treatment (3,4). According to some data approximately half of women with bipolar disorder become symptomatic during pregnancy (5). To some extent the risk may be predicted by the past history of illness frequency and severity.

Risk and course of bipolar disorder during the postpartum period

The postpartum period has been consistently recognized as a high risk period for relapse with rates well above 50% (4,5). BPD is closely related to postpartum psychosis, the risk is 10-20% in women with BPD and 0.1 - 0.2 % in the general population (6). Postpartum psychosis is a psychiatric emergency with a rapid onset within the first few days after delivery and a high risk of infanticide and suicide. Women with a history of postpartum psychosis have a risk as high as 90% in their subsequent pregnancies (7). Prophylactic treatment with mood stabilizer or atypical antipsychotics can reduce the risk by threefold to fivefold (7).

Treatment

Physicians caring for women with BPD face a clinical challenge: achieving the mental health and wellbeing of the mother with minimal risk to the fetus.
Pharmacotherapy

There is a 3-4% risk of malformations in the general population of newborns. Each organ system seems to be vulnerable to teratogenic effects during a certain period of time, for example formation of the heart and great vessels takes place between week 5 and 10 of gestation. Neural tube folding and closure occurs within the first 5-7 weeks of gestation (10).

Mood stabilisers: risk during pregnancy (from highest to lowest)

1. Valproate (neural tube defects, spina bifida 2%, other potential severe adversities – overall 22% risk). If planning a pregnancy, the woman should be switched to another treatment. Folate, vitamin B12 and vitamin B6 are recommended prophylactically for women in childbearing age on valproate (9).

2. Carbamazepine (spina bifida 0.5%, other minor malformations and mild developmental delay compensated in the first years – overall 8% risk of serious adverse events) (9).

3. Lithium (20 fold higher risk of Epstein’s malformation than in the general population – still a very low risk). Women with a moderate to high risk of relapse should continue the treatment and be carefully monitored with ultrasonography (10).

4. Lamotrigine (2% incidence of severe adverse events, about the same as the general population).

5. Atypical antipsychotics. No specific risk has been observed (8).

6. SSRI antidepressants. Little evidence of teratogenicity, with the exception of paroxetine with 1.5 to 2 fold increased risk of cardiac malformations with first trimester exposure (10).

7. Other potential treatments

ECT is sometimes recommended for severely depressed patients during pregnancy but the impact of a seizure on the fetus has not been systematically studied.

High dose folate treatment is widely recommended.

Risk of no treatment

Poor prenatal care.

Poor nutrition.

Increased use of alcohol or tobacco.

Stress and trouble with attachment and bonding.

High risk of hospitalization and more intense pharmacological treatment.

Psychoeducation

Women should be offered prepregnancy counselling. They should be informed of the potential risk of medication and risk of recurrent illness. Decisions about what is the best option ultimately rests with the informed patient.

Optimal clinical care of patients with BPD during pregnancy

Patients’ informed choices about pharmacological treatment.

Close psychiatric follow up.

Coordinated care with the obstetrician.

Increased psychosocial support.

Initiation or continuation of a psychotherapeutic modality (CBT, group therapy, etc.).

Breastfeeding

All psychotropic medications can enter human breast milk. Most are found in the milk at very low levels and are probably clinically insignificant to the neonate.

The risk/benefit ratio of breastfeeding should be considered individually.

Valproate appears in breast milk in only 10% of the maternal blood levels, breastfeeding is not contraindicated (8).

Carbamazepine data are limited but it is considered probably to be safe (8).
Lithium reported adverse events include lethargy, hypotonia and ECG changes. Its use during lactation is discouraged (8).

Atypical antipsychotics. Olanzapine appears to be the safest. Quetiapine and ziprasidone are not recommended during breastfeeding (8).

GP Comment

What have I learned from this paper?

The content of this paper is basic and extremely important, both for general practitioners and patients. There is need for GPs to pay careful attention to the management of bipolar disorder in pregnancy. Close working between GPs, obstetricians, midwives and psychiatrists, using a joint management approach is essential in this situation and needs to be set out clearly in a local management pathway for the management of bipolar disorder during pregnancy.

Dr Roshan Jayalath GP.

References

Abstract

Childhood adversity is related to an increased risk of developing mental disorders such as major depression, bipolar disorder, schizophrenia and substance abuse, post-traumatic stress disorder, substance abuse, affective problems, anxiety, personality disorders, and suicide. Bipolar disorder and depression are mental disorders that have been particularly associated with childhood abuse. The fact that there is a link between affective illnesses and childhood adversity emphasizes the need for proper assessment for bipolar disorder when these patients present with either depression or mood instability, and that these conditions, when identified, require effective treatment.

Key words: bipolar disorder, childhood adversity.

Introduction

Childhood abuse is known to cause significant negative effects on the mental wellbeing of children as they grow up, which persist as the child goes through their teenage years and enter adulthood (1). The prevalence of childhood abuse is unfortunately not rare, with sexual abuse being shown to be as high as 8% in a nationally-representative sample in England, with a prevalence of re-victimization as high as 2% (2). Child abuse can take various different forms and be of varying severity. Etain et al. 2008 (18) described the most detrimental environmental stresses as including emotional and physical parental abuse, multiple violent episodes and sexual abuse. Sexual abuse, in particular, has been shown to result in the greatest risk of developing all types of psychopathologies later in life (3). The experience of severe traumatic events during childhood is known to be associated with poor functioning, cognitive deficits and a number of psychiatric conditions in adulthood (4)(5). While the link between childhood abuse and mental health problems in adulthood is well established, what is more uncertain is the mechanism by which this downstream effect takes place. This mechanism could be via a latent effect, whereby the childhood adversity results in long-lasting biological, psychological and/or sociological damage, irrespective of later circumstances. Alternatively, there could be a pathway effect, whereby the childhood adversity results in unhealthy exposures during adulthood that in turn result in mental health problems (6-9). Bipolar disorder and depression are two examples of mental illness with a demonstrated link to child abuse. The link will be explored in this article.

Impact of childhood adversity in adulthood

There is much interest in understanding the effect of child abuse when the child grows and develops. A systematic review of prospective evidence of associations between poor parent-child relationships and common psychiatric disorders in later life reported that abusive relationships predicted depression, anxiety and PTSD (10). The same review further demonstrated that maternal emotional unavailability in early life predicted suicide attempts in adolescence. Epidemiological studies and clinical trials have gone on to show that childhood stress is related to an increased risk of developing mental disorders such as major depression, bipolar disorder, schizophrenia & substance abuse, post-traumatic stress disorder, substance abuse, affective problems, anxiety, personality disorders, and suicide (11,12) (3). It was concluded that there is robust evidence of the role of the environment,
specifically adverse childhood experiences, in various aspects of mental disorders (1). In the study by Chou (2), childhood abuse was significantly associated with mixed anxiety and depression, generalized anxiety disorder, eating disorders, post-traumatic stress disorder, and suicidal ideation. Similarly, re-victimization was significantly associated with mixed anxiety and depression, phobia, post-traumatic stress disorder and suicidal ideation.

Childhood adversity also increases the risk and severity of psychotic symptoms in adult life (12,13). Hence, many psychiatric patients with a history of childhood trauma will have worse outcomes when mentally disordered and higher rates of clinical disorders than those without such history (14,15) (17) (3).

Childhood abuse and bipolar disorder

Bipolar disorder (BPD) is a mental disorder that has been particularly associated with childhood abuse. 30-50% of those with of BPD report having endured traumatic childhood events, most commonly emotional abuse (18) (12) (19, 20). When comparing the rates of emotional abuse in these patients with sufferers of major depressive disorder the rates are higher for those with BPD (21). Conus et al. (22) reported that a history of childhood trauma in BPD patients is associated with recurrent depressive symptoms in adulthood, and also lower premorbid functional levels and reduced compliance to treatment. Furthermore, patients who suffered sexual and physical abuse present with more severe mania symptoms (23). One theory for this link between BPD and childhood trauma is that the trauma triggers the first episode of BPD, which is indeed often associated with psychosocial stressors (24). A history of physical or sexual abuse is associated with an earlier onset of BPD, increased comorbidity and higher rates of suicide attempt (25). Furthermore, these patients also present with higher rates of substance abuse, anxiety comorbidity, post-traumatic stress disorder and depressive symptoms of higher intensity, particularly women, when compared to patients without trauma (18) (17). Men with BPD are, however, more often exposed to sexual and physical abuse than men with major depressive disorder (21).

Childhood abuse and depression

Depression is another mental illness that has been shown to be associated with preceding adverse life events such as child abuse. Johnson (26) showed that subjects who have experienced negative life events take three times longer to show recovery in mood disorders. The symptoms of these patients may also be more severe usually with a higher risk of suicide attempt and the need for more health services in adulthood (12) (17). Schoedl et al. (27) were able to support this with their finding that depressive symptoms are more severe among those who were abused as children under the age of 12 than those abused after that age.

Other issues that need to be considered are that children who have a psychiatric disorder are more susceptible to experience a traumatic episode (18), and that there is a possible genetic factor that plays a role. Individuals who have genetic risks and a history of trauma seem to show an earlier development of mental disorder compared to those without genetic risks (19). These patients often have difficulties with interpersonal relationships and they tend to be more isolated, more refractory to treatment and at greater risk of recurrent mood episodes (12).

More research to establish the nature between child abuse and depression fully will be useful in the future but the data thus far suggests that childhood trauma is indeed associated with an increased severity of mental disorders like depression and the effect of such an adverse event can be long-lasting and persistent (12) (17).

Neurobiological changes associated with childhood abuse

In order to be able to understand the link between mental disorders such as bipolar disorder and the trauma of childhood abuse, it is important to understand the associated neurobiological changes.
Studies have provided evidence that adverse events in childhood can have important effects on the plasticity, morphology, physiology and functioning of the brain. Some of the neurostructural changes demonstrated include the reduction of the volume of the hippocampus and corpus callosum following trauma at an early age (1). Patients with a family risk of depression who have a history of emotional abuse have been shown to have significantly smaller left and right hippocampal heads. Voxel based morphometry has also shown smaller dorsolateral prefrontal cortices, medial prefrontal cortices and anterior cinguli in these patients. Hence high-risk individuals for depression have reduced volume of brain regions related to emotional processing when they additionally suffered childhood abuse, demonstrating that genetic and environmental factors such as childhood trauma influence brain structure possibly via epigenetic mechanisms and thus structural anomalies may precede the onset of the illness (28). Additionally, common genetic variation of the serotonin transporter-linked polymorphic region (S-HTTLPR) has been related to depressive symptoms, in particular after stressful life events. Gender modulates the interactive effect of the S-HTTLPR genotype and childhood adversity on hippocampal volume. While the short-allele is associated with hippocampal volume independent of childhood adversity in women, men only have smaller hippocampi if they carry the risk allele and experienced severe childhood adversity (29).

Gene polymorphisms may also interact with childhood adversity to affect the size of the hippocampus and the occurrence of major depressive disorder. One of the polymorphisms found to be associated with major depressive disorder is the Val66MET polymorphism of brain-derived neurotrophic factor (BDNF). In a study it was shown that MDD patients had smaller hippocampal volumes, both in the left and right hemispheres (F = 5.4, P = 0.022). There was a significant interaction between BDNF allele and history of childhood adversity (F = 6.1, P = 0.015): Met allele carriers showed significantly smaller hippocampal volumes when they did have a history of childhood adversity, both in patients and controls. Hence stress-gene interactions are relevant for hippocampal volume reductions. Subjects exposed to early life adversity developed smaller hippocampal volumes when they carry the Met-allele of the BDNF polymorphism (30).

Emerging evidence appears to indicate that the neurobiological effects of stress may vary at different developmental stages (1). Differences in brain image findings in studies with adults and children can also be attributed to differences in brain maturation (1). It is suggested that colossal abnormalities in children with PTSD are due to atrophy or neurodevelopmental deficits that result from traumatic experiences (31). Preclinical evidence shows that very early life experiences can dramatically impact the morphometry of the corpus callosum (32). Myelination of the corpus callosum begins between the ages of 6 months and 3 years and continues into the third decade of life (33-35)(1). As well as the effects of stress and glucocorticoids on cell proliferation in the hippocampus (36), glucocorticoids have been shown to inhibit the proliferation of the oligodendrocyte precursor throughout the brain (37). Given the role of oligodendrocyte precursors in myelination, prenatal glucocorticoid exposure is associated with reduced myelination of the corpus callosum and hence reduced myelin sheath thickness (38). Because of the rostral-to-caudal myelination sequence, it is suggested that different regions of the corpus callosum might have different windows of opportunity for vulnerability to early experiences (33)(1). Another possibility, however, is that abnormalities in corpus callosum morphology are due to genetic developmental factors which predispose individuals to develop PTSD after exposure to trauma (39).

**Conclusion**

The above review clearly demonstrates the relationship between childhood adversity and affective disorders, including bipolar disorder and major depressive disorder. It also demonstrates what is known of the underlying neurobiology. The fact that there is a link between affective illnesses and childhood adversity emphasises the need for proper assessment for bipolar disorder when these patients present with either depression or mood instability, and that these conditions, when identified, require effective treatment.
GP Comment

What have I learned from this paper?

This review shows us that the impact of abuse in early life can be long-lasting. Childhood adversity is a risk factor in the development of a range of mental health disorders, including bipolar affective disorder, and can also lead to increased severity. This reminds us of the importance of taking a history of childhood experiences during the psychiatric assessment.

Dr Jenny Hopwood, GP Trainee.

References


Understanding the bipolar spectrum: implications for management and diagnosis in primary care

Dean Hanafy
Faculty of Medical Sciences, Newcastle University, United Kingdom
Mark Agius
Clare College Cambridge, Department of Psychiatry University Of Cambridge, South Essex Partnership University Foundation Trust United Kingdom.

Abstract

Understanding the bipolar spectrum has significant implications for the management of affective disorders in primary care. In this article, we summarise the main consequences for the treatment of patients with bipolar and unipolar depression within the context of general practice. By having an integrated and coherent care pathway between primary and secondary care to treat unipolar depression and bipolar disorder, treatment can be optimised, comorbidities can be identified, iatrogenic disorders can be minimised and the risk of suicide can be reduced.

Key words: bipolar disorder, unipolar depression, diagnosis, treatment, guidelines, suicidality.

Our present understanding of the bipolar spectrum has many implications for the treatment of affective disorders in primary care. For example, there is now evidence that an illness that was previously thought to be a recurrent depressive disorder, may evolve into a bipolar illness. Furthermore, bipolar II disorders may develop into bipolar I (1-7). Additionally, it has been suggested that there may be important similarities between bipolar disorder and the mood lability of borderline personality disorder suggesting, controversially, that borderline personality disorder could be included in the bipolar spectrum (8,9).

Bipolar disorder, especially bipolar II disorder, remains an underdiagnosed condition and is frequently treated in an inappropriate way (10-13). Evidence has shown that many patients with bipolar disorder have a long period of untreated illness which parallels the duration of untreated psychosis in other psychotic illnesses (10,14,15). Agitated depression may be a mixed affective state, and the imprudent use of potent antidepressants in people with undiagnosed bipolar disorder may result in the development of mixed states or rapid cycling illness (which are linked to an increased suicide risk), in addition to a switch from depression to mania (16).

In recent years, the appropriate diagnosis and effective treatment of unipolar depression has come under scrutiny in the context of primary care (17). It has been demonstrated that often antidepressants in primary care may be prescribed for too short a time and, in the case of tricyclics, at too low a dose (17). Additionally, the NICE guidelines for unipolar depression and bipolar illness are distinct from each other, which may make management of these conditions more demanding unless the diagnosis has been made carefully, after having taken a longitudinal history. Guidelines for unipolar depression advocate a ‘stepped care’ model, which is centred around primary care, and which depends on the appropriate treatment with an adequate dose of antidepressants for six months, whereas for bipolar disorder, NICE emphasises the careful prescription of antidepressants and mood stabilisers to prevent ‘switching’ to mania (18-20).

General practitioners have not been advised to take a full longitudinal history in patients with depression in order to identify patients with bipolar illness. This makes diagnosis of these conditions for primary care physicians challenging. This is further augmented by an absence of clear direction on
the use of mood stabilisers in patients with bipolar II disorder, which may result in the inappropriate use of antidepressants. There appears to be a strong argument for providing general practitioners with further support to assist in the management of both unipolar depression and bipolar illness in an appropriate manner.

In practice, early bipolar disorder will be identified and treated correctly if primary care doctors are provided with the appropriate guidance and training so that these conditions can be diagnosed promptly (20). We would suggest that care should be taken to identify any period of elated mood which a patient who presents with major depression has experienced, both in primary and secondary care, even if this has lasted for only a few days. Previous episodes of hypomania, at least three recurrent depressive episodes, cyclothymia, a family history of bipolar illness or suicide, and a seasonal onset [winter in bipolar II and summer in bipolar I patients], and migraine have been acknowledged as possible indicators of bipolar illness (21). If these factors can be recognised in primary care, it may enable earlier diagnosis of bipolar disorder to be made (22-25).

As hypomanic or mixed states are strongly correlated with self-harm and completed suicide (26,27) there are concerns about the use of antidepressant monotherapy for bipolar disorder as this may trigger these states. Venlafaxine as well as tricyclic antidepressants (28) seem more likely than other antidepressants to produce a switch to mania in bipolar depression. Consequently, once bipolar depression is identified, guidelines should be in place that, where necessary, advise the use of mood stabilisers, including lithium, valproate, carbamazepine or atypical antipsychotics in order to treat bipolar disorder instead of antidepressant monotherapy. Thus, we would suggest that early diagnosis and appropriate treatment of bipolar disorder is likely to be the most effective way of reducing the risk of suicide in these patients (26,27,29). Additionally, the appropriate use and monitoring of venlafaxine as a first-line treatment in unipolar depression must be seen as secondary to this (14,30).

Since bipolar disorder has an inflammatory component, it would be prudent for physicians to consider whether patients with bipolar disorder have an autoimmune condition such as thyroiditis, Crohn's disease or ulcerative colitis, once their bipolar symptoms have improved (31,32). Finally, because of the possible toxicity of lithium it is necessary, in both primary and secondary care, for patients on lithium to have lithium levels, urea and electrolytes monitored every 3 months as well as thyroxine and TSH every 6 months. Each patient should have a shared care card to ensure both primary and secondary care are aware of all the results. (See paper: “Lithium therapy – from monitoring to shared care” in this focus issue.)

In summary, it is necessary to have an integrated care pathway to treat both unipolar depression and bipolar disorder in primary and secondary care in order to optimise the management of such patients (32). This will allow the identification of any comorbidities, prevent any iatrogenic disorders and reduce the risk of suicide.

**GP Comment**

**What have I learned from this paper?**

This paper highlights the importance of taking a longitudinal history in patients with depression to ensure that episodes of mania or hypomania, are not missed. To diagnose bipolar disorder promptly and therefore treat patients correctly we must remember to enquire about previous episodes of elated mood, recurrent depressive episodes, cyclothymia, a family history of bipolar illness or suicide, and seasonal onset as possible indicators of bipolar illness.

*Dr Jenny Hopwood, GP Trainee.*
References


Bipolar spectrum: consequences for the development of services.

Mark Agius
South Essex Partnership Foundation Trust, Department of Psychiatry University of Cambridge, Clare College Cambridge.

Abstract

There is a strong case for providing specialist services and structured clinics to manage bipolar disorder and mixed affective states, particularly to reduce suicide risk. Because mood can be very changeable in this disorder, especially in mixed affective states and rapid cycling bipolar disorder, the service must be responsive, implying that fixed occasional outpatient appointments might not constitute adequate management. A flexible approach is needed with a service that is tailored to the individual.

Key words: bipolar disorders, suicide risk, design of services.

The bipolar spectrum challenges the concept that it is reasonable to see patients in secondary care on the basis of a three-monthly outpatient assessment.

There are four factors that make such an arrangement inappropriate in managing patients with bipolar disorder.

1. Mood changes from time to time.
2. The patient with bipolar disorder needs to be assessed fully, often when he or she is euthymic or depressed, in order to establish the diagnosis.
3. Depressed patients need to be given antidepressants only for the time that they are depressed (1-3).
4. Because mixed states and rapid cycling cause an increase in suicide risk, patients with mixed states (or who are rapid cycling) need to be monitored closely and very frequently while medication is administered to treat the mixed affective state, so that the patient comes out of this state (4).

The assessment of a new patient will include an at least an hour-long consultation, in which the whole longitudinal history of the patient is elicited. Essential parts of the history will be establishing whether the patient has had hypomanic/manic episodes and recording when they occurred.

The Mood disorder Questionnaire is used to validate that the patient is subject to hypomanic episodes, and the PHQ9 and GAD7 are used to assess depression.

This assessment is carried out in our service as part of a new assessment service which has been specifically set up for the purpose. In our NHS Trust, this assessment service is carried out once weekly, on a specific morning, when only new patients are seen.

Management issues that imply that it is not adequate for patients to be seen ‘routinely’ at three-monthly intervals include the following.

When depressed, patients need to be given antidepressants only for the time that they are depressed.

Patients with mixed states (or who are rapid cycling) need to be monitored closely and very frequently, while medication is administered to treat the mixed affective state so that the medication can be adjusted promptly when the patient comes out of this state.

If patients are acutely suicidal, then they should be referred to the crisis or home treatment team; admission to hospital should be considered in the most serious cases. However, many patients with
bipolar disorder are not acutely suicidal, even if they may be seriously depressed, and therefore the crisis team may not consider that they should be involved. However, leaving patients on antidepressants when they are no longer depressed can increase the risk of switching to mania. Hence we have developed a special clinic, which we call “the emergency clinic” in which patients with bipolar depression who have been given antidepressants are seen every two weeks by the doctor, and the depression is monitored using the PHQ9 rating scale.

Also attending the emergency clinic are patients in mixed affective states who have had their antidepressants stopped, a mood stabiliser dose increased, and an atypical antipsychotic started, and who are not considered sufficiently high risk by the crisis team for the patient to be taken on by that team (5). These patients are seen every week, because of the risk of suicide developing.

The need for attendance at the emergency clinic is on the decision of the treating doctor alone. When the issue has passed, the patients return to attending the normal outpatient clinic.

By having an assessment clinic and an ‘emergency clinic’ as described above, the special medical needs of bipolar patients, including bipolar II patients, can be catered for, and the risk of suicide can be reduced. However there are also other needs that an outpatient service for bipolar disorder should fulfil.

It is important that patients should be offered care co-ordinators who will be able to offer psychoeducation, family support and cognitive interventions in order to help reduce stress.

Psychoeducation can also be offered to patients in groups.

In addition to controlling the general symptoms of bipolar disorder, the objectives of the service should include reducing suicide risk and controlling mixed affective states. There is a strong argument for arranging specially-structured clinics in order to respond adequately to these difficult-to-manage conditions. In our experience, the measures we have described go a long way towards fulfilling the needs of patients with bipolar disorder in secondary care (6).

**GP Comment**

**What have I learned from this paper?**

Treating bipolar affective disorder is a very complex task and patients would benefit from specialist services allowing frequent and easy access to a psychiatrist. It is hoped that changes in the structure of psychiatry clinics, as detailed above, could lead to a reduction in suicide risk. This should be an important consideration of commissioners when designing services to best meet the needs of patients.

Dr J Hopwood, GP Trainee.
References

The bipolar spectrum: consequences for neurobiology

Mark Agius (1) (2) (3). Shermayne Ng (4) (5)

(1)Department of Psychiatry, University of Cambridge, (2) South Essex Partnership University Foundation Trust, (3) Clare College Cambridge, (4) School of Clinical Medicine University of Cambridge, (5) Christ’s College Cambridge.

Abstract

There is an increasing interest in whether there is a commonality in the observations seen in MRI neuroimaging of a number of conditions, all of which are related to the affective disorders. These four conditions include untreated depression, bipolar disorder, post-traumatic stress disorder, and borderline personality disorder. If such a commonality in MRI findings can be confirmed by a careful meta-analysis, then these common findings may point to a spectrum of affective disorders which is broader than has been suggested until now and, in particular, may end the controversy as to whether borderline personality disorder is in fact part of the bipolar spectrum. Such considerations argue for the development of new classification systems, which are based not simply on symptoms but also on neurobiology.

Key words: bipolar disorder, unipolar depression, borderline personality disorder, post-traumatic stress disorder, neurobiology, MRI.

It is almost unequivocal that patients with untreated unipolar depression have reduced hippocampal volume. Sheline et al. (1) demonstrated that a prolonged period of depressive episodes untreated with antidepressant medication is associated with a significant decrease in hippocampal volume. This is one of the most replicated findings in unipolar depression. However, multiple individual studies have challenged the possibility of similar findings in bipolar depression. The majority of studies have shown preserved hippocampal volumes in those with bipolar disorder, in apparent contradiction to the observed impairment in declarative memory processing in both symptomatic and euthymic adult patients with bipolar disorder. Until quite recently, the majority consensus was that there were insignificant changes in the hippocampal volume of bipolar patients. Hajek et al. (2), in his recent meta-analysis involving 101 patients with bipolar disorder, found that hippocampal volume changes in bipolar disorder patients are dependent on their exposure to lithium. In the lithium-treated group, both left and right hippocampal volumes were observed to be significantly larger than in controls or in the non-lithium group, which showed marked decreases in both the left and right hippocampal volumes compared to that of the control group (3,4).

Similarly, magnetic resonance imaging (MRI) of post-traumatic stress disorder (PTSD) patients revealed a smaller hippocampal volume in these patients who were exposed to combat as well as childhood abuse (5). It is not surprising that brain areas implicated in the stress response, such as the amygdala and prefrontal cortex (as well as the hippocampus) are seen to be involved in depression (6). The somewhat congruous findings of neurobiological changes in unipolar and bipolar depression as well as PTSD may support the proposal that these disorders lie on the same spectrum.

The next question that arises is the relationship between bipolar disorder and borderline personality disorder. A modest interrelationship has been noticed where the diagnosis of combined bipolar disorder is significantly more common in borderline personality disorder patient groups than in other personality disorder groups (19.4% vs. 7.9%). When analysing anatomical changes occurring in the course of borderline personality disorder, Soloff et al. (7) identified that these patients had significant bilateral reductions in grey matter concentrations in the ventral cingulate gyrus and several regions of the medial temporal lobe, including the hippocampus, amygdala, parahippocampal gyrus and uncus. A gender bias was also noted amongst borderline personality disorder patients: women had marked reduction in the medial temporal lobe, including the amygdala, whereas men displayed...
diminished grey matter concentrations in the anterior cingulate gyrus compared to healthy controls. The diminished grey matter in the prefrontal cortex and medial temporal lobe may functionally explain the dysregulation of impulse and affect observed in borderline personality disorder (7). This may also explain Benazzi’s concept of ‘affective instability’ and ‘impulsivity’ which is pathognomonic of borderline personality disorder (8). Furthermore, these neuroanatomical changes observed in borderline personality disorder highly reflect the changes observed in bipolar disorder, perhaps explaining the relationship between the incidence of the two disorders described earlier and somewhat supporting the school of thought proposing that borderline personality disorder is a form of bipolar disorder which is unstable between episodes (9). As well as the hippocampal changes, borderline personality disorder patients also show smaller amygdala volumes and an increase in the size of the putamen (10,11). It is suggested that the latter may be a result of substance abuse which is common in many of these patients (12).

These findings indicate that the four conditions: unipolar depression, bipolar affective disorder, borderline personality disorder (12-14) and post-traumatic stress disorder (15-17) share a commonality – that of a reduced hippocampal volume on MRI. This has been supported by multiple studies involving MRI identification of neuroanatomical changes in these conditions (2-4,7,10,11). The amygdala is also seen to be involved in these disorders (18). Consistency in the result of these studies may imply important biological similarities underlying these conditions. This proposal also appears to be supported by evidence that the size of the hippocampus can be improved by treatments such as SSRIs, lithium and valproate in all these conditions.

A frequently featured trigger in all these conditions is stress. Frodl et al. (19) have previously analysed the mechanism in which stress, through its effect on the hypothalamo-pituitary-axis, its modulation of cortisol levels and effect on glucocorticoid receptors, influences not only the size of the hippocampus but also the balance between the trophic (BDNF and in bipolar disorder, Bcl-2 and BAG-1) factors and atrophic factors in the cells. This suggests a common mechanism in all these conditions where stress is a common causative factor (20).

The commonalities between psychiatric disorders are beginning to surface with discovery of multiple genes involved in their pathogenesis. It has long been stated that the principle of major ‘psychotic’ mental illnesses have polygenetic causes, each with small effects on the disorder (21). Certain genes such as the SERT, COMT and BDNF, with their polymorphisms have been identified to be common to all the disorders considered in this article.

In addition, there have been studies suggesting epigenetic regulation of genes as a possible link between depression, childhood adversity and suicidality, all of which are pertinent characteristics in the conditions described (22-26). Similar neuroanatomical changes, i.e. reduced hippocampal volume and pathophysiological responses to stress, were identified in patients with depression, a higher propensity to depression, PTSD and borderline personality disorder who have suffered abuse or childhood adversity, and in some war trauma cases (10,15,27-30). This further supports the possibility of these environmental factors interacting with the mechanisms of gene expression in the conditions being discussed.

There is substantial evidence suggesting the inter-relationship between the four conditions discussed in the article. The similar neuroanatomical changes as well as common biochemical mechanisms of stress and genetic causes appear to support this proposal. The heterogeneity of mood disorders could be a manifestation of their origin in multiple dysfunctional brain regions – the amygdala, nucleus accumbens, hippocampus, prefrontal cortex and cingulate cortex (31). SSR1 and lithium-induced neurogenesis in the hippocampus of patients with the conditions described further support the concept of a spectrum of psychotic illness (2-4,31-33). These few final observations of comparable neuroimaging results as well as a comparable relationship in neurogenesis, combined with clinical observations and the impact of environmental factors as triggers, seem to support the argument for including borderline personality disorder in a spectrum of illness ranging from unipolar depression to that of bipolar I affective disorder, which can be termed a ‘small hippocampus syndrome’. Such a group of disorders with similar neurobiology could suggest that it is now possible to develop a classification
of mental illness based on similarities in neurobiology, rather than being simply based on symptom clusters. Indeed, symptoms should be in future classifications, linked with neurobiology.

One further issue arises when considering neuroimaging findings in the bipolar spectrum. Bipolar illness is accompanied by some loss of grey matter in the cerebral cortex (34). Is there less loss of grey matter in bipolar II disorder than bipolar I? We have found only one paper, from Korea, which sheds light on this question (35). In this paper, it was reported that high-resolution magnetic resonance brain images were taken from 23 bipolar II patients, 23 sex-matched and age-matched patients with bipolar I disorder and 23 healthy controls. Both the bipolar II and bipolar I groups showed grey matter deficits in the ventromedial prefrontal regions, compared to controls. The bipolar I group had widespread grey matter reductions in bilateral frontal, temporal, parietal and parahippocampal cortices, compared to controls, but grey matter reductions in these regions were not found in the bipolar II group. Also, the bipolar II group showed additional grey matter deficits in the anterior limbic cortices. Thus, the different patterns of grey matter abnormalities in bipolar II and bipolar I found in this study suggest that the two subtypes may have different neurobiological characteristics, which supports the concept of a bipolar spectrum between these two conditions. It is necessary, however, that this study be replicated, since the numbers were small.

GP Comment

What have I learned from this paper?

In the last years there has been a relevant debate about whether there is a common spectrum in all four main affective disorders as they show neuroimaging similarities. These include: untreated depression, bipolar disorder, post traumatic stress disorder, and borderline personality disorder. The last of these may be included, despite controversies. There is a need of a new classification system.

Dr Juan Mendive, Family Physician, Barcelona.

References


Some useful web resources for depression and bipolar disorder

Sarah Chadwick
South Essex Partnership University Foundation Trust

The following websites and other resources will be found to be of help to persons suffering from depression and bipolar disorder.

DEPRESSION AND BIPOLAR DISORDER WEBSITES

Depression Alliance: 0845 123 2320
e-mail: information@depressionalliance.org
www.depressionalliance.org
Confidential listening and support service. Also offers a range of information on depression and treatment options. National network of self-help groups for people experiencing depression. National pen friend scheme offering support and fellowship to people with depression and their carers. Quarterly newsletter, booklets and leaflets on depression.

TheSite.org
http://www.thesite.org/healthandwellbeing/mentalhealth/depression

Turn2me.org
www.turn2me.org/DepressionSupport

Overcome depression
www.overcomedepression.co.uk - Depression help and advice

MDF/The Bipolar Association: 020 7931 6480
e-mail: mdf@mdf.org.uk
www.mdf.org.uk
Advice and information for people with manic depression (bipolar disorder) and their families, carers and mental health professionals. Supply a range of information leaflets, books and tapes. Network of self-help groups for people with manic depression, relatives and friends. Self-management training programmes.

Manic Depression Fellowship
Offer advice, support, and courses in managing manic depression (bipolar disorder). National website with links to local groups at Tel: 020 7793 2600
www.mdf.org.uk
Nearest bipolar self-help support group to Bedfordshire is based in Northampton - Tel: 08456 340540

Mood Swings: Helpline: 0845 123 6050
www.moodswings.org.uk
National Helpline and online support providing free and confidential information, advice and support to people with mood disorders, family, friends and health & social care professionals. Also one-to-one, support groups and workshops at a centre in Manchester.

Pendulum.org
www.pendulum.org (American site) - Online support group for people with manic depression (bipolar disorder).
PSYCHOLOGICAL SELF-HELP WEBSITES

The following are some useful psychological self-help websites.

Living life to the full
www.livinglifetothefull.com/index.php
Free to use cognitive behavioural therapy (CBT) based self-help site for a range of mental health difficulties.

Mood Gym
http://www.moodgym.anu.edu.au/
Australian-based CBT online help programme. Free to use.

CBT Resources

Beating the blues
www.beatingtheblues.co.uk

Get self help
www.getselfhelp.co.uk
Bipolar Disorder – Guidance on recognition in Primary Care

Daniel Dietch  
GP Principal, Lonsdale Medical Centre, 24 Lonsdale Road, London NW6 6RR

Daniel Martin  
Clinical Research Fellow Institute of Health and Wellbeing, University of Glasgow, Mental Health and Wellbeing, Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow G12 0XH

Daniel J Smith Reader/Hon Consultant Psychiatrist, Institute of Health and Wellbeing, University of Glasgow, Mental Health and Wellbeing, Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow G12 0XH

Carolyn Chew-Graham  
Professor of General Practice Research, Arthritis Research UK Primary Care Centre, Primary Care Sciences, Keele University, Keele, Staffordshire, ST5 5BG

Abstract

Bipolar Disorder (BPD) is a complex condition with variable clinical presentations and diagnosis can be difficult. In particular, recognising new or previously undiagnosed BPD can be especially challenging within the pressures of primary care where patients present with a wide variety of medical or social issues rather than with diagnostic labels. Moreover, there may be conceptual difficulties between the academic classification of emotional and mental health symptoms into discrete entities versus the broader contexts that GPs encounter daily. It should also be noted that GPs are adept at managing uncertainty with pragmatism.

Key words: bipolar disorder, depression, cycling, diagnosis, treatment, primary care.

Introduction

It has been shown that the clinical features and time course of BPD (especially Bipolar-II, which GPs are likely to encounter fairly frequently) differ from unipolar depression in several key ways and, crucially, BPD carries a much higher suicide risk (1–8). However, because the diagnosis is difficult, BPD is frequently, although unintentionally, misdiagnosed as unipolar depression with anxiety and consequently incorrectly treated in both primary and specialist care. This leads to long delays and protracted suffering and, for some patients, increased risk of suicide (4,9–13).

GPs have a key role in recognising possible Bipolar Disorder (BPD) - ask about a family history of BPD and screen for a history of mania/hypomania in individuals with anxiety, depression or irritability, especially if there are recurrent episodes, suicidal thoughts or previous suicides attempt.

This brief paper therefore aims to help GPs recognise when a patient might have BPD. Referral to a psychiatrist (where referral pathways allow, ideally with expertise in mood disorders) for formal diagnosis is recommended. For further discussion of aetiology, treatment issues, BPD in pregnancy, children and in individuals with comorbid alcohol/substance misuse, see later: “Selected Resources” and also the relevant papers in this focus issue.

Key points

1. Bipolar Disorder is a relatively common but complex group (‘spectrum’) of conditions that cause recurrent changes in mood and energy. Mania or hypomania are the defining features but diagnosis can be difficult because depression and anxiety are far commoner (14–16).
Bipolar subtypes (figures 1-3)

**Bipolar I** (BD-1) Mania (≥7 days, see box below) with or without major depression. Diagnosis usually straightforward: behaviour often markedly disturbed. Help often sought via a third party as patients usually have impaired insight. The prodrome of mania may be misdiagnosed as anxiety or an anger management problem.

**Bipolar II** (BD-II) Hypomania (≥4 days) and recurrent major depression, often severe, with a high suicide risk. Diagnosis difficult – often misdiagnosed as unipolar depression - hypomania undetected as patients may not seek help. Hypomania may be misdiagnosed as anxiety or an anger management problem.

**Bipolar Spectrum Disorder** (Bipolar Not Otherwise Specified (BD-NOS) including Cyclothymia (recurrent hypomania with sub-threshold depression). Less severe and shorter mood swings - hypomania < 4 days - but diagnostic criteria and treatment options less well defined.

**Epidemiology**

Severe BPD (BD-I, BD-II) affects ~ 2-3% of the population (17,18) (BD-I 1%, BD-II 1-2%) but bipolar spectrum disorders and cyclothymia may be more prevalent (19). It has been found that between 5-10% of primary care patients with a working diagnosis of unipolar depression may have bipolar disorder (6) and this rises to 16% - 47% in secondary care and specialist settings (2). Thus, for an average UK GP list size of ~ 1600, at least 16 patients will have BD-I, at least 32 will have BD-II and a significant proportion of those with unipolar depression or treatment-resistant depression may also have an unrecognised bipolar spectrum disorder.

**Onset**

Bipolar disorder may initially present with either a depressive or a hypomanic/manic episode and the peak age of onset lies in the teens or early twenties. In some, it may be later, but 90% of individuals experience their first episode before the age of 50. Onset of symptoms in old age has been reported but this should raise suspicion of an underlying organic cause.

**Time course, ‘cycling’ and staging**

Bipolar disorder is a lifelong condition but the severity and frequency of symptoms vary considerably. Many individuals manage the disorder successfully with the help of primary and secondary care services and some patients are highly creative and productive but most suffer long-term difficulties with depressive symptoms and intermittent manic and/or hypomanic relapses. Mania and hypomania tend to begin abruptly. They are often triggered by stressful life events and sometimes by daylight changes in spring and autumn. Mania usually lasts between 2 weeks and 4-5 months. Bipolar depression tends to last longer, often 6 months, but may be much shorter. ‘Mixed episodes’, where mania/hypomania and depression occur at the same time are common (20) but under-recognised. In mixed episodes, the predominant mood may vary during the day with depression in the mornings and hypo/mania at night.

The term ‘Cycling’ refers to the frequency of mood changes. It is somewhat arbitrary but useful for assessing severity and treatment response. ‘Rapid cycling’ refers to 4 or more episodes of mania or depression in 1 year. The terms ‘Ultra rapid’ and ‘ultradian’ cycling are sometimes used interchangeably with the term ‘mixed episodes’. In recent years a tentative staging model based on symptom severity, illness course and treatment response has been suggested (21).
BPD causes suffering and reduced life expectancy

Whilst some individuals may be highly productive (typically when hypomanic), many suffer recurrent depression/anxiety, mood swings and cognitive problems. They may experience difficulties with relationships, employment, financial stability and reputation. Around 40-50% of individuals with BPD will have a previous or current alcohol +/- substance misuse problem (22). Associated physical comorbidity includes obesity, metabolic syndrome, Type 2 diabetes, IHD, COPD, asthma, migraine, back pain, HIV and Hepatitis B/C (16,18,23). The risk of suicide is >20x the general population (12,13). Mixed symptoms (depression + mania/hypomania) are common and increase the risk of suicide. (20,24).

2. Most depression/anxiety is treated in primary care. Some of these patients may have unrecognised bipolar disorder (especially BD-II) - antidepressants may not work here and might even cause harm (9,10,25).

BPD, especially bipolar II, is under-recognized under-treated or inappropriately treated in both primary and secondary care (2,6,7,26,27). Average delay to diagnosis is ~ 10 years (27). Delayed diagnosis means ongoing suffering and increased suicide risk (4,11,12).

‘Atypical Depression’ symptoms are commoner in Bipolar depression (28,29)

‘Lead-like’ limb heaviness with marked fatigue, severe guilt, psychomotor retardation, excessive eating / sleeping, labile mood or mixed episode, psychosis

The probability of BPD is increased if (2,5,6,28,29):

There is a history of BPD in a first degree relative, age at onset <30 yrs., recurrent depression, ‘atypical depression’, antidepressant failure (e.g. 3 or more antidepressants have been tried but did not work) or wear-off, mania/hypomania with antidepressants, post-natal depression, history of a suicide attempt, psychosis, alcohol/substance misuse and borderline personality disorder (Figure 4),

Treatment of BPD differs from unipolar depression

Bipolar-specific psychoeducation (understanding mood triggers and the importance of sleep, diet, exercise and daily routines) and holistic social support are crucial to building resilience. Depending on the subtype and severity, medication, typically with ‘mood stabilisers’, is often required.

Medication strategies are complex (23,30–32) and include lithium, antiepileptic drugs (e.g. valproate, lamotrigine) antipsychotics (e.g. quetiapine) and short-term benzodiazepines. Medication options, combinations, doses and duration of treatment may need to be varied according to the mood state and whether the context is acute or prophylactic maintenance. There is debate about the exact role of antidepressants in BPD but, in contrast to unipolar depression, antidepressants are often ineffective and in some individuals may precipitate hypomania, mania and suicidality (9,10,24). In situations where a trial of antidepressants is deemed necessary, a ‘mood stabiliser’ should usually be taken at the same time.

3. Putting this into practice in Primary Care (figures 1-5)

NB: Not all individuals who have mood swings have BPD - be wary about medicalising normal mood reactions, personality traits and temperaments. Where necessary, review the patient to assess further. Mood swings are not a diagnostic term and may occur in many situations e.g. adolescence, menstrual cycle changes, the menopause, anxiety disorders, ADHD, in organic brain syndromes (e.g. fetal alcohol syndrome, multiple sclerosis, Parkinson’s disease, frontal lobe tumours, dementia) personality disorders and following a head injury.

However, consider BPD in the following situations, which may overlap

• Suicidal ideation or a previous suicide attempt.
• Psychosis.
• Irritability - difficult consultations, anger management issues, relationship and employment problems.
• Anxiety/depression - esp. recurrent depression, lack of response to or agitation with antidepressants, ‘atypical depression’, post-natal depression, seasonal mood changes e.g. SAD in winter, ‘reverse’ SAD in summer, irritability or unusually energised in spring/summer/autumn.
• Significant mood swings.
• Unexplained fatigue.
• Insomnia - especially going for days with little sleep or middle insomnia with agitation and racing thoughts.
• Eating disorders.
• ADHD.
• Alcohol/substance misuse.
• Borderline Personality Disorder.

In these situations consider the following BPD screening questions:

• ‘Is there a family history of Bipolar Disorder?’
• ‘Do you ever feel ‘hyper’ or irritable or have thoughts that you can’t slow down?’
• ‘Do you ever experience changes in mood and energy that seem more extreme than other people and has anyone ever mentioned this to you?’

For positive responses, refer to a Psychiatrist for further assessment (where referral pathways allow, ideally with expertise in mood disorders)

Urgency of referral depends on risk assessment. For milder symptoms, a period of observation and information gathering in primary care may be appropriate. A formal mood questionnaire (see below) may help identify hypo/manic symptoms and thereby gauge the probability of BPD but these questionnaires are not diagnostic.

Mood questionnaires

A self-rating mood questionnaire can identify previous hypomania provided the patient has enough insight to recognise this. Information from a third party (with consent) may increase accuracy. However, these tools are not diagnostic and do not replace detailed psychiatric evaluation. Those below are in common use and GPs may wish to familiarise themselves with one of them, being mindful that most were developed for secondary care settings where there are more resources for detailed evaluation. Mood questionnaires take about 10 minutes and can be completed in the consultation or at home with someone who knows the patient well and brought to a follow-up consultation. The probability of bipolar disorder increases with the number of manic symptoms (specific details for each tool); reliability rests on sensitivity (% of true bipolar cases correctly identified as bipolar) and specificity (% of unipolar depression cases correctly identified as unipolar). Mood questionnaires include the following.

MDQ Mood Disorders Questionnaire score >7/13 (33–35).
Widely used benchmark. BPD probable if score > 7/13 + ‘yes’ + ‘moderate or serious’ problem. Sensitivity 58%. Specificity 93% in primary care. MDQ has good sensitivity in insightful patients with bipolar I disorder, but may be less useful in patients with impaired insight or milder bipolar spectrum.

BSDS Bipolar Spectrum Diagnostic Scale score >13/25 (36).
BPD probable if score >13/25 Sensitivity 0.76 (Bipolar I and II/NOS) specificity 0.85

HCL32 Hypomania Check List - 32 score >14/32 (37)
BPD probable if score >14/32 Sensitivity 80% specificity 51%. Does not Distinguish between bipolar I and bipolar II. Identifies “active/elated” hypomania and “risk-taking/irritable” hypomania.
MSQ Mood Swings Questionnaire Score >22/27 (38) (39)
BPD probable if score >22/27 sensitivity 81.7 specificity 77.9%

Mood diaries may add further valuable information. Several versions are available on-line and there are also many mood-monitoring apps for smartphones.


BEAM http://www.psychiatry24x7.com/bgdisplay.jhtml?itemname=mooddiary

Oxford True Colours http://oxtext.psych.ox.ac.uk/true-colours

4. Differential diagnosis: what else could this be?

Borderline Personality Disorder

Borderline personality disorder (40) is a complex entity that is sometimes confused with BPD. It is common for a patient to be misdiagnosed with BPD when they actually have borderline personality disorder and vice-versa. Some patients may be diagnosed with both and it has been suggested that borderline personality disorder may be part of the bipolar spectrum (41). Advances in neuroscience, imaging and genetics may clarify this issue. Key clinical differences (42) are that patients with borderline personality disorder have rapidly unstable emotions and impulsivity, no family history of bipolar disorder, and do not have severe depression or hypomania. Patients with bipolar disorder usually require medication whereas patients with borderline personality disorder respond poorly to medication but may be helped by behavioural therapy.

ADHD

Impulse control disorder

The symptoms of ADHD have some similarity to the distractibility experienced in hypomania and mania. Some patients have ADHD as well as bipolar disorder (43)

Schizophrenia & Schizoaffective Disorder

Psychosis may be present in severe mania and also in schizophrenia. However, hallucinations, delusions and thought disorder are usually only present in schizophrenia or schizoaffective disorder. In first episode psychosis, a formal underlying diagnosis may be deferred until subsequent developments clarify the situation.

Organic pathology

The following organic conditions can manifest with psychiatric symptoms that overlap with bipolar disorder. Hyperthyroidism (mania), hypothyroidism (depression), Cushings disease (mania), Addisons disease (depression, fatigue), anaemia, renal failure, delerium (e.g. meningo-encephalitis) metabolic (e.g. hyponatraemia, hypercalcaemia, liver dysfunction, Folate, B12 deficiency), frontal lobe lesions, dementia, cerebral lupus, multiple sclerosis, HIV. Rarely: phaeochromocytoma or porphyria.

Iatrogenic

Many drugs affect mood.
Mania/hypomania: corticosteroids, L-dopa, stimulants (e.g. methylphenidate, cocaine, amphetamines)
Depression: corticosteroids, beta-blockers, calcium channel blockers alpha-blockers and statins.
Consider a trial off relevant medication if possible.
**Chronic Fatigue Syndrome, Sleep disorders**

Primary insomnias; Sleep apnoea causing fatigue and behavioural changes.

**5. What investigations are helpful in Primary Care?**

Baseline: Thyroid function, FBC, U&E, LFTs, Calcium, Glucose, Urate (hyperuricaemia linked with metabolic syndrome and possibly implicated in BD), B12, Folate and Vitamin D. If BPD confirmed additional blood tests (lipids, prolactin HbA1c) may be required for monitoring.

Additional tests where appropriate: Urine drug screen, cerebral imaging if neurology or older patient (likely to be suggested by psychiatry), sleep study (sleep apnoea), ESR, CRP autoantibody screen (lupus), urine phaeochromocytoma screen, urine/stool porphyria screen.

**6. A Bipolar diagnosis should be made with care**

Where resources and referral pathways allow, refer to a psychiatrist with expertise in mood disorders for detailed assessment and further management advice. Given that bipolar disorder may be difficult to diagnose, a discussion with the psychiatrist and/or a referral for a second opinion should be considered if an initial psychiatric assessment proves inconclusive or if the patient does not respond to treatment. If BPD is confirmed, GPs play a key ongoing role, alongside secondary care colleagues, in holistic support, coordinating care, prescribing and monitoring.

**7. Be mindful of iatrogenic harm**

Antidepressants or systemic corticosteroids (e.g. for asthma or COPD) may precipitate serious mood episodes in patients with BPD. Where relevant, screen for BPD before prescribing. Medications for BPD (e.g. lithium, valproate, antipsychotics) may cause significant adverse effects, warranting careful risk/benefit assessment and vigilant monitoring.

**8. Increasing awareness and diagnosis of bipolar disorder has significant resource implications for primary and secondary care and for the third sector**

There is a need to raise awareness of bipolar disorder in primary care. GPs will need increased expertise in mental health and psychopharmacology. Longer consultation times will be needed. Prescribing budgets and monitoring resources will also need to be better resourced. GPs will need prompt access to responsive and expert secondary care services and especially wider provision of psychological support including bipolar-specific psycho-education. From a health economics perspective, BPD carries major costs (32,33), which are likely to rise further. GPs will need to work closely together and with both secondary care colleagues and the third sector to meet the challenges of these important issues.

**9. Early diagnosis, careful treatment and good psychosocial support can help individuals with BPD feel better and significantly improve their quality of life.**
Figure 1
Diagnostic criteria in brief for the busy GP after DSM-IV-TR

**Mania** – a distinct period of abnormally elevated (e.g. euphoric or expansive) or irritable mood lasting ≥7 days with 3 or more (4 if the mood is only irritable) of:-

- inflated self-esteem or grandiosity
- decreased need for sleep (e.g. feels rested after only 3 hours)
- more talkative than usual or pressured speech – difficult to interrupt
- flight of ideas or a feeling of racing thoughts
- distractibility - lack of attention and drawn to unimportant stimuli
- increased goal-directed activation or agitation
- pursuit of ‘heedless pleasure’ or risk-taking behaviour, due to impaired judgement, resulting in serious consequences (e.g. excessive spending, unwise business ventures or inappropriate sexual behaviour)

Energy levels are usually significantly increased. Symptoms need to be severe enough to significantly impair functioning (work, social, relationships) or require hospitalization (to prevent harm to self or others). Psychosis (loss of insight, delusions, hallucinations) may occur.

*The symptoms do not meet criteria for a mixed episode and are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).*

**Hypomania** – symptoms are similar to but less severe than mania and do not significantly impair function. No delusions or hallucinations - Psychosis does not occur. For a diagnosis of Bipolar II, hypomania should last ≥4 days. Shorter duration hypomania = Bipolar Not Otherwise Specified, Bipolar Spectrum Disorders.

**Mixed states** – simultaneous hypomania or mania with depression symptoms. Symptoms include dysphoria, irritability, anxiety, agitation, suspicion and hostility.

**Depression** (5) or more of the following symptoms for at least 2 weeks. One of the symptoms must be depressed mood or loss of interest.

- Depressed mood most of the day
- Markedly diminished interest or pleasure in all or almost all activities (anhedonia)
- Significant weight loss or gain (e.g. >5% change body weight in a month) or increase or decrease in appetite
- Insomnia or hypersomnia
- Psychomotor agitation or Psychomotor retardation
- Fatigue or loss of energy
- Feelings of worthlessness or inappropriate guilt
- Diminished concentration or indecisiveness
- Recurrent thoughts of death, recurrent suicidal thoughts or a specific suicide plan or a suicide attempt.

*Symptoms cause significant functional impairment. Psychosis (delusions, hallucinations) may occur. Symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g. hypothyroidism).*
Bipolar Depression

'Atypical' depression symptoms more likely but not always present:

- "Lead-like" limb heaviness
- Marked fatigue, severe guilt
- Psychomotor retardation
- Excessive eating +/- weight gain
- Excessive sleeping (esp. during the day)
- Labile Mood or mixed episode - manic features during episode - rapid on/off depression
- Psychosis

Mixed States are common

Depression and hypomania/mania are not necessarily opposites. Simultaneous symptoms occur in many patients but may not be recognised. Increased suicide risk

Irritability common in hypomania / mania, depression and mixed states

Sensory hypersensitivity (like migraine): noise, light, colour, touch

Insight may be impaired

BEHAVIOUR

Loses interest in work, hobbies, pleasurable activities

Difficulty with tasks, housework, decisions

Withdrawn from family friends and work

Marked fatigue and listlessness

Limbs heavy 'like lead' (similarities with chronic fatigue syndrome)

Eating more esp. carbohydrates -> weight gain & sluggish

Sleep Diurnal rhythm changes: Sleeping more during the day – but may be more alert in evenings, go to bed late and get up late

SPEECH

Slowed, flat tone, difficulty speaking

COGNITION

Slowed thinking

Marked fatigue – no 'starter motor'

Difficulty concentrating, poor memory

Insight may be impaired

Mania/Hypomania

Mania usually obvious: significant behavioural disturbance. Help often sought via a third party as patients usually have impaired insight.

Hypomania Energised - often feels good - uncommon to seek medical advice - patients rarely seen in this state - but may seek help for racing thoughts and insomnia if becoming tired.

Hypomania can be subtle unless patient well known. Irritability / impulsivity are common

Insight may be impaired

BEHAVIOUR

Energised, lots of interests, multitasking, more sociable

Energized -> movement much easier than when depressed - may need to exercise to burn off energy

Decreased sleep

Distractable +/- disorganised

Increased confidence, self esteem, grandiosity (mania)

Over-familiarity, restless, Impatient, irritable, agitated

Hostility/violence (mania)

SPEECH

Louder, faster, difficult to interrupt, puns and jokes, which may be inappropriate, flight of ideas

COGNITION

Racing thoughts

Fast, crisp thinking, sharpened memory

Increased goal orientated plans and ideas - often unrealistic

Sharpened sensations: colour & sounds brighter and crisper

Dis-inhibition with ‘heedless’ pleasure and risk-taking- e.g. financial or sexual

Difficulty completing tasks

Insight may be impaired - Psychosis (severe mania) – e.g. grandiose delusions

Figure 2

BIPOLAR DISORDER: SIGNS & SYMPTOMS
Bipolar I (BD-I)
Mania (at least 7 days) with or without major depression.

Bipolar II (BD-II)
One or more episodes of hypomania (>4 days) + recurrent major depression.

Diagnosis of mania usually straightforward: behaviour often markedly disturbed. Help often sought via a third party as patients usually have impaired insight. The prodrome of mania with hypomanic irritability and insomnia may be misdiagnosed as anxiety or an anger management problem.

Psychosis may occur in mania or depression. Depression may be severe and mixed symptoms are common. First episode often warrants hospitalization; patient may recognize early relapse signs of subsequent episodes. BD-I may present as severe depression in a teenager or young adult before the first manic episode - 'Atypical depression' features may indicate BD.

Diagnosis difficult: patients only seek help when depressed. Hypomania not recognised by patient or doctor so misdiagnosed as unipolar depression => long delays to correct treatment. Hypomania with irritability and insomnia may be misdiagnosed as anxiety or an anger management problem. Mood symptoms or family history may help identify history of hypomania.

No psychosis and less dramatic than BD-I but depression may be relentless and severe and carry a high suicide risk, especially if mixed symptoms. BD-II may present as severe depression in a teenager or young adult before the first hypomanic episode – 'Atypical Depression' features may indicate BD.

Bipolar Spectrum Disorder
Bipolar Elsewhere Defined (BD-NED)
Cyclotymia

This group is often referred to as 'Bipolar Spectrum Disorder'. Includes Cyclothymia (recurrent hypomania with subthreshold depression) and less severe and shorter mood swings with hypomania < 4 days. Diagnostic criteria and treatment options less well defined.

Cycling – the frequency of mood changes of any subtype
Rapid cycling – 4 or more mood episodes per year
Ultra-rapid cycling – mood changes every few weeks/days
Ultra-radian cycling – mood changes every few hours

Mixed symptoms - depression and mania/hypomania at the same time – common but difficult to diagnose. Sometimes referred to as 'irritable depression' or 'dysphoric hypomania' depending on the predominant symptom. May present with perplexity, confusion, or suspiciousness.

Increased risk of suicide.

Fig 2. A simplified classification of Bipolar Disorder
Adapted from Bipolar Disorder (Oxford Psychiatry Library) Yatham Malhi OUP Oxford; 1 edition (2011) page 10 with permission
<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Bipolar Depression</th>
<th>Unipolar Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of bipolar disorder or psychosis</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Antidepressant associated mania or hypomania</td>
<td>++++</td>
<td>--</td>
</tr>
<tr>
<td>Psychotic depression &lt; age 35</td>
<td>++++</td>
<td>--</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Alcohol/Substance abuse</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Borderline Personality Disorder</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Significant seasonal mood changes</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Onset of depression before age 25</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Postpartum onset of depression</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Mood reaction with systemic corticosteroids</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>‘Atypical’ features of depression -</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>‘Lead-like’ limb heaviness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marked fatigue, severe guilt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive eating / sleeping</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labile Mood or mixed episode - manic features during episode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid on/off pattern of symptoms</td>
<td>++</td>
<td>--</td>
</tr>
<tr>
<td>Frequent recurrence of depressive episodes</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Antidepressant wear-off</td>
<td>++</td>
<td>--</td>
</tr>
<tr>
<td>Brief episodes of depression (&lt;3 months)</td>
<td>++</td>
<td>--</td>
</tr>
<tr>
<td>ADHD</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Eating Disorders</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

**Figure 4. CLINICAL DIFFERENCES BETWEEN BIPOLAR AND UNIPOLAR DEPRESSION.**

Based on Angst (2,3), Mitchell (28,29) and adapted from Smith (5,44)
Bipolar I Mania (≥7 days) with or without major depression – often severe – diagnosis usually straightforward – but prodrome may be misdiagnosed as anxiety or an anger management problem.
Bipolar II Hypomania (≥4 days) + recurrent major depression – often severe - high suicide risk.
Diagnosis difficult: patients only seek help when depressed ->Hypomania not recognised by patient or doctor -> misdiagnosed as unipolar depression ->long delays to correct treatment. Hypomania with irritability and insomnia may be misdiagnosed as anxiety or an anger management problem.
Bipolar Spectrum (BPD-Not Otherwise Specified including Cyclothymia) – diagnostic criteria less well-defined - milder mood swings with hypomania < 4 days and subthreshold depression.

Fig 5. RECOGNISING BIPOLAR DISORDER – A DECISION AID FOR PRIMARY CARE

Primary Care context:
Anxiety, depression, mood swings, fatigue, insomnia
Anger, irritability, or difficult consultations
Relationship or employment difficulties
Alcohol/substance misuse
Self-harm/Suicide attempt

Rule out organic/iatrogenic causes and avoid medicalising normal stress reactions or temperaments – but could this be unrecognised Bipolar Disorder?

If resources allow assess over longer (or several) consultations
Screen for hypomania/mania:
1. 'Is there a family history of Bipolar Disorder?'
2. 'Do you ever feel 'hyper' or irritable or have thoughts that you can't slow down?'
3. 'Do you ever experience changes in mood and energy that seem more extreme than other people and has anyone ever mentioned this to you?'
4. Are there any features that make bipolar disorder more likely?

BPD unlikely but reassess if symptoms change

• Refer for Psychiatric assessment – a Bipolar diagnosis should usually be made by a Psychiatrist. Severity of symptoms and risk to self or others determines urgency of referral.
• Avoid antidepressants (in Bipolar Disorder may worsen symptoms or increase suicide risk) until seen by / discussed with Psychiatrist. Short term promethazine or benzo diazepine safer interim option if insomnia or agitated
• Consider a Mood Questionnaire and suggest a mood chart - include with referral letter or patient to take to appointment
• Consider watchful waiting if symptoms not marked and no functional impairment; refer if concerns persist
• If Psychiatrist’s assessment inconclusive/patient does not improve discuss with Psychiatrist / consider referral for second opinion

Diagnosis difficult: patients only seek help when depressed ->Hypomania not recognised by patient or doctor -> misdiagnosed as unipolar depression ->long delays to correct treatment. Hypomania with irritability and insomnia may be misdiagnosed as anxiety or an anger management problem.

<table>
<thead>
<tr>
<th></th>
<th>Bipolar Depression</th>
<th>Unipolar Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of bipolar disorder or psychosis</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Antidepressant associated mania or hypomania</td>
<td>++++</td>
<td>--</td>
</tr>
<tr>
<td>Psychotic depression &lt; age 35</td>
<td>++++</td>
<td>--</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Alcohol/Substance abuse</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Borderline Personality disorder</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Significant seasonal mood changes</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Onset of depression before age 25</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Postpartum onset of depression</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Mood reaction with systemic corticosteroids</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>‘Atypical’ features of depression - 'Lead-like' limb heaviness</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Marked fatigue, severe guilt</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Excessive eating / sleeping</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Labile Mood or mixed episode - manic features during episode</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Rapid on/off pattern of symptoms</td>
<td>++</td>
<td>--</td>
</tr>
<tr>
<td>Frequent recurrence of depressive episodes</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Antidepressant wear-off</td>
<td>++</td>
<td>--</td>
</tr>
<tr>
<td>Brief episodes of depression (&lt;3 months)</td>
<td>++</td>
<td>--</td>
</tr>
<tr>
<td>ADHD</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

Mood questionnaires (5-10 minutes) may help identify previous hypomanic symptoms - if patient has insight. Probability of BPD increases with the number of positive responses - but NOT diagnostic – see individuals tools and interpret with caution.

MDQ Mood Disorders Questionnaire
score >7/13

BDS Bipolar Spectrum Diagnostic Scale
score >13/25

HCL-32 Hypomania Check List - 32 R
score >14/32

MSQ Mood Swings Questionnaire Score >22/27
Suggest patient records a daily mood chart
Selected Resources

Online for professionals

Bipolar Education Programme Cymru (BEP-C) [www.bep-c.org](http://www.bep-c.org)

The BEP-C programme at Cardiff University run both web-based and group psychoeducational treatment for individuals with Bipolar Disorder. They have also developed a number of web-based packages of information for service users and professionals: For primary care practitioners: [http://www.beatingBipolar.org/primary_care_practitioners/](http://www.beatingBipolar.org/primary_care_practitioners/)


NICE [http://guidance.nice.org.uk/CG38 in the process of being updated for 2014](http://guidance.nice.org.uk/CG38 in the process of being updated for 2014)

www.psycheducation.org US website with detailed information on all aspects of Bipolar Disorder

Suicide Mitigation in Primary Care [http://www.rcgp.org.uk/pdf/RCGP%20RCPsych%20Suicide%20Mitigation%20in%20Primary%20Care%20factsheet%20June%202012.pdf](http://www.rcgp.org.uk/pdf/RCGP%20RCPsych%20Suicide%20Mitigation%20in%20Primary%20Care%20factsheet%20June%202012.pdf)


Books for Professionals


Bipolar Disorder (Oxford Psychiatry Library) Yatham,Malhi OUP Oxford; 1 ed (6 Jan 2011)

Bipolar II Disorder Modelling Measuring and Managing Parker Cambridge 2nd Ed (Apr 2012)

Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression Goodwin and Redfield Jamison, Oxford University Press, USA; 2 edition (March 22, 2007)


Books for patients, family and those close to them

An Unquiet Mind: A memoir of moods and madness Redfield Jamison Picador (5 Aug 2011)

Bipolar Disorder - The Ultimate Guide Owen,SaundersOneworld Publications (1 July 2008)

Lithium for Bipolar Disorder: A Guide for Patients (Bipolar Information Series) Stafford My Mind Books (1 Jun 2011)

Mood Mapping: Plot your way to emotional health and happiness Miller Rodale (7 Jan 2011)

Overcoming Mood Swings Scott Robinson (25 Mar 2010)

Online for patients

Bipolar Education Programme Cymru (BEP-C) www.bep-c.org
The BEP-C programme at Cardiff University run both web-based and group psychoeducational treatment for individuals with Bipolar Disorder. They have also developed a number of web-based packages of information for service users and professionals:

For families and carers: http://www.beatingBipolar.org/families_and_carers/

For women with Bipolar Disorder: http://www.beatingBipolar.org/women_and_Bipolar/

Bipolar UK www.mdf.org.uk
Bipolar UK is the United Kingdom's largest user-led voluntary organisation for Bipolar Disorder. They have a comprehensive programme of support for individuals and families, including advice on medication, psychological treatments and occupational issues. Bipolar UK also run self-management training courses locally across the UK.

Depression Alliance http://www.depressionalliance.org
Leading UK charity for people affected by depression

Equilibrium http://www.bipolar-foundation.org
An independent, international, non-governmental organisation dedicated to improving life for people with bipolar disorders

Mind http://www.mind.org.uk/help/diagnoses_and_conditions/bipolar_disorder_manic_depression
A charity providing advice and support to empower anyone experiencing a mental health problem. Mind campaigns to improve services, raise awareness and promote understanding.

Royal College of Psychiatrists ‘Help is at Hand’ leaflet on Bipolar Disorder: http://www.rcpsych.ac.uk/mentalhealthinfo/problems/BipolarDisorder/BipolarDisorder.aspx_

References


6. Smith DJ, Griffiths E, Kelly MJ, Hood K, Craddock NJ, Simpson SA. Unrecognised bipolar disorder in


Cutting Edge Psychiatry in Practice

Providing Partnership Services in Bedfordshire, Essex and Luton

Providing up-to-date information in a way that is of practical value to GPs and psychiatrists in training