

Comorbidities in bipolar disorder: models and management

Gordon B Parker

Comorbidity in manic-depressive illness ... is the rule rather than the exception.

Frederick Goodwin and Kay Jamison,
*Bipolar disorders and recurrent depression*¹

Bipolar disorders are widely recognised as being associated with considerable clinical comorbidity and affecting patients' work, family life and interpersonal functioning. Two-thirds of patients with a bipolar disorder have a comorbid (psychiatric) condition; such comorbid conditions worsen the outcome of the bipolar disorder, and can compromise its management (eg, treating associated panic disorder with a selective serotonin reuptake inhibitor antidepressant can trigger a manic or mixed episode); and anxiety and substance use disorders are the most common comorbid psychiatric conditions identified in community-based and clinical studies.¹

Quantifying comorbid conditions associated with bipolar disorders

One seminal report from the National Comorbidity Survey Replication (NCS-R), which comprises a representative sample of more than 9000 English-speaking adults in the United States, illustrates the over-representation of comorbid conditions in bipolar disorders.² The authors of this report distinguished between bipolar I disorder (involving manic episodes), bipolar II disorder (involving non-psychotic hypomanic episodes) and subthreshold bipolar disorder (where individuals experienced fewer hypomanic symptoms, with or without episodes of major depression). The lifetime prevalence of these three diagnoses was quantified as 1.0%, 1.1% and 2.4%, respectively.

Patients with any bipolar disorder had a six times increased lifetime comorbidity of any anxiety disorder; all anxiety disorders — including panic attacks, agoraphobia, generalised anxiety, obsessive compulsive disorder (OCD), and specific and social phobias — were over-represented. The most distinct increase was for OCD (odds ratios [ORs] of 21.4, 16.7 and 3.0 in the three respective groups of bipolar disorder, and 10.2 for any bipolar disorder).

A similar picture emerged for impulse-control disorders — intermittent explosive disorder, attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder and conduct disorder — with all of these over-represented (ORs of 8.3, 8.1 and 4.2 in the three respective groups, and 5.6 for any bipolar disorder). A similar over-representation also occurred for substance use disorders (ie, alcohol use, alcohol dependence, drug use and drug dependence), with any substance disorder being over-represented (ORs of 8.8, 3.9 and 3.2 in the three respective groups, and 4.2 for any bipolar disorder).

Such data — and similar findings from population-based and clinical studies that were referenced by the authors — suggest very high and over-represented rates of anxiety, impulse-control disorders and drug and alcohol use comorbidity in patients with bipolar disorder, with rates generally higher in the bipolar I and bipolar II groups compared with the subthreshold group. There was, however, a different picture for drug and alcohol problems, where

ABSTRACT

- Rates of conditions comorbid with bipolar disorder are very high, with anxiety disorders, impulse-control disorders, and drug and alcohol problems being the most distinctly over-represented conditions.
- Although the high rates of comorbid conditions may be overestimates — owing to measurement distortions in community surveys, and because definitions of comorbidity generally include antecedent and consequential conditions (not merely coterminous ones) — they are clinically distinctive.
- Clinical comorbidity can be explained by at least four different models, which each have clinical management implications.
- If the bipolar disorder and the comorbid conditions are deemed to be interdependent, two broad approaches are appropriate: hierarchical management strategies and sequential management strategies.
- Successful management of bipolar disorder often involves the development of a wellbeing plan that addresses comorbid issues iterative to the bipolar disorder.

MJA 2010; 193: S18–S20

over-representation was most distinctive for those with a bipolar II condition.

What is comorbidity?

There is wisdom in stepping back from such seemingly impressive comorbidity data and asking what is actually meant by the term comorbidity. Strictly, it should mean the co-occurrence or coterminous presence of two independent conditions, at above chance levels.³ However, most population-based studies (including the NCS-R) report lifetime or 12-month data, rather than current status, hence a strict definition of comorbidity is rarely applied and the results distinctly inflate comorbidity estimates.

The first amplifying factor — conflating current with longer-term status — reflects standard psychiatric survey approaches in a community sample, where interviewees receive a set of stem questions (in relation to each disorder) which, if affirmed, generate secondary questions to determine if sufficient criteria are met for that disorder. As patients with a bipolar disorder are likely to have mood states driving anger, behavioural disturbances, poor concentration and inner tension, the risk of false-positive diagnoses of conduct disorder and ADHD is high. The second contribution to inflating the sample numbers defined this way emerges from moving beyond the precise definition of comorbidity (ie, two independent conditions at one time point) and including any additional lifetime diagnosis. Such criticisms in relation to bipolar disorder have been raised previously, with one author commenting that comorbidity is “a ‘parasite’ of modern diagnostic systems”, that the responsible classificatory models have become “a ‘splitter’s dream’ and ‘lumper’s nightmare’”, and that the clinical significance of comorbidity is often debatable.⁴

Loose definition allows four possible models of comorbidity

The current loose definition of comorbidity allows bipolar comorbidity, in practice, to reflect four principal sequences, each of which has clinical management implications.

1. Bipolar disorder is associated with an increased rate of antecedent and *forme fruste* conditions.
2. The bipolar condition increases the chance of the other condition.
3. The other condition increases the chance of bipolar disorder emerging.
4. Higher-order factors increase the chance of both the bipolar disorder and the other condition as interdependent or independent disorders (and so creating spurious comorbidity).

Model 1 — bipolar disorder is associated with an increased rate of antecedent and *forme fruste* conditions

Before formal onset of a bipolar disorder, many patients experience other psychiatric conditions or states, especially anxiety. Rarer conditions (eg, eating disorders) are also over-represented, but their clinical relevance is difficult to establish before the onset of bipolar disorder. While such antecedent states may presage an incipient bipolar condition, it is my personal view that it is inappropriate to treat individuals at that stage as if they had a bipolar condition (being aware of the false-positive risks). Others might argue for a more assertive approach.

Model 2 — the bipolar condition increases the chance of the other condition

The second model positions the bipolar condition as primary and driving a set of secondary conditions, with the anxiety disorders (especially panic attacks) being particularly common concomitants of depression in bipolar patients.

Over-representation of OCD is less readily explained. To the degree that OCD is a containment condition for handling free-floating anxiety, its occurrence may simply reflect this pathway. Also, some medications used to manage bipolar disorder can increase OCD-type symptoms, allowing another explanation. In addition, it has been suggested that their coexistence may reflect the “expression of a single underlying [central nervous system] dysfunction” (an explanation which would provide more support for Model 4).¹

Another example is drug and alcohol dependence. Patients with a bipolar disorder are distinctly more likely to use alcohol during depressive phases to self-medicate against their psychological pain. Conversely, stimulant drugs (including coffee) as well as alcohol are often used by bipolar patients to take themselves into, or advance, a high. During such periods, their threshold for alcohol consumption is lowered, so they will often consume very large amounts of alcohol to further fuel the high.⁵ Not only is the alcohol intake a problem in and of itself, but alcohol is generally depressogenic and may compromise the action of antidepressants. Predictably, such coping strategies can become autonomous, but again the model is of the bipolar condition increasing the chance of such other conditions.

How is the clinician to respond to this model? A parsimonious approach is to seek to bring the bipolar disorder under control and then see what is left. The advantages are obvious but, in particular, many secondary conditions (eg, anxiety states) and social problems (eg, gambling and aggression) which initially appear to be distinct problem areas, may no longer be relevant when the bipolar condi-

tion is controlled. For conditions that are still significant, many patients will benefit from a pluralistic bipolar wellbeing plan.⁶

Model 3 — the other condition increases the chance of the bipolar disorder emerging

The possibility that some independent psychiatric condition might predispose to bipolar disorder is unlikely, as the evidence for bipolar disorder having a strong genetic basis is convincing. However, if bipolar disorder is positioned as a “genetic diathesis” condition, it may be that some factors contribute more to initial onset (ie, as predisposing environmental factors) and to subsequent episodes (ie, as environmental precipitants). Again, from clinical observation, certain drugs (particularly stimulants) and alcohol are candidates for this role. Patients who reduce such triggers will commonly report fewer episode recurrences.

The possibility that certain organic conditions can increase the risk of bipolar disorder is also recognised. For example, over-representation of cardiovascular disease, thyroid dysfunction, diabetes and migraines has been considered, and other explanations have been noted (eg, many medical consequences may reflect drug treatments for the bipolar conditions, as well as lifestyle factors).¹

Certain drugs (eg, antidepressants and steroids) and cerebral conditions (eg, head injury, brain tumour, cerebral HIV and multiple sclerosis) may increase the chance of mood swings. While such conditions are not officially classified as true bipolar disorders, management commonly requires treating the mood swings as if the patient did have a bipolar disorder and addressing any organic precipitants.

Model 4 — higher-order factors increase the chance of both the bipolar disorder and the other condition

This model considers the possibility that some higher-order processes shape quite different disorders, with downstream conditions or consequences being theoretically independent or interdependent.

Many individuals who develop a bipolar disorder will report significant anxiety. We can extend this model beyond psychiatric diagnoses to note that patients with a bipolar disorder are held to be more likely to be creative,⁷ and also more likely to report greater identity diffusion. While any such increase in anxiety may be more an early prodromal manifestation, or a concomitant of established bipolar disorder, the possibility of shared higher-order determinants should be conceded. However, specific mechanisms are conjectural. For example, based on data indicating that comorbidity between bipolar disorder, schizophrenia, ADHD and OCD may reflect contribution of a brain-derived neurotrophic factor (BDNF), separate (seemingly independent) diagnostic conditions may share some higher-order genetic or other biological factor.⁸ The implications of this model allow several alternative clinical approaches, but I recommend a focus on the current diagnostically defined condition.

Clinical management overview

The first clinical priority in managing a patient with a bipolar disorder is a diagnostic one — to establish that the patient has a true bipolar disorder — and, after excluding an alternative primary condition, to consider whether suggested comorbid conditions may be a manifestation of the identified bipolar disorder. Two common

clinical issues are relevant here — the suggestion of alternative or additional diagnoses of ADHD, and borderline personality style.

Although ADHD is held to be over-represented in patients with bipolar disorder (with one or the other being the comorbid condition), the clinical priority should be to determine whether only one condition is present. In this instance, clinical differentiation involves consideration of a few issues. ADHD is commonly evident in early childhood, while this is rare for bipolar disorder. Secondly, ADHD shows much greater continuity of symptoms, while bipolar disorder is more of an episodic condition. Thus, asking an individual whether their periods of poor concentration, behavioural and sleep disturbance and other factors in childhood were continuous or episodic is likely to differentiate these two conditions. An individual with true ADHD will generally state that they were never able to read a book or sit through a film in childhood, while those with a bipolar disorder will report only episodic perturbations.

Many patients with a true bipolar condition will receive a false primary or comorbid diagnosis of a borderline personality style or disorder as a consequence of the mood dysregulation and the common identity diffusion experienced by patients with a bipolar disorder (not quite knowing “who they are” or “that they are”). The diagnosis is again usually clarified by focusing on the longitudinal pattern where, once the bipolar condition has been brought under control, many of the pseudo-signals of a borderline personality disappear.

The next issue is to identify — in those with a diagnosed bipolar condition — any substantive comorbid conditions. As mirrored in community-based studies, the average patient with a bipolar disorder will meet criteria for a number of other conditions, including anxiety disorders, drug and alcohol problems, and some personality dysfunction. The clinician should seek to establish what is primary, what is secondary, and whether there are any truly independent conditions. In most instances, bipolar disorder will be the primary condition and the condition that is prioritised for treatment — first, because this is a parsimonious sequential model and, second, because many of the identified secondary conditions will attenuate or disappear when the bipolar condition is brought under control. Thus, the therapeutic priority will initially be to bring the bipolar disorder under control and to then re-evaluate the presence and salience of other conditions.

If operating to the “clinical management overview” approach, what happens in real-life clinical practice?

The term comorbidity is a descriptive one that does not imply any particular mechanism.³ It is therefore the clinician’s task to contemplate the nature of any comorbidity and consider management implications. If the bipolar disorder can be brought under complete or near-complete control — which will usually involve a pluralistic approach involving medication, education and a well-being plan — secondary conditions may or may not need to be addressed, largely depending on whether they reflect the common risk factor (bipolar disorder and its antecedents) or not. Anxiety conditions are rarely relevant (if they are concomitants of the bipolar depressed state) and the wellbeing plan will address triggers such as stimulant drugs and alcohol.

If the bipolar condition is unable to be brought under strict control, many of the so-called comorbid conditions will continue and some (especially alcohol use) can seriously disrupt management. An independent approach (particularly for addressing drug and alcohol use) may be required, with referral to a specialist practitioner. Support groups are highly appreciated by patients, in

that they feel less alone when they hear stories from others who also struggle with the roller-coaster ride of a bipolar condition.⁹

If the bipolar disorder and the comorbid conditions are inter-dependent, there are two broad management strategies: adopting either a sequential or a hierarchical approach. The sequential approach involves identifying and managing the first temporal condition, and then managing any subsequent or secondary conditions that remain. The hierarchical approach involves determining the most clinically important or pressing factor, managing it, and then considering whether the less important condition has been corrected, has attenuated, or is still present and requires management. Certain management issues (eg, safety) can reprioritise the operative model. For example, an individual may be severely intoxicated with drugs or alcohol but, while this might clearly be the primary current condition, any suicidal or homicidal propensities should dictate immediate treatment options.

Conclusions

Comorbidity is common in bipolar disorder and requires assessment by clinicians such that all elements of the individual patient’s problems can be addressed. The clinical approach to addressing comorbidity issues in patients with bipolar disorder is akin to much of the rest of medicine, with the clinician needing to undertake a pattern analysis, determine what is substantive and worthy of attention, and then determine whether to adopt a sequential or hierarchical approach to the identified conditions.

Acknowledgements

My thanks to Kerrie Eyers for editing the manuscript. This study was funded by a National Health and Medical Research Council Program Grant (510135).

Author details

Gordon B Parker, MD, PhD, FRANZCP, Scientia Professor of Psychiatry,¹ and Executive Director²

1 School of Psychiatry, University of New South Wales, Sydney, NSW.

2 Black Dog Institute, Prince of Wales Hospital, Sydney, NSW.

Correspondence: g.parker@unsw.edu.au

References

- Goodwin FK, Jamison KR. Manic-depressive illness. Bipolar disorders and recurrent depression. 2nd Ed. New York: Oxford University Press, 2007.
- Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. *Arch Gen Psychiat* 2007; 64: 543-552.
- Rutter M. Comorbidity: meanings and mechanisms. *Clin Psychol: Sci Pract* 1994; 1: 100-103.
- Brieger P. Comorbidity in bipolar disorder. In: Marneros A, Angst J, editors. Bipolar disorders: 100 years after manic depressive insanity. Dordrecht: Kluwer, 2000: 215-219.
- Parker G. In high spirits: some links between alcohol use and bipolar disorder. *Aust N Z J Psychiatry* 2008; 42: 1075-1076.
- Orum M. The role of wellbeing plans in managing bipolar II disorder. In: Parker G, editor. Bipolar II disorder: modelling, measuring and managing. Cambridge: Cambridge University Press, 2008: 177-194.
- Jamison KR. Touched with fire: manic depressive illness and the artistic temperament. New York: Simon and Shuster, 1996.
- Müller DJ, Kennedy JL. Recent advances in genetics of bipolar disorder. In: McDonald C, Schulze K, Murray RM, Tohen M, editors. Bipolar disorder: the upswing in research and treatment. London: Taylor and Francis, 2005: 77-92.
- Eyers K, Parker G. Mastering bipolar disorder: an insider’s guide to managing mood swings and finding balance. Sydney: Allen and Unwin, 2008.

(Received 9 Feb 2010, accepted 16 Jun 2010)

□