Editorial

Carving bipolarity using a lithium sword
Gin S. Malhi and John R. Geddes

Summary
The classification of mood disorders lacks precision and consequently there has been no recent meaningful advance in their treatment. By virtue of its therapeudic specificity, lithium responsiveness offers an opportunity to diagnose a definitive subtype of mood disorders that may provide a platform for the development of targeted therapy.

Diagnostic problems caused by polarity

The conventional clinical picture of bipolar disorder is that of an illness characterised by discrete episodes of mania and depression, sometimes alternating, but often not. The occurrence of mania separates bipolar disorder from major depression, and in essence defines the illness. However, undue emphasis on polarity has created a number of serious diagnostic problems.

First, the fact that ‘mixed states’ commonly occur in clinical practice, and by definition do not conform to either syndrome of depression or mania, challenges the fundamental validity of an axial model of bipolar disorder with diametrically opposing mood states. Second, diagnostic weighting of polarity in classification systems has unwittingly diverted clinical attention away from other more important aspects of affective disorders such as their longitudinal pattern, in particular, the prominence of interepisodic symptoms and mood instability and the recurrence of mood episodes over the course of the illness. Third, the lack of clinical validity of a classification of mood disorders based on polarity has given impetus to the development of spectrum models, which lack purpose with respect to treatment.

In an attempt to iron out the diagnostic wrinkles caused by DSM-IV mixed episodes, DSM-5 removed their codification altogether and introduced a mixed features specifier, which can be used to nuance mood episodes when deemed necessary. But reconfiguring the classification of mixed states in this manner does not explain their aetiology, and the overarching paradigm for mood disorders based on antipodal phases of affective illness remains incomplete and unrealistic; after all, it is impossible to conceive of a mental state in which an individual’s mood is simultaneously elevated and depressed.

In contrast to mixed episodes, which should not have been included in DSM-IV, a lack of emphasis on the longitudinal pattern of affective disorders is an error of omission. This is because the course of mood disorders is an important feature that meaningfully groups subtypes and informs treatment. For example, the classic diagnosis of manic–depressive illness contained all patients with recurrent mood episodes irrespective of polarity. But this emphasis on recurrence was lost when bipolar disorder was formalised in DSM-III and polarity gained primacy. Hence modern-day bipolar disorder is not synonymous with manic–depressive illness and this is evident with respect to treatment.

The categorical classification of mood disorders has proven to be problematic. For example, clinically an episode of depression within major depressive disorder is indistinguishable from that within bipolar disorder, but their treatment responses differ. Within bipolar disorder, definition of the type II bipolar subtype rests on identifying a moderate form of mania, but the upper and lower duration cut-offs used to delineate hypomania are completely arbitrary, and have been shown to have no clinical or biological correlates. Indeed, in practice, periods of manic symptoms of fewer than 4 consecutive days’ duration are common and can cause as much disability as longer episodes of illness. Similarly, the transition from hypomania to mania on the basis of loosely defined ‘marked impairment’ and/or a consequence of illness, namely ‘hospitalisation’, lacks credence. In part because of these difficulties, but also because symptoms appear to manifest dimensionally, the concept of a spectrum, both in terms of symptoms and disorders, is intrinsically appealing; but it too has failed to provide a better understanding of mood disorders and advance clinical management.

Fundamentally, the inadequacies of contemporary diagnostic systems highlight our sciolism concerning the pathophysiology of bipolar disorder. Yet we can probably do much better if we move away from clinical assessment based on retrospective anamnesis and towards detailed, prospective measurements using the big data delivered by pervasive modern communication technologies and wearable devices. Such deep phenotyping is likely to yield insights into underlying neurobiology and to aid the development of treatments for bipolar disorder. It is worth noting that, despite heightened interest in bipolar disorder, its pharmacological treatment remains woefully suboptimal, with no new medications being developed specifically for the treatment of mania or bipolar depression since the advent of lithium.

Lithium’s cutting edge

To achieve a more meaningful taxonomy of mood disorders, and to develop better treatments, a new diagnostic paradigm and a

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different approach to treatment development is necessary. Traditionally, psychiatric disorders have been diagnosed according to signs and symptoms on the assumption that these form relatively homogeneous groups, which lend themselves to systematic investigation. But, in actuality, psychiatric diagnoses have generated loosely defined categories with composite aetiologies, and this has made it difficult to determine their pathophysiology. An alternative approach is to use treatment response to guide us to underlying processes – a reverse translation.

In mood disorders, lithium has both antimanic and antidepressant properties, but its effects when treating acute episodes are slow, for example, in comparison with second-generation antipsychotics. In contrast, its effectiveness longer term, and in particular with respect to prophylaxis, is unparalleled. Clinically, this is its most important effect and one that confers a significant advantage. Lithium’s specific action of mood stabilisation is its cutting edge.

**Defining lithium response**

Longitudinal studies that have examined the clinical effects of lithium have managed to characterise those patients with mood disorder most likely to respond. The clinical profile of an individual who responds to lithium is essentially that of someone disorder most likely to respond. The clinical profile of an individual who responds to lithium is essentially that of someone responsive mood disorders outside of this group. It is time to redefine mood disorders and to discover new targets for treatments based on a deep understanding of biology.

**Conclusions**

Lithium remains the best pharmacological agent for the long-term treatment of recurrent mood disorders, in particular, bipolar disorder. It has specific actions, which need to be better understood to allow development of more targeted treatments for mood disorders. Elucidating the precise effects of lithium at clinical and molecular levels is likely to aid further clinical and basic research into bipolar disorder and to drive forward much needed drug discovery. Specifically, defining a lithium-responsive subtype within mood disorders will provide a cornerstone for the construction of a therapeutically meaningful taxonomy. The clinical circumcision of lithium responders will introduce greater homogeneity both within the taxon and in non-lithium responsive mood disorders outside of this group. It is time to return to lithium, both for its clinical benefits and for the scientific potential provided by close study of its effects. We should take advantage of the unique properties of lithium – to help redefine mood disorders and to discover new targets for treatments based on a deep understanding of biology.

**References**


**Out-patient institutionalisation**

Nicholas Kontos, Oliver Freudenreich and John Querques

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