

# **Mood Instability and Regulatory Oversight: Checkpoints on the Pursuit of ‘True’ Mood Stabilisers**

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Bipolar disorder is a complex disorder with multi-dimensional phenotypes across axes of mood, cognition, and activity. Treatment of mood disturbances in bipolar disorder has long been the cornerstone of management, with a growing number of pharmacotherapies demonstrating variable ‘Mood Stabiliser’ effects. While the widely-used label has stimulated much debate over its defining criteria, relapse prevention – as one of the most central objectives and challenges of long-term management - is arguably the principal metric to be used when evaluating drugs for their mood-stabilising properties. However, paralleling a growing understanding of the bipolar disorder phenotype, there has been an interesting move towards classifying mood stabilisers based on their stabilising effects on cognition and activity as well (Malhi et al., 2017). A refined understanding of the repertoire of available treatments – each with differential effects on mood, cognition, and activity – can facilitate the use of tactical combinations of treatments tailored to individual patient needs (Malhi et al., 2015). In this commentary, using chronic mood instability as an example, we suggest a paradigm shift that accounts for finer fluctuations of symptoms through time. Finally, there is a discussion to be had on the role of regulatory agencies as the final gatekeepers to the translation of any changes into clinical practice.

### **Uncaptured Phenotypes: Towards Continuous Assessment of Mood, Cognition, and Activity**

A traditional view of mood disturbances in bipolar disorder, whereby episodes of debilitating mania or depression interrupt otherwise normal mood with relatively normal functioning, has shaped much of the discussion on desired outcomes of treatment. This categorical classification of discrete mood states in bipolar disorder has proven to be probably too simplistic, insofar as it fails to capture prominent, inter-episodic mood *instability* (Harrison et al., 2016). In clinical settings, chronic mood instability is associated with poorer outcomes and is often reported by patients with bipolar disorder as one of the most disabling features, particularly in young patients early in their disease course.. Given its clinical significance, reducing inter-episodic mood instability should be taken into consideration in the definition of the properties that a true mood stabiliser ought to display.

The use of self-rated, remote mood-monitoring systems has enabled clinicians and patients to collect the longitudinal data necessary to demonstrate the impact of chronic mood instability (Bonsall et al.,

2012). True Colours ([oxfordhealth.truecolours.nhs.uk/www/en/](http://oxfordhealth.truecolours.nhs.uk/www/en/)) is a clear example of how prospective data collection embedded in routine care settings can overcome the clinical and technical challenge of capturing rapid fluctuations in mood symptoms. This is a worthwhile endeavour, as it overcomes the logistical limitations of consultation-based assessments and allows clinicians and researchers to develop a more fine-grained picture of the disorder phenotype. The incorporation of novel technologies, such as wearable devices and smartphone apps, has the potential to augment trials in bipolar disorder by capturing, in a continuous and ideally passive manner, the effects of drugs on mood, cognitive, and biological parameters. Such data lends itself to quantitative assessment that can be coupled to mathematical methods of data analysis to better understand the effects of drugs through time and, ultimately, to titrate treatment to patient needs.

### **Enrichment Designs and the Battle on the Regulatory Front**

In defining the criteria of mood stabilisers, it is necessary to involve regulatory agencies and the pharmaceutical industry in the discussion for this to translate into meaningful change downstream. The evidence for efficacy of second-generation antipsychotics (SGAs) in maintenance treatment of bipolar disorder provides an example of when shortcomings in regulatory oversight can lead to distorted interpretations and potentially inappropriate prescribing patterns (Cipriani et al., 2014). As a general pattern in such randomised controlled trials (RCTs): in the first phase of the study, acutely symptomatic patients are recruited and receive open-label treatment with an SGA (as monotherapy or as add-on treatment to lithium or valproate). Patients who do not remit with an SGA are excluded and only those who achieve stable remission are randomised to the second phase of the study, a double-blind treatment with the same SGA or placebo. Such enrichment design RCTs, therefore, represent *continuation* studies (i.e. they answer the question: how long should we continue the treatment that worked for a patient who was acutely ill?), rather than pure *maintenance* studies (what is the best treatment to be prescribed to a non-acutely ill patient in order to reduce the risk of relapse?). As expected, such long-term trials demonstrate that the proportion of acutely symptomatic patients who remit with acute treatment may benefit from continuing the same treatment longer-term. This is quite different from claiming that a drug is effective for relapse prevention in patients who are euthymic at

baseline and need long-term treatment to reduce the risk of relapse – the property that clinicians and patients arguably seek in mood stabilisers. Unfortunately, prescribing labels tend to brush over this nuance; despite the well-known use of enrichment design RCTs, the indication on prescribing information sheets for SGAs is broadened to ‘maintenance treatment’ for bipolar disorder, with no attempt to qualify the enriched population in whom the drug was shown to have an effect in the study. The described situation in the field of bipolar disorder research probably applies to psychiatry in general, and it ought to be addressed if we are to develop new treatments that will eventually bring about better outcomes for our patients. It is essential that regulatory agencies, as gatekeepers to the approval and licensing of new treatments, adopt stricter definitions and a priori criteria that require more compelling evidence before a drug is approved. Regulators, industry, and academia should work together in that direction because, ultimately, as long as drugs are granted approval, the arguments about design flaws and misleading labels, however convincing, will be of little impact.

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