

The Lancet Series on bipolar disorder

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Bipolar disorder – where patients experience recurrent episodes of mood disturbance, ranging from extreme elation (mania) to severe depression – is thought to affect roughly 2% of the world's population in its most pronounced forms (bipolar I and II), with milder forms of the disorder affecting another 2%. A new *Lancet* Series provides a comprehensive overview of the genetics, diagnosis, and treatment of bipolar disorder, outlining future challenges, and debating imminent changes to the criteria that psychiatrists use to diagnose the illness.

According to a *Lancet* Editorial accompanying the Series, "[Bipolar disorder](#) is not just about the extremes of emotion: it is also about the individual who exists both at, and between, those extremes. The psychiatrist of the future must be able to ally human and scientific understanding; to collaborate meaningfully and respectfully with patients in planning care; and to be confident and pragmatic, but receptive to [new discoveries](#) that may challenge the very basis of his or her understanding of [mental illness](#). Psychiatry demands exceptional doctors."

Series paper 1 – Scientists may be on verge of identifying biological mechanisms that lead to bipolar disorder

Bipolar disorder is currently diagnosed purely on the basis of clinical symptoms, typically presenting as alternating periods of depression and mania. These episodes may differ in severity and may be accompanied by other symptoms such as [hallucination](#) and delusions. However, there

is now compelling evidence that genes affect [predisposition](#) to bipolar disorder, and the authors of the first Series paper review current knowledge in this area.

While the contribution of environmental and [social factors](#) towards an individual's risk of developing bipolar disorder should not be underestimated, scientists' growing knowledge of the contribution of genetics to bipolar disorder nonetheless leads to the tantalising possibility that scientists might be on the verge of being able to identify some of the biological systems that lead to illness in bipolar disorder, which could in turn lead to substantial improvements in diagnosis and treatment of the illness.

According to Professor Nick Craddock, one of the paper's authors, "The association between genotype and phenotype for psychiatric disorders is clearly complex. Reductionist thinking has no place, and to think of any case as being either genetic or environmental, or to talk about a gene for bipolar disorder, makes no sense. The key point is that most cases of bipolar disorder involve the interplay of several genes or more complex genetic mechanisms, together with the effects of the environment, and chance."

The authors emphasise that bipolar disorder research now needs to follow up genetic studies with imaging and psychological studies, to try to unravel the complex [biological mechanisms](#) involved in bipolar disorder, and bring biological understanding closer to the experience of the patient. While several genes which increase a patient's risk of acquiring bipolar disorder have been discovered, to date, no clear biological mechanism to explain why these genes affect a person's risk of developing bipolar has been elucidated.

Series Paper 2 – Neuroimaging research could

transform bipolar diagnosis

The second Series paper outlines the substantial difficulties in diagnosing bipolar disorder: misdiagnosis of bipolar as unipolar depression is thought to occur in many patients seeking treatment for depression, and there is an average delay of 5 – 10 years between the onset of bipolar disorder and diagnosis. Depressive symptoms are considerably more prevalent than manic symptoms over the course of the illness for most people with bipolar disorder, and people are more likely to seek treatment for depressive symptoms.

Evidence suggests that a proportion of people diagnosed with unipolar depression may, in fact, have bipolar disorder, and this can be a major problem, because medication used to treat unipolar depression is not the same as that used to treat bipolar disorder, and medicine for unipolar depression could even exacerbate the manic symptoms seen in bipolar.

According to Professor Mary Phillips, one of the paper's authors, "Identifying objective biomarkers that differ between bipolar and unipolar depression would not only lead to more accurate diagnosis but potentially to new, personalised treatments, yet very little research has been undertaken in this area. For instance, very few neuroimaging studies have been done in which the brains of people with bipolar disorder have been compared to those of people with unipolar disorder, and further research into this area is urgently needed."

Series paper 3 – Search for new treatments for bipolar is being hampered by scarce knowledge of basic disease mechanisms

There have been no fundamental advances in the search for more effective treatment for bipolar disorder in the last twenty years, despite a

substantial expansion of research into the subject. The authors of the third Series paper point out that development of effective treatments is being hampered by scarce knowledge of basic disease mechanisms or clear targets for medicines.

Treating bipolar is complex, because the same treatments that alleviate depression can cause mania or mood swings, and treatments that reduce mania might cause rebound depressive episodes. While antidepressants are commonly used to treat the depressive phase of the disorder, there is scarce evidence for their efficacy.

Lithium – first introduced in 1949 – remains the best established long-term treatment for bipolar disorder, but its benefits are restricted by adverse effects, and alternatives are often needed for long-term treatment.

According to Professor John Geddes, one of the paper's authors, "Combining psychosocial treatments – which can include not just psychotherapy for the patient, but family therapy involving education for their family or caregiver – with mood stabilising drugs might well be one of the most promising lines of treatment for bipolar disorder. However, drug and psychological treatment studies have largely proceeded independently of one another, and research including both would help to move the field forward."

Viewpoint – Working Group members explain new thinking on stress-related mental disorders in ICD-11

WHO is currently developing the International Classification of Diseases, version 11 (ICD-11), a comprehensive, internationally-recognised diagnostic guide for all major diseases, including psychiatric illness. In a Viewpoint published alongside the Series, members of the

ICD-11 Working Group on mental disorders associated with stress outline the reasoning behind some of the updates in this area that will appear in the new edition. This includes a substantial tightening of the way in which ICD describes post-traumatic stress disorder (PTSD), a description of normal stress responses that are not considered disorders; the addition of "complex PTSD" to describe extensive reactions arising from severe and prolonged stressors; and inclusion of "prolonged grief disorder", used to describe patients that undergo an intensely painful, disabling, and abnormally persistent response to bereavement.

Comment – DSM-5 criteria for bipolar will "further obfuscate an already confusing diagnostic landscape"

Preparation for an updated version of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has been underway for some years, and the manual is due to appear this month, but in a Comment published alongside the Series, Professor Gin Malhi of the University of Sydney, Australia, expresses concern that the inclusion of a "mixed states specifier" (broadly defined as the coexistence of depressive and manic features) in the criteria for bipolar disorder may lead to diagnostic confusion, and complicate treatment implications. According to Professor Malhi, "the risk is that the diagnostic criterion of mixed states will be used loosely and its application will expand far beyond the most pronounced type of bipolar disorder across the whole bipolar spectrum, without any prognostic significance of therapeutic benefit. The present mix of features in bipolar disorder that will be 'specified' by the new classificatory system will produce a myriad of manifestations and further obfuscate an already confusing diagnostic landscape."

More information: www.thelancet.com/themed/bipolar-disorder

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