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PATHOPROFILE
BIPOLAR DISORDER

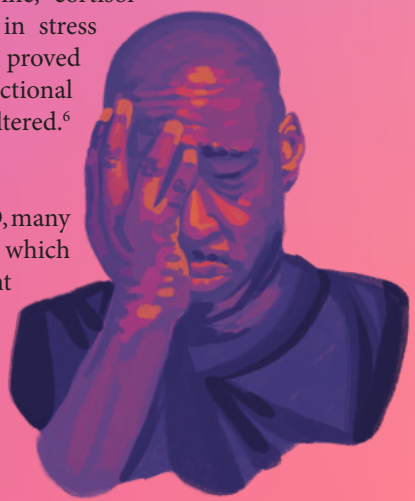
INTRODUCTION

Bipolar disorder (BD), previously known as "manic depressive illness," is a recurrent chronic disorder characterised by mood and energy-state fluctuations.[1] People who have BD comprise more than 1% of the world's population from all nationalities, ethnic origins, and socioeconomic statuses. There are four different types of bipolar-related disorders: bipolar disorder I, bipolar disorder II, cyclothymic disorder, and unspecified BD, which are classified by different patterns of manic, hypomanic, and depressive episodes.[1] Where manic and hypomanic episodes are both states of increased activity, energy, or agitation, hypomanic episodes only last around four consecutive days and are less severe compared to manic episodes, which last around one week. Depressive episodes are characterised by feelings of despair and a loss of interest in previously enjoyed activities.[1] Like many other psychological disorders, BD is often difficult to diagnose accurately in clinical practice due to large variations in individual symptoms, symptom overlap, or lack of approved biomarkers.[1] Additionally, because many patients with BD only seek treatment for depressive episodes, many BD patients are initially misdiagnosed.[2] Two studies conducted in 1999 and 2000 found that nearly 40% of patients with BD are initially diagnosed with unipolar depression.[2] Previous diagnosis criteria for the types of BD were also overly restrictive. For example, according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-4) criteria, bipolar disorder II requires an episode of mania or hypomania lasting four days, even though many experts believe that the average duration of the hypomanic state ranges between one to three days.[2] Moreover, it is often difficult to elicit a past history of hypomanic episodes from patients because of its milder presentation. For many patients, the increased energy and activity experienced during hypomanic episodes may not even be considered negative, and thus will go unreported.[2] Currently, the DSM-5 contains the most widely acknowledged diagnostic classifications for bipolar disorder.[1]

PATHWAYS

Current literature provides evidence that certain autoimmune illnesses influence the onset of BD. In a study of non-bipolar twins, Vonk et al. found a higher prevalence of autoimmune thyroiditis in discordant monozygotic (27%) and dizygotic non-bipolar co-twins (17%) and matched healthy control twins (16%).[3] In the study's total sample of 51 bipolar and 35 control twin pairs, the pairwise concordance rate for positive thyroperoxidase antibodies (TPO-Abs) in monozygotic twins was 50% compared with 20% for dizygotic twins.[3] This seems to suggest that increased TPO-Abs levels are related to the genetic vulnerability of developing BD and not the disease process. Additionally, existing literature also suggests that there are elevated levels of autoantibodies in patients with mood disorders. A 2002 study by Kupka et al. found that the presence of TPO-Abs was more prevalent in patients with BD (28%) than in population and psychiatric controls (3–18%), irrespective of age, gender, or mood state.[4] Together, these two areas of research suggest that TPO-Abs have the potential to act as a biomarker for the diagnosis of BD.

Concerning heredity, it has also been recognized that BD tends to run in families. First-degree relatives of affected individuals are about 10 times more at risk of BD compared to relatives of unaffected individuals.[5] Twin studies reveal similar findings. Smoller and Finn found that monozygotic twins had a greater concordance (75%) for BD compared to dizygotic twins (10.5%).[5] Despite differences in ascertainment, assessment, and diagnostic methods, this trend has been observed in several twin studies. This provides compelling evidence for the existence of genes that can increase an individual's susceptibility to BD in addition to factors like environment. Furthermore, several research groups are currently focusing on BD candidate genes involved in many neurohormone pathways that have been implicated in BD. Ongoing investigation into increased dopamine, norepinephrine, cortisol levels and the resulting increase in stress and inflammatory responses has proved fruitful in discovering how the functional structure of brain activity is altered.[6]



TREATMENTS

While no cure currently exists for BD, many pharmacological therapies exist which aim to provide continued treatment to reduce symptom burden and increase patient function. The current gold standard treatment for BD is lithium, which serves as a

mood stabilizer drug aimed at treating manic episodes and preventing suicides.[6,8] Alongside lithium, other pharmaceutical treatments, including atypical antipsychotic drugs (e.g. quetiapine), are used to treat manic episodes with varying levels of efficacy.[7] Aside from pharmaceutical treatments, many psychosocial and physiological treatments including cognitive behavioural therapy and psychoeducation are gaining traction as alternative treatments which avoid harmful side-effects.[9] The development of adjunctive psychosocial and pharmacological interventions provides an opportunity for effective individualised long-term stabilisation of BD symptoms.[10]

Furthermore, the isolation experienced by many during the COVID-19 pandemic has increased the burden of mental health challenges.[11] This "hidden pandemic" has thus sparked an interest in championing accessible mental health care with a focus on the use of technology in more personalized care provision.[11] An example of this type of innovation is the introduction of daily monitoring technologies and devices which capture the dynamic nature of BD.[12] This may include tracking behavioural patterns and mood variability to better accommodate for the cyclical nature of the disorder and help guide early intervention into potential future episodes.[12] This may pave the road in assessing prognostic factors and providing more timely treatment to ultimately prevent any adverse events.

AREAS FOR FURTHER INVESTIGATION

A major focus of current BD research involves improving diagnostic methods, with an additional goal of expanding current treatment options and care systems. One avenue of current research involves the use of neuroimaging to identify neural circuit biomarkers for BD.[13] The identification of biomarkers which represent the pathophysiological processes involved in BD could not only support the early and accurate diagnosis of BD, but also help develop targets for future pharmacological interventions and gain a better understanding of its mechanisms.[13] Traditionally undetected or misdiagnosed cases of BD using current diagnostic methods may thus be better detected in cases when patients do not clearly fit DSM-5 criteria or when the distinction between unipolar depression and BD is not clearly evident, particularly during depressive episodes.[14] One identified area for discovery of these biomarkers include genetic factors that alter susceptibility to BD and the limbic system, which has been implicated in emotion and reward processing —areas that are often altered in affective disorders.[13] Furthermore, studies from Versace et al. and Silverstone et al. found that patients with BD had an increased number of abnormalities and hyperintensities in emotion-processing neural circuits compared to those with depression.[15,16] This provides another potential location of biomarkers to help differentiate BD and unipolar depression during depressive episodes.[15,16] Ultimately, the benefits of discovering BD-specific biomarkers are multifold as it will improve diagnostic accuracy, support the development of novel therapies, and potentially help provide a better understanding of the pathophysiology of BD.[14]

Alongside this, many physicians and care providers are advocating for the development of safer and more effective pharmacological treatments, while also broadening available non-pharmacological cognitive and psychological options.[17] Concerning the former, many current therapies for BD, such as lithium-based therapies, provide adequate stabilisation, but also have harmful side effects such as kidney failure.[8,17] Increasing availability of non-pharmacological treatments would require further research on the efficacy of other biological treatments. Particularly, further research on psychological and psychosocial interventions, such as family-focused therapy or dialectical behavioural therapy, may lead to more holistic care for patients with BD.[17-19]

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