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Snips from the Journals

Update on bipolar affective disorder: Hi Bipolar! WAIT !!!! Do I really know you?

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Introduction

The ancient illness, which Kraepelin named manic-depressive psychosis, has developed in the terminology and taxology over the years and is now known as Bipolar Disorder (BD) according to the International Classification of Diseases, eleventh revision (ICD-11). ICD-11 explains several subtypes of bipolar disorder, namely bipolar type I, bipolar type II, cyclothymic, other specified bipolar or related disorders, and bipolar or related disorders unspecified (6A60 to 6A6Z) (1). Bipolar disorder is known to be one of the top ten leading causes of disability in the world (2), with a lifetime prevalence of 1% for bipolar I and II collectively and 2-3% when the whole bipolar spectrum is considered (3). It is estimated that about 40 million individuals in the world have been diagnosed with BD (4).

Interestingly, Nowrouzi et al. (2016) mention two peaks in the age of onset of BD, like in schizophrenia. The most common diagnosis is at 15-24 years of age, where about 70% of patients get the diagnosis, and another peak is at 45-54 years of age (5). Depression is the most frequent first presentation and dominates the BD illness by having about 75% of the total illness burden. Initial depressive presentations also delay the actual diagnosis and treatment of BD by about nine years (4). Apart from that, personality traits, substance use disorders, non-specific symptomatology and inability to identify mood elevations also contribute to the delayed diagnosis of BD (3).

Studies have found that more than 50% of patients do not adhere to treatment, and there is a reduction in life expectancy in about 12-14 years with a 2-fold increase in cardiovascular mortality. Rates of relapse are found to be high despite treatment (6). Prevalence of tobacco smoking (45%), metabolic syndrome (37%), obesity (21%) and type 2 diabetes (14%) also contribute to the increased mortality in BD. There is an annual suicide rate of 0.9% in BD, where 15-20% of patients die by suicide, being the psychiatric disorder with the highest rate of completed suicide (4,7,8). Two-thirds of people do not return to work in the year after hospitalization due to a manic episode (9). Poverty, homelessness, and incarceration are commonly associated with the BD diagnosis (10).

Although BD has existed for many years, we are yet to understand it completely. Many sub-aspects of the disease are yet to be explored. Among these, bipolar disorder in children and older persons, rapid cycling bipolar disorder, cognitive impairment and anxiety are some of the areas that we highlight in this article.

Paediatric bipolar disorder (PBD)

BD has been known to be a mental health diagnosis in adults for over a century. When it was introduced as a legitimate diagnosis in youth in the early 90s, clinicians were skeptical, but in a short period, this perspective drastically changed. New research was helping practitioners to understand the symptoms of pediatric bipolar disorder better (PBD). However, many controversies are still associated with BD among the young, from the diagnostic criteria to epidemiological research to management.

During earlier days, severe irritability, anger outbursts and ultra-cycling affective episodes characteristic of 'mixed states' in adult BD were considered defining features of PBD. However, there has been a marked change in this criterion in the recent past (11). DSM-5 emphasises the presence of unequivocal euphoria and episodic course as peculiar features in pre-pubertal BD and the longitudinal clinical observation before the diagnosis. The irritability in mood has been recognised in a new diagnosis, namely disruptive mood dysregulation disorder (DMDD), which is not a BD diagnosis and is more common than the BD diagnosis.

Experts suggest that a definitive diagnosis should not be made in childhood before puberty and conceptualise this probable clinical presentation as 'pre-pubertal miasma' or a syndrome rather than BD. Also, when making the diagnosis of 'adolescent bipolar disorder' in post-puberty, to be more cautious than in adults (12).

The epidemiological studies that have estimated the prevalence of PBD have been criticised for many reasons. Earlier studies show the prevalence of BD spectrum as

high as 4% in the less than 18 years age group, while the prevalence of adults with BD showed only 3%. With time, researchers criticised the methodological errors in 'case identification' and issues in sampling (prevalence becomes high in juvenile centres) in PBD studies (12). Experts later clinically identified that there were conditions like obsessive-compulsive disorder, attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder, anxiety, depressive disorders or conduct disorders, which were misidentified as BD.

Bipolar disorder in old age

In the recent past, more attention was given to Older Age Bipolar Disorder (OABD) as a complex subgroup due to the increased risk of physical comorbidities, cognitive impairment, poor psychosocial functioning and premature death associated with this condition. The International Society of Bipolar Disorder (ISBD) established the OABD task force and the Global Aging and Geriatric Experiments in Bipolar Disorder (GAGE-BD) project to survey this special form of BD.

In the current terminology, OABD refers to patients with BD aged 50 years and over (13). However, there are two other terminologies used, namely, Late Onset Bipolar Disorder (LOBD), where BD onset is ≥40 years and Early Onset Bipolar Disorder (EOBD), where the illness onset is <40 years (14).

Evidence for OABD from the GAGE-BD project is emerging, but some are at the preliminary level (14). The following are some of the key findings of the project.

- There is no distinction between BD-I and BD-II in EOBD and LOBD.
- There is no difference in the severity of manic and depressive symptoms in EOBD and LOBD.
- Mixed symptoms (e.g. simultaneous depressive and manic symptoms) are common in OABD, which is associated with worsened functionality.
- The female sex is associated with higher levels of anxiety, hypochondriasis and psychiatric hospitalisations and the male sex is associated with increased substance use disorders.
- On average, two or more physical comorbidities are present in OABD, so it is important to screen for cardiovascular risk factors and physical comorbidities and pay attention to lifestyle modifications.
- Cardiovascular diseases and some forms of cancers are increased in OABD.
- Lithium is effective and safe as a maintenance monotherapy in OABD, and it is associated with less depressive symptoms, less rapid cycling and fewer cardiovascular comorbidities compared to non-lithium users. Lithium users have also shown better cognitive functions than nonusers.
- Individuals with OABD and on antipsychotics have more severe illness and frequent hospitalisations.
- There is low-quality evidence for nutritional interventions (e.g. Vitamin D and B12) and improvement in cognitive, affective and overall outcomes in OABD.
- The OABD treatment plan should aim to improve personal and social functioning and quality of life.

However, these data are preliminary, and much information is needed to manage OABD.

Rapid cycling bipolar disorder

According to the ICD-11, rapid cycling bipolar disorder (RCBD) has been defined as having at least four distinct mood episodes (major depressive, manic, hypomanic, or mixed episodes) during the previous twelve months in a person with bipolar I or II disorder (1). It can be considered a discrete BD pattern with a substantially increased illness burden. Patients with RCBD have an early age at onset, a longer course of illness, greater episode burden, higher rates of substance abuse, increased suicidality, higher physical health issues and poorer psychosocial functioning (15). The lifetime prevalence of RCBD ranges from 26% to 43% in patients diagnosed with BD (15,16). Female sex, concomitant hypothyroidism and being treated with antidepressants are commonly associated factors with this condition (17), while childhood maltreatment and genetic predisposition are being discussed as potential associations (16).

The detection and management of RCBD is often a significant clinical challenge to psychiatrists. Though the evidence is scarce, there is a broad consensus that the treatment response is relatively poor in RCBD compared to non-RCBD (15). For example, RCBD is a predictor of poor response to lithium maintenance treatment (18). New evidence suggests that patients with RCBD have to be treated with more medications and higher doses compared to non-RCBD patients (19). However, the 2023 updated National Institute for Health and Care Excellence (NICE) guidelines recommend using the same therapeutic interventions used in non-RCBD patients in the management of RCBD as there is no conclusive evidence for the treatment of RCBD differently (20). In contrast, The Maudsley Prescribing Guidelines in Psychiatry recommend a step-wise treatment strategy for RCBD broadly based on the findings of systematic reviews (21). This includes withdrawing antidepressants, evaluating and managing precipitants (thyroid dysfunction, alcohol use and external stressors, etc.), optimising mood stabilisers guided by plasma levels, combining mood stabilisers, and using adjunctive treatment options such as aripiprazole, olanzapine and quetiapine. In a recent systematic review and meta-

analysis, Strawbridge et al. demonstrated that quetiapine has a consistently large effect size across outcomes in managing RCBD (15). In addition to the pharmacological management options, data concerning the role of electroconvulsive therapy, hormonal treatments and specific psychotherapies in the management of RCBD are limited to make conclusive recommendations.

Cognitive impairment

Cognitive impairment in schizophrenia is a well-established association. However, recent studies are also emerging to explain the cognitive impairment in BD. Although many findings are preliminary, it is worth highlighting this aspect as evidence postulates that cognitive functioning in BD predicts future general functioning better than affective symptomatology. It is also postulated that cognitive functioning is associated with social and occupational functioning. The cognitive impairment in BD is found to be persistent in euthymic states (22), and there is significant cognitive impairment in patients with recurrent episodes compared to patients with a single episode (23). Although the early studies explored cognition and emotional regulations separately, the newer studies have found that the two are intricately linked, and the executive functions are mainly affected in the BD (24).

Currently, there are only few studies showing management options for cognitive impairment associated with BD. In their randomised control trial, Miskowiak KW et al, in 2021 found that cognitive remediation (also used in schizophrenia) shows the most consistent cognitive benefits, and pharmacologically, modafinil and lurasidone have early positive results (25). Recent studies have also shown the association between executive functioning and emotional regulation. More studies are underway to improve working memory (which is a part of executive functioning) with the aim of improving emotional regulation and cognition (26).

Anxiety

Several longitudinal studies conducted over the past three decades showed that anxiety disorders are seen in nearly half of bipolar patients (27,28). Several meta-analyses of the lifetime prevalence of anxiety disorders among adults with bipolar disorder yielded consistent results ranging from 41% to 47% (28). Among anxiety disorders, panic disorder had the highest lifetime prevalence (17% to 22%), followed by generalised anxiety disorder (13% to 20%), social phobia (13% to 20%), specific phobias (11%) and agoraphobia (8%) (28). Considering this significant association, DSM-V and ICD-11 classification systems encourage clinicians to identify anxiety symptoms in bipolar patients and specify using the 'with anxious distress' and 'with prominent anxiety symptoms' specifiers, respectively, to plan treatment and monitoring (29).

The presence of comorbid anxiety disorder in bipolar patients is associated with more adverse consequences, such as having more frequent and severe depressive episodes, longer duration of illness, increased substance abuse, higher rates of suicidal attempts, and greater likelihood of treatment nonresponse (29-31). Though there is a significant influence of anxiety symptoms on the course and outcome of bipolar disorder, the identification and effective management of anxiety disorders in bipolar patients often remain neglected.

Studies concerning bipolar disorder comorbid with anxiety disorders largely focus on demographic factors, and there are limited interventional studies to guide treatment strategies in such patients. There is a considerable risk of using standard treatments for anxiety disorders, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) in bipolar patients, due to the risk of mood destabilisation and manic switch. In general, mood stabilisation is the priority over addressing anxiety disorders in bipolar patients. Following the initial standard treatment with second-generation antipsychotics and mood stabilisers, antidepressants can be used to manage anxiety symptoms with caution and close monitoring (32).

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