AFFECT

Souvenir-cum-Scientific Update for the 29th Annual Conference of the Indian Psychiatric Society, Assam State Branch (IPSASBCon 2019)

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No. DME/ 15355 Dated: 03 -10-2019

MESSAGE

I am highly glad to know that Department of Psychiatry, GMC, Guwahati and Psychiatrists of Guwahati is going to organize the 29th Annual Conference of Indian Psychiatric Society, Assam State Branch on 12th & 13th October 2019 at Srimanta Sankardeva Kalashetra with a theme "Bipolar Disorders-Evolving concepts and Paradigms".

I hope the discussions and deliberations as well as the exchange of views and experiences of faculties and delegates from different corner of the country would create a good academic environment for the Psychiatrists of Assam to learn the latest advances in the technology made in the field of Medical Education and Research.

I believe that the Scientific Book to be published on the occasion of this conference will reflect various aspect of Psychiatry & Mental Health with its latest advances.

I wish a grand success of the Conference.

(Prof. A.K. Barman)
Director of Medical Education, Planning & Research, Assam.

Message from the President

It gives me an immense pleasure to welcome you to the 29th Annual Conference of IPS, Assam State Branch to be held at Guwahati, hosted by Department of Psychiatry, GMCH and Guwahati Psychiatry Club on 12 and 13th October 2019.

I am happy to know that keeping with traditions there will be an Orations in the name of "Dr. Noni Bordoloi"- Doyen of Psychiatry of Assam. There will be award papers, in name of Professor Indreswar Dutta and other academic activities. The organisers have planned a workshop on EEG and Essay writing competition and Quiz competition among school and college students, to create awareness about mental illness among youth and society.

The theme of the conference is "Bipolar disorders - Evolving concepts and paradigms". The evolution of the concepts of bipolar disorder is an ongoing process. The roots can be found in the work of Araeteus of Capadocia, who assumed that melancholia and mania were the two forms of the same disease. The modern understanding of bipolar disorder begin in France through the work of Falret (1851) and Baillarger (1854).

The pivotal concepts of Emil Kraepelin changed the basis of psychiatric nosology, and Kraepelin's unitary concept of manic depressive insanity was largely accepted. Kraepelin and Weigandt's idea of mixed state laid the cornerstone of this unitary concept. After Kraepelin, however, the ideas of Klaist and Leonhard, as well as work of Angst, Perri's, Winokur, emphasised the distinction between bipolar and unipolar depression.

The Organising Committee has tried their best to make this conference a memorable one. I hope all of you will enjoy the academic activities, and be a part of this conference.

Wishing you all the best in this autumn festival from the core of my heart .....

Long live IPS, Assam State Branch!

Dr. Suresh Chakravarty; President, IPS, ASB

Message from the Honorary Secretary

I am glad to know that the 29th annual conference of the Indian Psychiatric Society, Assam State Branch is being organised by the Department of Psychiatry, Gauhati Medical College and Psychiatrists of Guwahati, Assam at the Srimanta Sankardeva Kalakshetra, Guwahati under the able leadership of Dr J Das and Dr U Bora on the 12th and 13th October, 2019.

Bipolar disorder is one of the major psychiatric disorders affecting a major population with equal prevalence among men and women. In recent times there has been a considerable rise in bipolar spectrum disorders especially among the youth. The theme of this year's conference "Bipolar Disorders - Evolving Concepts and Paradigms" is significant in the practice of psychiatry as this mental health disorder tends to run a chronic course and proper management of the patient is very important to reduce morbidity and disease burden in the affected person and their families.

I am sure the discussions and deliberations in the conference will be of great benefit to the delegates in the optimum management of their bipolar patients. I convey my best wishes to the organising committee for the grand success of the conference.

Long live IPS!

Long live IPS, Assam State Branch!

Nahid S Islam
Honorary Secretary
IPS Assam State Branch
(2018-19)

Message from the Organising Committee

Dear Esteemed Members,

Greetings from the Organising Committee of 29th Annual Conference of Indian Psychiatric Society Assam State Branch..!

At the onset, we thank the office bearers of IPS Assam State Branch 2018-2019 for giving us the responsibility of hosting 29th Annual Conference of the society. With the guidance of the Senior Psychiatrists of Guwahati, we have been trying our best for a successful conference. This year, along with the regular scheduled programme of the conference, we have organised an "All Assam Essay Writing Competition" among the class 9 to 12 standard students and "All Guwahati Quiz Competition" among the class 11 & 12 standard students as social awareness initiatives. An EEG workshop is also planned which should be beneficial to the PG students and young Psychiatrists. We are quite confident about the standards of the scientific deliberations by our guest speakers which surely will be enriching our understanding about Bipolar Disorder. Our editorial team lead by Dr. Shyamanta Das has done painstaking work of collecting articles and doing the editing for this conference commemorative book. Our heartfelt thanks to the team. We must thank all the members of the subcommittees of the organising body without whose help organising the conference would not have been possible.

But, whatsoever may be the effort, there will certainly be some glitches and nothing will be fruitful without your participation and cooperation.

We welcome you all and hope for your whole hearted participation for a successful conference.

Thank you.

Long live Indian Psychiatric Society..!
Long Live Indian Psychiatric Society Assam State Branch..!

Dr. Jayanta Das, Organising Chairperson
Dr. Utpal Bora, Organising Secretary

EDITORIAL

Bipolar disorder: evolving concepts and paradigms

Shyamanta Das, Uddip Talukdar, Dipjyoti Bora, Devyani Borkataki

This year (i.e. 2019), the Open Journal of Psychiatry & Allied Sciences (OJPAS®), formerly Dysphrenia, completes a decade of publication.[1] During the period, the journal published several articles on bipolar disorder.

Bipolar disorder is predominantly a disorder of mood or affect. But, cognitive symptoms are not uncommon. Mandal *et al.*[2] described a patient with symptoms of both these domains, raising the question whether it was a chance association or the risk factor had a shared genetic linkage. Cognitive dysfunction here was similar to frontotemporal dementia.

Muraleedharan *et al.*[3] presented the case report of an 88-year-old man having mania. It is a challenge in the elderly to make a diagnosis of primary psychiatric disorder. Here, not only secondary causes were ruled out but also low-dose of olanzapine helped in successful management.

Nath[4] presented a case of bipolar affective disorder where the 19-year-old boy student had manic symptoms with psychotic features and was successfully treated with divalproex and lorazepam as inpatient. Sharma[5] also reported a case where the patient was a 25-year-old man having bipolar affective disorder, current episode manic with psychotic symptoms.

Clinical characteristics in the form of prodrome can signify impending mania and may be target of early intervention. Motichand *et al.*[6] reported 58.8% patients of mania with psychotic symptoms having prodromal symptoms. Irritability, anxiety, and sleep disturbance were the prodromal symptoms. Moreover, patients with prodrome has higher hypomanic/depressive temperaments.

Hallucination is hallmark of psychosis. Bhuyan *et al.*[7] studied hallucination in mania, schizophrenia, and other psychoses. Hallucination in mania was lesser (13.33%) than schizophrenia (66.67%) and other psychoses (53.33%). In addition, mood incongruency was more in schizophrenia than in mania and other psychoses.

Bhuyan *et al.*[8] compared the mood, motor, and speech abnormalities of mania with those in schizophrenia and other psychotic disorders like acute and transient psychotic disorder, persistent delusional disorder, and unspecified nonorganic psychotic disorders. Expansive and irritable mood were high in mania. Less sleep and behaviour that was socially embarrassing did not differ in mania from the rest.

Life events precede mood symptoms. Rathee and Kumar[9] compared and found that patients with mood disorder scored higher than healthy controls. In relation to mania, depressive patients had more stressful life events. Ghosh and Dutta[10] also found close

relation of major life events with depression and mania, in relation to schizophreniform psychoses and schizophrenia. In mood disorders, bereavement as a life event was specially linked.

Barman and Chakravortty[11] assessed and found no significant difference as far as stress of family members were concerned in relation to patients suffering from schizophrenia or mood disorder. Twenty two per cent each had severe and mild stress while the rest 56% family members has moderate level of stress.

In an interesting piece of work, Gupta[12] highlighted the association of bipolar disorder, depression, violent behaviour, and suicidal ideation with aggressive lowering of cholesterol by using medications. Serotonin is the chemical responsible for mood. Low serotonin results from low cholesterol. "Dietary supplements like coenzyme Q10 (CoQ10), omega-3 fatty acids, niacin, and physical activity like Yoga" can be beneficial alternatives under the circumstances.

Sahu[13] approached a patient who had his relationship with family strained because of bipolar disorder. Using family-focused treatment (FFT) and interpersonal and social rhythm therapy (IPSRT), positive outcome was achieved. Thus, integration of psychosocial treatments with pharmacological treatments can be an effective regiment.

Das[14] wrote about the role of emotion in human life. She also discussed the importance of affect in not only communication and perception but also in decision making, attention, and memory. The relation of mood disorders with creativity was explored by Ghosh.[15]

It is worth noting here about the cover of the July-December 2016, Volume 7 Issue 2 of the journal (Figure 1): an acrylic on paper by

Pradip Kumar Thakuria, titled "Mood".[16] Another cove that deserves mention in the one of the January-June 2012, Volume 3 Issue 1 (Figure 2): titled "Rapid cycle", it is a collage of photographs by Simanta Talukdar "taken on alternate evenings during the first half of the lunar cycle".[17]

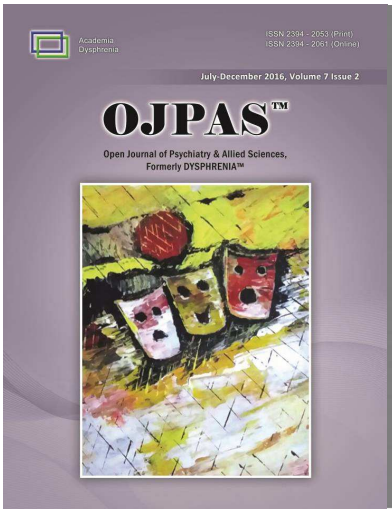

Figure 1: The cover of the July-December 2016, Volume 7 Issue 2 of the Open Journal of Psychiatry & Allied Sciences (OJPAS®), formerly Dysphrenia.

Figure 2: The cover of the January-June 2012, Volume 3 Issue 1 of the Open Journal of Psychiatry & Allied Sciences (OJPAS®), formerly Dysphrenia.

This ten-year-old journey of the journal that includes publications on bipolar disorder, culminates in this editorial of 'Affect', the souvenir-cum-scientific update to eternalise the 29th Annual Conference of the Indian Psychiatric Society, Assam State Branch (IPS-ASBCon 2019) held on 12 and 13 October, 2019 at Guwahati. This International Standard Book Number (ISBN) publication (978-81-

935934-3-1) contains 11 chapters on the theme of the conference, "Bipolar disorder: evolving concepts and paradigms".

Happy reading!

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CHAPTER I

Conundrums of bipolar disorder

Vijay Gogoi

Introduction

From the first description of melancholia and mania as part of the same disease by Aretaeus of Cappadocia, in the first century AD, to the concept of the soft bipolar spectrum by Akiskal, the nosological and conceptual evolution of bipolar disorder (BD) has been a continuous process. Over the years, International Statistical Classification of Diseases and Related Health Problems (ICD) and Diagnostic and Statistical Manual of Mental Disorders (DSM) have incorporated changes in their classification system for the diagnosis of this disorder. However, even after two centuries, controversies and debates still surround this severe mental disorder concerning classification, diagnosis and treatment strategies. Compared to other psychiatric disorders, research on BD aetiopathogenesis, prevalence estimates, treatment strategies were lacking until two decades ago.[1] BD presents as an emerging pathology from the scientific research perspective and substantial morbidity from a clinical perspective.

The present article reviews the significant issues of contention surrounding this disorder.

Bipolar disorder as dichotomous vs spectrum concept

By the end of the 19th century, many authors had described the connection between mania and melancholia. Falret gave folie circulaire (circular insanity) and Baillarger folie à double forme (dual-form insanity) in 1851, describing alternating forms of mania and depression. Kahlbaum too supported Griesinger (1845) who made observations that change from melancholia to mania was standard. Despite these observations, most clinicians at that time considered mania and melancholia to be separate entities. It was Emil Kraepelin in 1899, who adopted the unitary view and brought depressive states, mania and circular insanity under the rubric of manic-depressive illness (MDI). This unification concept gradually moved to different parts of the world which is evident in the DSM and ICD classification systems.

In 1957, Karl Leonhard established polarity in MDI, the unipolar and bipolar forms. According to his classification, unipolar forms are pure forms of illness (pure mania, pure euphoria, pure melancholia, pure depression) and bipolar forms are polymorphs (manic depressive illness & cycloid psychosis).[2] However, in 1980, this idea of Leonhard was revised, and the MDI concept was officially divided by DSM III into BD and major depressive disorder (MDD), motivated by the professional political preferences of the American Psychiatric Association (APA).[3] The MDD category now included neurotic depression, which was different from unipolar depression, in not being severe, not recurrent, more anxiety symptoms and not episodic. The term "illness" was replaced with "disorder", many types of depression included in MDD, and the

concept of BD became narrow. Bipolarity was determined by the presence or absence of manic episodes, rather than the episodicity of mood symptoms in MDI.[4]

Later, researchers such as Hagop Akiskal from the United States and Koukopoulus from Rome found many patients who did not fit into the dichotomous unipolar/bipolar category. The observations which led to the proposal of the spectrum concept were the atypical presentation in depressive patients, presence of mood temperaments, non-responsiveness to antidepressants and presence of mixed states.[4] Similar observations were also made by Goodwin who found that depression did not run in families separate from mania and lithium was effective for depression too. With further advancements in psychopharmacology, genetic and neurobiological studies, the unipolar/bipolar dichotomy gradually weakened, and spectrum concepts evolved. Bipolar type II with hypomania and mixed states were accepted in DSM. Other concepts, such as antidepressant-induced hypomania, family history of BD, presence of mood temperaments were also suggested as part of bipolar spectrum concept.

The years leading up to the publication of DSM-5 has seen much controversy regarding the classification of mood disorders. Despite recommendations for inclusion of bipolar spectrum disorder definition in the nosology, by a task force experts convened by International Society for Bipolar Disorders (ISBD), DSM-5 refused to consider the idea.[5] Strakowski *et al.* point out that currently the definitions of the bipolar spectrum are varied and evidence that adoption of such concept will lead to improvements in treatment and understanding of the aetiopathogenesis lacks.[6] To settle this conundrum, National Institute of Mental Health (NIMH), Research Domain Criteria (RDoC) has adopted a scientific psychiatric

nosological approach[7] by viewing mental disorders through five relevant domains: negative valence systems; positive valence systems, cognitive systems; system for social processes and arousal regulatory systems.[8]

Borderline personality vs soft bipolarity

Broadening the concept of BD to spectrum concept has widened the challenges for diagnosis and research by the inclusion of a more heterogeneous population.[9] While distinguishing personality from a mood disorder, borderline personality disorder (BPD) is usually discussed along with bipolar spectrum concept mainly due to its mood lability and impulsivity criteria. Mood temperaments like hyperthymia and cyclothymia of bipolar spectrum, which are chronic and not episodic could be seen as character flaws rather than affective instability and diagnosed with personality disorder.[10] Others propose that BPD is essentially an ultra-rapid-cycling disorder.[11] In addition to symptom overlap, chaotic fluctuations in mood and behaviour before a diagnosis of BD,[12] marital discord, promiscuity, poor work performance and substance use could be understood as psychosocial complications of mood disorder.[13] Hence, several authors argue that BPD would be better diagnosed and treated if they were considered to have a BD.

However, the constructs of BPD and BD are quite different from each other with respect to their conceptual evolution: BD is a disease of the brain and body with standard medical concepts, genetics and biology whereas BPD is a Freudian interpretation of dissociative symptoms with history of early sexual trauma, poorly understood biology and less genetic evidence.[4] Features of BD include a family history of bipolar illness and severe episodic course while BPD includes child sexual abuse and repeated non-suicidal

self-injury.[14] In a literature review of the relationship between BD and BPD and their diagnostic concordance,[15] found that obsessive-compulsive and histrionic personality disorders were more frequently diagnosed in patients with BD, and each disorder is diagnosed independently of the other in the vast majority of the cases.

Diagnosing bipolar disorder in children

Early diagnosis and management of BD in children are of particular importance to avoid an unfavourable outcome. Both under-diagnosis and over-diagnosis can have negative consequences. Recent years have seen an increasing diagnosis of BD in children, particularly in the US. This increase in diagnostic rates has led researchers to disagree about the diagnostic labels for some of the behavioural symptoms in children. While on the one hand, some argue that BD was not diagnosed in children earlier due to lack of knowledge and different presentation in children, others defend that the increase is due to a redefinition of mania, a more palatable diagnosis for parents.[16] Due to the overlap of symptoms across disorders (oppositional defiant disorder, conduct disorder, attention deficit hyperactivity disorder [ADHD]), difficulty in describing symptoms and rapid neuro-cognitive development, diagnosing BD in children is challenging.

Classical BD in children is well described in the literature with symptoms of episodic irritability and elation. The subtypes BP-I, BP-II and cyclothymia, all describe a distinct period of persistently elevated, expansive or irritable mood, albeit with varying levels of severity. They have a frequent family history of the disorder and high continuity over the lifetime.[17] However, the debate in the paediatric age group is about the episodicity criterion, where a group

of children presents with chronic non-episodic irritability presenting with easy annoyance and temper tantrums.[18] Moreover, identifying elated mood or irritability as part of BD is challenging to interpret in children as, "normal children display numerous behaviours and beliefs that would be considered pathological by adult standards".[19] This group of children, either does not fit into any diagnostic category or receive a different diagnosis in different settings. Over the years, researchers have discussed this group either as a developmental presentation of BD, as a severe form of ADHD, or as a new diagnostic entity.[18]

A broad concept of severe mood dysregulation (SMD) with core features as persistent negative mood, marked hyperarousal, and chronic non-episodic irritability was put forward by Leibenluft *et al.*[20] in 2003. Further studies on this have found that SMD does increase the risk of depressive and anxiety disorders but not BD.[21] Although both bipolar and SMD groups display neurophysiological and neuropsychological deficits, they differ in their neural mechanisms,[22] family history, and lifetime course which negates the idea of being a developmental presentation of BD. In line with SMD, DSM-5 came with the diagnosis of disruptive mood dysregulation disorder (DMDD) to fit these children with chronic irritability, albeit with criticism of pathologising healthy children.[23] DMDD includes a persistently irritable mood for 12 months, recurrent temper outburst in two out of three settings (in school, at home, with peers).[24] Only longitudinal studies in the future will clarify how well this new diagnostic entity serves the purpose.

Use of antidepressants in bipolar disorder

Since the first conception of BD, depression seems to be the determining polarity for classification and categorisation of the

illness, defining mood stabilisers, and determining the course and outcome of the illness. Patients spend more time being depressed than manic or hypomanic.[25] After the division of MDI into MDD and BD, efficacy and safety of use of antidepressants in unipolar depression has been reasonably established. However, antidepressants for bipolar depression and bipolar spectrum disorders are a contentious issue for years.

Distinguishing bipolar from unipolar depression is difficult because the range of symptoms of depression does not differ much. Apart from efficacy and side effects, treatment of depression with antidepressants in BD is of further concern because of the potential threat to switching into mania or hypomania and induction of rapid cycling.[26] At present, there is no robust literature to support the use of antidepressants, either as monotherapy or adjunctive to mood stabilisers in this disorder.[27] Moreover, the systematic treatment enhancement program for bipolar disorder (STEP-BD) study has convincing evidence that newer antidepressants are not particularly effective.[28]

Treatment emergent affective switch (TEAS), earlier called switching into mania/hypomania, has been observed with the use of antidepressants. Much of the literature arose particularly with the use of older antidepressants, such as tricyclic antidepressants. However, some argue that it is challenging to diagnose TEAS as a significant number of individuals of BD follow a naturalistic course from depression to mania/hypomania,[26] and depression itself increases the risk for mania in BD.[29] Hence, some authors have provided an arbitrary definition of TEAS as the emergence of a syndromal mania/hypomania within eight weeks of either the initiation of the antidepressant or an increase in its dose.[30] Although short-term studies of antidepressants with mood stabilisers[31] and

antidepressants as monotherapy[32] found similar switch rates with placebo, evidence that mood stabilisers diminish the risk of TEAS is lacking.[33] Of the antidepressants, selective serotonin reuptake inhibitors (SSRIs) and bupropion was found to confer the lowest risk of switching.[34] Induction of rapid cycling or cycle acceleration with antidepressants has been documented for older antidepressants. Very few prospective studies have shown a link between rapid cycling and the use of modern antidepressants.[35]

Second generation antipsychotics for maintenance therapy

BD characteristically has recurrences,[36,37] which warrants prophylactic treatment to prevent further episodes of depression and mania/hypomania. Meta-analysis and placebo-controlled trials have clearly shown the benefits of lithium in preventing manic episodes. However, discontinuation rates of lithium were found to be high due to its adverse effect profile and less controlled depressive episodes.[38] Evidence for the use of antipsychotics in BD, mostly for acute mania is abundant. Trials have studied the efficacy of antipsychotics, starting with first-generation haloperidol, to second-generation olanzapine, risperidone, clozapine, quetiapine, aripiprazole, ziprasidone, paliperidone, and long-acting antipsychotics, either as monotherapy or adjunctive therapy. Almost all these antipsychotics in the studies prevent further relapses of mood episodes. However, most of these studies had a low follow up rates, with participants excluded from the study due to relapses.[38]

Moreover, these studies adopted an enriched design, meaning that the respondents have been preselected to respond to the antipsychotic. They were initially stabilised by the antipsychotic and then selected for randomisation. Hence, as Ghaemi and Strakowski[39] mention, it is difficult to comment on whether the

control group has re-experienced the manic symptoms of the previous episode or is that a new episode after stopping the neuroleptic. It would be more convincing if the opposite polarity episodes were prevented in the placebo group. Most guidelines suggest the use of lithium as first-line in maintenance treatment[40] with selective use of antipsychotics based on individual characteristics, efficacy, tolerability, and side effect profile.

Mood stabilisers for maintenance in bipolar disorder

Recurrent mood episodes cause various changes in the brain, such as a decrease in levels of brain derived neurotrophic factor, increase oxidative stress, decreased prefrontal volumes, increased amygdala functions, increase in a load of short telomeres and cognitive dysfunction.[41] Prevention of relapses and recurrences of mood episodes should be the primary aim of maintenance therapy. Choosing mood stabilisers for maintenance therapy is a clinical dilemma. The BALANCE study suggests that monotherapy with valproate should be avoided as a first-line maintenance treatment.[42] Lithium monotherapy was advised as first-line with the addition of valproate if no improvements were observed with lithium alone. Many other studies have suggested the use of combination therapy for maintenance in BD targeting full symptomatology of the disorder. Combination therapy allows the use of lower and better-tolerated doses of medications.[43] However, such patients require regular assessment for tolerability issues and adverse effects.

Conclusion

Given the morbidity and mortality associated with mood disorders, it becomes necessary to settle the contentious issues related to its classification and management. The current nosological system has

not been able to address the various clinical types observed in longitudinal, meta-analytical and observational studies, leading to either overdiagnosis or more often underdiagnosis of BD. At present, the diagnostic status of the spectrum concept is still uncertain, and only longitudinal studies would further its advances in understanding the illness. Because mood and temperamental behaviours are generally distributed in the population with extensive overlap of symptoms, it becomes imperative to distinguish between the mood disorders and disorders of personality for proper management strategies. Similarly, to avoid incorrect labelling and prevent adverse effects of psychotherapeutic agents, longitudinal studies should conclusively demonstrate the clinical features, course, prognosis, and outcome for various childhood behavioural disorders.

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CHAPTER II

The neurobiology underlying bipolar disorder

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Bipolar disorders could well be said to be mankind's oldest mental illness. As early as the first century AD, Greek physician Arataeus of Cappadocia gave accounts of mania and depression as being part of the same illness. Much later, Hippocrates gave a scientific basis to this disorder. Later, French scientists Falret and Baillager described them as a separate entity- a continuous cycle of depression, mania with intervening periods of normalcy.[1] Building on this, Emil Kraepelin's concept of manic depressive illness in the beginning of the 20th century influenced psychiatric thinking all over the world.[2] Shortly afterwards, German scientists Wernicke, Kleist, and Leonhard described various forms of affective disorders which were supported by the studies of Angst and Perry.[2] Bipolar disorders are now well defined by the ICD-10 and the DSM-5, after dynamic changes in a clear delineation of the disorder.

Bipolar disorders (both type I and type II) affect up to two to three per cent of the general population worldwide. The mean age of onset of bipolar disorders varies between 20-30 years. It appears to

have a roughly equal distribution between the two genders. A meta-analysis of 25 studies has found the lifetime prevalence of bipolar disorder-I to be 1.06% and that of bipolar disorder-II to be around 1.57%. Quite a number of studies have investigated the role of sociodemographic factors on the rates of bipolar disorders and have found some evidence of higher rates in those belonging to lower socioeconomic status, unemployed, and unmarried groups. However, strong evidence is still lacking, as the findings are limited by small sample sizes and lack of replication. Bipolar disorder is associated with a higher rate of premature mortality- as high as 15% people with bipolar disorder die by suicide and is now considered to be the sixth leading cause of disability in the world.[2]

With the massive prevalence of bipolar disorder worldwide, its aetiology still remains to be well understood and manages to confound researchers till today. Over the past few decades, there has been an expansive base of studies venturing into the possible genetic, developmental, neurophysiological, and neuroanatomical factors that could play a role in the pathogenesis of bipolar disorders. Risk and vulnerability factors, probable interplay of gene and environment have also been studied extensively. Of late, neuroendocrine mechanisms and changes in the intracellular mechanisms have also been found to play a role in dipolar disorders.

This article humbly aims to summarise the burgeoning research into the neurobiology of bipolar disorders. Relevant literature were identified by conducting searches in PubMed with the keywords "bipolar disorder", "neurobiology", "neural basis", apart from consulting recent editions of relevant textbooks. The results were reviewed with a focus on recent evidence and further individual studies were then expanded. As the neurobiology of bipolar

disorders becomes further defined, treatment is expected to make advances towards a more targeted therapy approach.

Genetic basis of bipolar disorder

Of late, evidences have suggested that bipolar disorder is inherited in most individuals. In the span of roughly 33 years, from 1967 to 1990, there have been at least six studies of bipolar disorder in twins. The concordance rates for identical twins have been found to range from 20% to as high as 70%, with the heritability estimated to reach as high as 90%. The Genome Wide Association Study (GWAS) has found that bipolar I disorder is characterised by polygenic inheritance, i.e. there are many common variants, with each having a small effect size, causative to the disease. The genetic risks appear to be coalescing into a final common pathway. Recent evidence has found that there is enrichment of single nucleotide polymorphisms (SNP) in multiple pathways: corticotrophin releasing hormone signaling pathway, cardiac beta-adrenergic signaling, phospholipase C signaling, glutamate receptor signaling, endothelin 1 signaling, and cardiac hypertrophy signaling. Despite multiple genetic studies to identify candidate genes, no single gene has been implicated as yet. This is attributed to the relatively small individual contributions, inadequate sample size or to the heterogeneity of the disease. However, studies have found genes involved in brain-specific functions like transmission, cell differentiation, cytoskeleton formation, and stress response to be implicated. CACNA1C gene malfunction, which under normal circumstances codes for the alpha subunit of the L-type voltage gated calcium channel, has been the most often replicated finding. It is associated with cognitive and attention problems, both playing a role in the psychopathology of the bipolar disorder. ODZ4, coding for cell surface protein, is another gene that has been replicated.[3]

There have been many candidate gene studies which have recognised several genes including catechol-O-methyl transferase (COMT), brain derived neurotrophic factor (BDNF), neuregulin-1 (NRG-1), disrupted in schizophrenia (DISC1) which seem to be shared risk factors for both schizophrenia and bipolar disorders. Polymorphisms in genes coding for other monoamine transporters, receptors, synthetic and catabolic enzymes like monoamine oxidase, dopamine transporter, serotonin transporter, tryptophan hydroxylase, D2, D4, 5HT4 and 5HT2A receptors have also been found to be associated with bipolar disorder.[4,5]

Certain studies have also found a relationship between the 66 Val/Met polymorphism of the BDNF gene and disease severity, early adolescent onset, a propensity towards rapid cycling, cognitive and executive function deficits in bipolar disorder.[6-8] The BDNF gene is associated with neuro-resilience, plasticity, and proliferation.

Studies have also found an association between glycogen synthase kinase-3 gene polymorphism and presence of psychotic symptoms and lithium responsiveness.[9] Glycogen synthase kinase-3 is a pro-apoptotic peptide and also found to be acting antagonistically against proteins involved in neuroplasticity, differentiation, and cytoskeletal assembly.

All in all, studies into the role of genes in bipolar disorder have consistently found a complex polygenetic pattern of inheritance. Multiple genes have been found to be involved with small to moderate individual effects. One can firmly say that bipolar disorder is vastly heterogeneous.

Neurophysiological and neuroanatomical changes

The fundamental neuroanatomical and neurophysiological alterations in bipolar disorders have been of keen interest for a century now. Fortunately, advances in structural and functional neuroimaging have made it possible to study and understand the how of the pathophysiology of bipolar disorder.

Bipolar disorders cannot be defined by any single lesion of regional brain dysfunction. Rather, a diverse set of brain structures including the prefrontal cortex, anterior cingulated cortex, subgenual cingulated cortex, hippocampus, amygdala as well as subcortical structures including ventral striatum, thalamus, hypothalamus. However, there has been noteworthy variability in the findings from different studies, which may be accounted for by the heterogeneity of the bipolar disorder. Magnetic resonance imaging (MRI) studies of comparison of cerebral ventricle volumes in healthy controls vs. patients who are suffering from the first episode of bipolar disorder or those who had experienced multiple episodes revealed significantly larger lateral ventricular volume. Also, it was found that the increased volume of lateral ventricles directly correlated with the number of manic episodes the patient had suffered.

Of late, there has been an emphasis on the critical role of two interrelated prefrontal-limbic networks- the automatic/internal emotional regulatory network and the volitional/external regulatory network. The automatic/internal emotional regulatory network involves a duplicative loop consisting of the ventromedial prefrontal cortex, subgenual anterior cingulate cortex, nucleus accumbens, globus pallidus, and thalamus. This network is said to modulate the response of the amygdala to endogenous feelings. The volitional/external regulatory network consists of the ventrolateral

prefrontal cortex, mid- and dorsal cingulate cortex, ventromedial striatum, globus pallidus, and the thalamus. It is involved in modulation of externally induced emotional states, voluntary emotional regulation, and suppression of maladaptive affect. When compared with healthy populations, it has been found that there is alteration of both structure and function of these two networks.[10] Apart from these two networks, the default mode network which comprises of interconnected midline structures like the subgenual anterior cingulated cortex, ventromedial prefrontal cortex, dorsomedial prefrontal cortex, precuneus, and mesotemporal structures has also been implicated in bipolar disorders. It has been found that the interconnectedness of these structures is impaired in those with bipolar disorders.[11]

Furthermore, impaired ventrolateral prefrontal cortex function has been found to be responsible for disinhibited and inappropriate behaviour.[12] Decreased activity of the dorsolateral prefrontal cortex maybe responsible for impaired attention and concentration and compromised executive function.[13] The anterior cingulate cortex also plays a vital role in cognitive-emotional integration. Studies have noted a considerably decreased volume of the anterior cingulate cortex in bipolar patients.[14]

Besides these, various white matter abnormalities have been noted by several imaging studies. One study has found alterations in the white matter tracts connecting the subgenual anterior cingulate cortex with the amygdala-hippocampas complex and frontal lobe-insula-hippocampas-amygdala-occipital lobe complex, when compared to healthy controls.[15]

To summarise, imaging studies have found a definite compromise of the integrity of frontal-subcortical and prefrontal-limbic circuits in

bipolar disorder. This only puts forward a possible organic basis for the cognitive, emotional, and neuroendocrine symptomatology.

Neuroendocrine disturbances

The involvement of the hypothalamic pituitary adrenal (HPA) axis and its alteration in bipolar disorder has long been corroborated across multiple studies. A discrepancy in the cortico-limbic regulation in bipolar disorder results in exaggerated release of corticotrophin releasing factor (CRF) leading to greater adrenocorticotropic hormone and a consequent rise of circulating glucocorticoids. There is also a subsequent amygdale over-activity and compromised hippocampal regulation.[16,17] It has also been observed that glucocorticoid receptors have reduced sensitivity in mood disorders and thus resulting in disruption of the HPA axis and the immune system. It has also been noted that these changes intensify with increasing number of episodes of bipolar disorder.[18]

Excessive activity of the sympathetic nervous system may also be associated with bipolar disorder, as per recent studies. In one study by Grossman and Potter in 1999,[18] extra neuronal norepinephrine levels were found to be elevated in bipolar disorder patients as compared to healthy controls. Decreased parasympathetic activity and increased sympathetic activity may even be acknowledged as a trait marker for bipolar disorder.

Alterations in monoaminergic transmission and GABA, Glutamate system

What led to the growing interest in studies of the biogenic amines was the breakthrough of effective pharmacological treatments for depression and mania. Various pharmacological evidences have accumulated to bring forward the proposition of dopamine

dysfunction in bipolar disorder. It suggests that during mania, there is excessive dopaminergic activity which leads to a dopamine receptor down-regulation, which in turn is responsible for transition into a depressed state.[19] So far, the strongest direct evidence implicating dopamine in depression has come from clinical studies which have found reduced homovanillic acid (a major dopamine metabolite) in the CSF.[20] Manipulation of the dopaminergic system has the potential for modulating the disease itself. Administration of dopamine agonists can lead to development of manic symptoms.[20]

Data from imaging studies, serotonin receptor and reuptake site binding studies, pharmacologic studies have led to conflicting results about the role of serotonin in bipolar disorder. Studies of 5-hydroxyindole-acetic acid (5-HIAA) levels in CSF of bipolar disorder patients have revealed inconsistent results. Both increase and decrease in the levels of 5-HIAA have been reported along with some studies reporting no change.[21] PET studies have shown a decrease in 5-HT1A receptor in raphe and hippocampus-amygdala of brain in depressed patients of bipolar disorder. Another study has also noted reduced 5HT transporter binding in midbrain, amygdala, hippocampus, thalamus, putamen of patients with bipolar depression, not on medications.[22] However, evidence has been largely inconsistent and has been lacking replication.

Studies have ventured into the possible role of gamma aminobutyric acid (GABA) in bipolar disorders and have found increased GABA platelet uptake in patients with bipolar depression and decreased GABA uptake in mania. Contradictory to that, it has been found that glutamate platelet uptake is increased in patients during the course of manic episodes. Also, it was found that altered GABA and

glutamate platelet uptake correlated with the severity of depression and mania respectively.[23]

Glutamate is an excitatory neurotransmitter and has been implicated in mood disorders. Glutamate also acts as a substrate in protein metabolism and also a precursor for glutamine, GABA and glutathione.[19] Studies have also found a significant decrease in expression of the NR1 and the NR2A subunits of the N-methyl-D-aspartate (NMDA) glutamate receptors in the hippocampus.[24] Meta-analytical studies have also found increased levels of glutamate metabolites in the anterior cingulate cortex, prefrontal cortex, parieto-occipital cortex, insula, and hippocampus in bipolar disorder patients. The findings were persistent even in euthymic states of bipolar disorder patients. It has also been found that there are decreased levels of glutamine and glutamate in the hippocampus, amygdala, anterior cingulate cortex, left dorsolateral prefrontal cortex, dorsomedial prefrontal cortex, and ventromedial prefrontal cortex of patients with depression.[24] Hence, a likely understanding is that alteration of glutaminergic signals in cortico-limbic structures may be reflective of bipolar clinical symptomatology.

Changes in neuroplasticity and neurotrophin signaling

Among the members of the neurotrophin family, BDNF has been the focus of most studies. BDNF is involved in neuronal maturation, differentiation, synaptic plasticity, and memory consolidation. Apart from various genetic polymorphisms of the BDNF gene that has been implicated in bipolar disorder, studies have found decreased levels of BDNF in bipolar depressed and manic patients. It was also found that low levels of BDNF correlated with severity of depression and mania. Longer duration of the illness, repeated episodes, and ageing has been found to have a

synergistic effect on the decrease of BDNF levels and neurotrophic signaling and an increase in inflammation.[23] However, the role of BDNF needs further elucidation as an increase of BDNF levels in amygdala is associated with addictive behaviours and a negative affect.[23]

Glial cell line Derived Neurotrophic Factor (GDNF), neurotrophin-3, neurotrophin-4/5 have also been found to be altered in bipolar disorder. GDNF is known to be a regulator of neuroplasticity, monoamine and GABA signaling, and microglia activation. While some studies have found reduced GDNF levels in mania that correlated with symptom severity, others have found an elevation of GDNF in mania.[20] A variability of GDNF levels may also be explained by the biological heterogeneity of bipolar disorder. Further studies are needed however, to obtain a more lucid comprehension of the role of GDNF in the pathology of bipolar disorder.

Changes in intracellular signaling cascades

Intracellular signaling pathways interact at various levels leading to formation of complex signaling networks which allow for the cell to receive, process, and respond to information. In the CNS, these pathways are responsible for diverse functions like mood, appetite, wakefulness, etc. Antipsychotics used in the treatment of bipolar disorder most likely rely on the interface with intracellular signaling cascades and the eventual changes that follow like change in gene expression, alteration in neuroplasticity, and neurotransmission.

The phosphoinositide-3-kinase (PI3K) pathway is known to be a general signal transduction pathway, especially for BDNF and also for BCL-2. Again, the glycogen synthase kinase-3 (GSK-3) pathway is also engaged in modulation apoptosis and synaptic plasticity. So, an increase in the activity of the GSK-3 pathway potentiates

apoptosis while decreased activity causes upregulation of BCL-2 and consequently, an enhancement of neuroplasticity and resilience.[25] It has been found that manipulation of the GSK-3 pathway produces both antimanic and antidepressant effects. Lithium is known to inhibit GSK-3 pathway along with valproate, which also indirectly affect the PI3K pathway.[26,27] Thus, there is alteration of the neuroplasticty and cell survival in the mature cells.

An improved understanding of these intracellular signaling pathways is necessary to gather valuable insight about the underlying pathology of bipolar disorder and to devise more effective treatment strategies.

Conclusion

Putting together all available evidence and integrating the current findings for a well-articulated perspective of the neurobiology of bipolar disorder has always been a challenge and still remains so. But one can firmly say that bipolar disorder is a heterogenous condition. The disorder itself comes in two exquisite flavours- depression and mania, and understanding it is a challenge that many studies have now taken up.

Recent findings have coherently emphasized one cohesive understanding of the disease- no single gene, no single pathway or abnormality can fully be implicated in the pathogenesis of bipolar disorder. This only emphasises the complexity of bipolar disorder and with changing perspectives of the neurobiology of the disorder, change in ways of diagnosis and treatment strategies should follow. The varying nature of the disorder requires different treatment modalities which track changes in substrate and the pathophysiological mechanisms of the disease.

To make noteworthy strides towards better treatment, there needs to be an understanding of the dynamics of the disorder and replacement of current treatment with modalities that consider all perspectives of the pathophysiology of the disease and are equally dynamic while still being integrative.

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CHAPTER III

Neuroimaging in bipolar disorder

Angshuman Kalita

Introduction

Bipolar disorder is one of the most debilitating illnesses in the world and it affects around one per cent of our total population. It puts a huge burden on caregivers financially. It is associated with poor outcome, both clinically and functionally and also increases the risk of suicide in the patients.[1]

Psychiatrists face two major dilemmas while treating patients of bipolar disorder. The first dilemma is the issue of misdiagnosis or late diagnosis as depression can be part of both bipolar disorder and unipolar depression. The second issue is how to initiate and individualise treatment for each patient as early as possible.

DSM-5 (published in 2013) focuses on aetiology-based and pathophysiology-based diagnostic system. For individuals suffering from psychiatric illnesses, it involves a dynamic interaction among genetic, epigenetic, and environmental factors which are called as phenotype. "Endophenotype" or "biomarkers" are closely related to

the disorder's underlying aetiology and pathophysiology. These can be very useful to diagnose and classify complex psychiatric diseases.[2]

If we can identify endophenotypes or biomarkers for bipolar disorders it will serve our two purposes. First, it will diagnose bipolar disorders and also help us to differentiate depression in bipolar disorder and unipolar depression. Second, it will help us to diagnose and identify at-risk individuals.

Use of neuroimaging techniques such as magnetic resonance imaging (MRI), positron emission tomography (PET), and diffusion tensor imaging (DTI) have been exponentially increasing in psychiatric illnesses. These will help us to identify neural system abnormalities associated with bipolar disorder. These will provide direct evidence of disorder-specific abnormalities in neural systems. These abnormalities are endophenotypes associated with bipolar disorder which will help us in our diagnosis.

Underlying pathology in bipolar disorder

One major domain of pathology is instability of mood which may present as symptoms of mania, hypomania, or depression. Another domain is impaired executive control and emotion processing.[3]

Functional neuroimaging studies have shown that networks of subcortical anterior limbic structures are responsible for appropriate emotion processing. These structures are the amygdala, ventral striatum, subgenual (ventral) cingulate, ventromedial prefrontal cortex, anterior hippocampus, and anterior insula.[4]

On the other hand, neural systems responsible for coordinating appropriate executive function are dorsolateral (DLPFC) and

ventrolateral prefrontal cortex (VLPFC)[5] which is closely connected to striatal regions and hippocampus.[6]

This review will first describe the functional neuroimaging studies which will try to elucidate the abnormalities in the neural system responsible for emotion processing and executive control neural system in bipolar disorder. Then it will review most important studies on structural neuroimaging findings in bipolar disorder.

Functional neuroimaging in bipolar disorder

The majority of recent functional neuroimaging studies have used functional MRI (fMRI). Most of the studies are done on patients who are either depressed or manic.

Emotional processing

The most common stimulus to use mood instability and emotion processing is the human face. It carries a lot of information regarding social (age, sex, identity) and affective cues which are used to represent specific emotions in different races and cultures.[7]

Remitted bipolar disorder: These studies are done in a euthymic state or remitted state of bipolar disorders. One study showed increased subcortical (amygdala and ventral striatal) activity to mildly happy (positive stimuli) and intense fearful expressions (negative stimuli).[8]

Another study which used emotional words instead of faces has revealed widespread decreases activity in subcortical and prefrontal cortical areas in remitted patients.[9]

From this inference can be drawn that remitted individuals with bipolar disorder process emotional facial expression differently from other emotional stimuli.

Bipolar depression: A small number of the studies have reported that in patients with bipolar patients with depression there is increased amygdala and ventral striatal activity to emotional facial expressions[8,10] and visualised scenes (captioned photographs).[11]

Also, these patients have demonstrated increased amygdala and ventral striatal activity to positive stimuli such as happy faces.[12] This pattern of increased subcortical limbic activity to positive emotional stimuli may distinguish bipolar depression from unipolar depressed individuals.

Mania: Studies in bipolar patients with mania have demonstrated increased amygdala, insula, subcortical limbic activity to negative emotional stimuli such as negative emotional facial expressions and negative scenes.[12,13]

Executive control

Another major domain of pathology observed in bipolar disorder patients is executive dysfunction. In these patients areas of executive functions such as working memory and attention are impaired. In the digit-sorting task, which is a test for working memory it has been observed that DLPFC activity is increased.

Again in Stroop test which is an attentional task has shown that DLPFC, dorsal regions of the anterior cingulate gyrus, and VLPFC are involved.[14,15]

Remitted bipolar disorder: Euthymic patients of bipolar disorder have shown poor task performance Stroop test, with reduced DLPFC and VLPFC.[16] They have also showed reduced dorsal cingulate activity on working memory tasks.[17]

Bipolar depression: One study was done with individuals with remitted bipolar disorder with subsyndromal depression. In this

study during an attentional task, it was found that VLPFC activity is decreased in depression. However, the severity of depression was inversely related to the magnitude of VLPFC decrease (i.e. greater is the depression severity, more normal is the VLPFC activity).[18]

In another study where the neural activity was compared in euthymic versus depressed individuals with bipolar disorder during attentional Stroop task performance. It showed relative increases in ventrolateral pre-frontal cortical activity in bipolar depressed individuals.[19]

Mania: fMRI studies have demonstrated in manic patients decreased VLPFC activity and decreased DLPFC activity during the performance of a variety of cognitive control tasks.[20]

Findings from PET studies in bipolar disorder

PET has certain disadvantages when compared to fMRI as it invasive procedure and has a poorer spatial resolution. But it is advantageous over fMRI as it can measure perfusion and metabolism. So, it is being used to measure resting-state activity in patients with bipolar disorder.

Resting-state

In manic, bipolar depressed, and bipolar-II patients, PET have shown increased activity in the amygdala and ventral striatal limbic subcortical areas.[21-23]

Emotional processing

In remitted euthymic patients of bipolar disorder and bipolar depressed patients, studies have shown that there is decreased blood flow in medial PFC during the negative emotional stimulus. There is

also decreased blood flow in the lateral PFC which is very much unique to depressed patients.[24]

In another study which was conducted on mania patients by using decision-making tasks showed increased blood flow in dorsal anterior cingulate and decreased orbitofrontal cortex (OFC).[25]

Executive control

To study executive control, various researchers have used the auditory discrimination continuous performance task (CPT).

In the case of bipolar depressed patients, it was found that absolute decreased metabolism in PFC. They have also reported increased or normalised metabolism in the ventral striatum, thalamus, and right amygdala.[26]

Another study with depressed bipolar patients has showed decreased subgenual prefrontal metabolism.[27]

Structural neuroimaging findings in bipolar disorder

Structural neuroimaging studies are done with bipolar disorder-I patients. Their findings are more or less similar to functional neuroimaging studies.

In adults, it has revealed enlarged amygdala,[28] smaller DLPFC and VLPFC,[29] and almost no change in the size of hippocampus.[30]

Taken together, these findings implicate functional and structural abnormalities in distinct, distributed neural systems for emotion processing and executive control in bipolar disorder.

Recent advances in neuroimaging in bipolar disorder

Some of the areas where neuroimaging in psychiatry, especially in bipolar disorder, looks promising are neuroimaging in childhood-onset bipolar disorder, neuroimaging differences in bipolar-I and II, and examining medication effects.

Childhood-onset bipolar disorder

As in adults, functional neuroimaging studies have revealed that in childhood-onset and adolescent-onset bipolar disorder, there is impaired executive function[31] and emotional regulation.[32]

Studies in remitted, euthymic adolescents with bipolar disorder have observed increases in activity within subcortical regions associated with emotion processing. But, it was not observed during working memory test or attention test during Stroop attentional task performance.[19]

During an emotional face-processing task, adolescents with bipolar disorder demonstrated increased subcortical activity to emotional faces.[31]

Another study showed increased DLPFC activity to negative stimuli in adolescents with bipolar disorder but, increased subcortical activity to positive stimuli.[33]

But, the majority of studies done on childhood and adolescent bipolar disorder are structural neuroimaging studies. Some of these studies have shown cortical[34] and subcortical[10] area abnormality. One longitudinal study on adolescent bipolar disorder[10] demonstrates smaller amygdala and smaller[30] or no change in the

hippocampus. These findings are different from some studies where the enlarged amygdala is found in adults.

One study where prefrontal volumes were measured showed the decreased volume of DLPFC and amygdala and specific striatal structures.[34] Few other studies indicated decreased VLPFC in adolescents with bipolar disorder.[35]

As there is a discrepancy in neuroimaging findings among childhood or adolescent bipolar disorder and adults regarding some key areas like amygdala, there is need of more detailed studies in this area.

Bipolar-I vs. bipolar-II disorders

There is a scarcity of data on neuroimaging in bipolar-II disorders as most of the studies are done on patients with bipolar-I. In future, it can be a major area of research.

One recent study in bipolar-II using PET has demonstrated increased limbic subcortical activity.[22]

Effects of medication in neuroimaging

As more and more patients are taking help of medications almost all of the neuroimaging studies are being done on medicated patients. So, this may present as a confounding factor in these studies. Some of the studies have divided their patients into different related subgroups like medication-free, lithium, anticonvulsive, antipsychotic, antidepressant, etc.[8]

Studies, where emotional processing was examined in medicated vs. unmedicated subgroup, found no significant[36] or decreased amygdala activity.[10]

Studies in which cognitive functions were assessed among medicated vs. unmedicated subgroup, no significant[19] or increased DLPFC activation.[37]

Few other studies found significant positive correlations between antipsychotic dose and DLPFC activity during selective attention tasks in bipolar disorder in adults.[17]

From these findings, we can conclude that medicated bipolar individuals show decreased subcortical limbic activity during emotion processing and increased DLPFC activity during cognitive-control paradigms.

Emerging technologies

Most of our studies are done using fMRI and PET scan. Two emerging modalities- magnetoencephalography (MEG) and DTI are being gradually used for neuroimaging in psychiatric illnesses.

Soon combination of neuroimaging techniques may be used in case of psychiatric illnesses. For example, fMRI or DTI could be used along with MEG or PET to provide spatial information. The outcome of these efforts in bipolar disorder would help us to identify the timing of onset of disease and localise the circuits implicated in bipolar disorder. It will help us to understand the etiopathogenesis to detect treatment-relevant endophenotypes or biomarkers of bipolar disorder.

Conclusions

Neuroimaging in psychiatry is still in its nascent stage. We are just beginning to understand its full capabilities. Studies in neuroimaging are validating our clinical findings in bipolar disorder. Most of the time we are observing altered emotion processing and disrupted executive control. Many of the studies are helping us to identify

endophenotypes so that we can differentiate between bipolar illness and unipolar depression.

Some studies are examining the core domains of pathology in bipolar illness in children and in those individual, who are at risk of developing a bipolar illness. Hopefully, soon we can identify the treatment relevant endophenotypes and we will be able to provide rational treatment for bipolar disorder.

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CHAPTER IV

Bipolar and creativity: agony since antiquity

Devyani Borkataki, Himabrata Das

Mental health has been a subject of historical interest for different cultures at different times. Though the presently used classifications and diagnosis criterions are fairly recent, there has been different terminologies used to refer to the symptoms. Recognising specific symptoms as mental health conditions must have been difficult as it was often overshadowed by belief systems and practices. Moreover, in traditional ways of diagnosis and medicine, physical, emotional, and moral aspects of patient was almost inseparable.

Contemporary conceptualisation

Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5)[1] and International Classification of Diseases (ICD-10)[2] are internationally accepted diagnostic criteria in the field of mental health.

Bipolar and related disorders are defined in DSM-5 by periods of depression and abnormally elevated moods. Bipolar I is characterised by at least one manic episode, with or without mixed

or psychotic features whereas Bipolar II is characterised by at least one episode of hypomania and at least one episode of depression. Dysthymia is characterised by mild but chronic symptoms of depression whereas cyclothymia is a lesser severe form of bipolar disorder characterised by periods of symptoms of mild depression and periods of symptoms of hypomania. ICD-10 classifies bipolar affective disorder into ten categories depending on the manifestation of symptoms in the current episode.

A historical overview

Greco-Roman era

Nomenclature in most of the modern discourses has a lot indebted to the Greco-Roman heritage. Even more in the field of medical science. Mental health is no exception. The Greek term 'mania' meaning 'madness' or 'frenzy' is popularly referred as the origin of the notion of bipolar disorder.[3] Ancient Greek Physician Arataeus, was known to have written about a unified approach to manic-depressive illness by establishing a connection between mania and melancholia, considering them different aspects of the same illness.[4] However, David Healy is of a different view. Though he attributes the 'social entity' of bipolar disorder to time and space specific ideas, practices and institutions, 'conceptual entity' is argued to be the product of contemporary world.[5]

Chinese culture

The idea of harmony is integral to Chinese culture and tradition including medical aspects.[6] In China, Traditional Chinese Medicine (TCM) is the standard diagnostic criteria dating back to the ancient times. TCM diagnosis differentiates mania into four distinct patterns: heart-liver fire, phlegm fire harassing the heart, yang ming

bowel heat (yang ming is one of the six major meridians through which vital force qi flows) and blood amassment; and depressive phase of bipolar disorder into four main patterns: liver qi stagnation, qi stagnating with phlegm, heart-gallbladder qi deficiency; and heart spleen disharmony.[7] The word qi (or chi) is means 'vital life force' in English translation but the concept of qi has two main branches according to TCM – the physical or nourishing portion including air, water, and food intake and the other branch of vital fluids and energy that flows through our bodies.[8] Qi is interlinked with the concept of yin and yang (dark-bright or negative-positive) and balancing all three is considered the way of healthy living.[9] Any imbalance or disharmony is believed to cause illness according to TCM.

Japanese tradition

In Japanese tradition, recognition and public acceptance of mental health issues came comparatively late.[10] In Japan, diagnosis and medicine used to be directed by Traditional Japanese Medicine (TJM) also known as Kampo which is an adaptation of TCM. "Kampo medicine that combines the advantages of Western medicine with those of traditional Japanese medicine" is based on the physical constitution and current symptoms of each patient. For this reason, it is referred to as "tailor-made medicine" and has properties similar to "mind and body" or psychosomatic medicine.[11] Distinct reference to bipolar disorder is hard to find as approach was customised and in case of emotional disorders physical and moral aspects were rarely left alone.[12]

Indian subcontinent

Religion always had a big part to play right from ancient to modern Indian traditions. Rather than being a sacred path of worship,

religious traditions or belief systems decided ways of life. Health was no different. Four vedas, their innumerable samhitas and upanishads along with thirty-six puranas are considered the basis of thought formation in ancient India. The Charaka Samhita by Charaka, and the Sushruta Samhita by Sushruta are well known for establishing Ayurvedic roots of modern Indian medicine. The Atharva-Veda, mentions that mental illness may result from divine curses.[13] Descriptions of conditions similar to schizophrenia and bipolar disorder believed to make appear in the vedic texts. Other traditional medical systems such as Siddha in Southern India and Unani recognised various types of mental disorders but, clear reference to manic-depressive symptoms are rarely evident. Either best kept secret or disguised in other dilemmas, prominent faces with the link between creativity and bipolar was hard to find in Indian subcontinental history. Bollywood celebrities are recently seen coming out and addressing depression and related issues no doubt paving the way for more.

Bipolarity and creativity

Bipolar disorder and creativity

Though different communities had their own understanding and explanation of manic-depressive symptoms, in popular memory bipolar disorder is manifested through famous historical figures who were extraordinarily creative. Thus, the link between creativity and bipolar disorder has intrigued researchers and the general public alike. Understanding this link has the potential to improve the public conceptualisation of the disorder on one hand and focusing on the adaptive aspects of the disorder might improve therapeutic outcomes as well. Mild forms of the disorder, which are more

prevalent, are understood to be related to enhanced creativity while severe forms limit creative accomplishments.

Creativity is a relative term and there is no universal definition. But novelty and originality are integral part. Rest is on the beholder and sometimes- time. Apart from drive and motivation, achieving recognition through creative accomplishments also require resources and opportunities. Creativity involves both convergent and divergent thinking along with the ability to form atypical associations while at the same time being fluent and flexible.[14] Creativity is manifested in two distinct processes- a) analytic which is conscious and b) insight which is the result of unconscious combinations of distantly related concepts.[14] It is possible for those at risk for bipolar disorder to enjoy creative benefits. Less severe forms of mania may be related to artistic occupations more than the severity. More severe forms of bipolar disorder are characterised by cognitive impairment leading to impaired judgement and reasoning and lack of insight. Less sever forms such as hypomania, on the other hand, are associated with increased energy and reduced need for sleep in the absence of delusions and hallucinations which typify more sever episodes. This could be a rational explanation why less severe forms of bipolar disorder are more strongly associated with creative achievements. Studies also show that bipolar disorder is related to a greater likelihood of choosing a creative profession and lifetime creative accomplishments are higher in them. People with bipolar disorder prefer novel and complex stimuli just like all creative people. But the preferences change with repeated experiences of the illness. Many famous artists, musicians and authors are believed to have gone through periods of manic symptoms or bipolar features. Creativity is linked with bipolar disorder both by trait-like and state-dependent mechanisms. Few such historical figures will be discussed below.

While creative personalities from the western world like Vincent van Gogh, Sylvia Plath, Vivien Leigh, Virginia Woolf etc. are widely mentioned in discussions of creativity and bipolar, there is a discrepancy in the orient. In countries like India, China, and Japan, not many makes to the list. Explanation lies in socio-cultural and historical differences in recognising, understanding, accepting, and owning the mental health related issues.

Akio Chiba

Japanese manga (comics or graphic novels) artist Akio Chiba is a notable mention. The creator and contributor to several manga magazines committed suicide in 1984 due to issues related to bipolar disorder. Manga art has been giving a platform for addressing social concerns in creative form. Lately Manga authors have "turned inward in a number of personal essay comics detailing struggles with mental health issues, social expectations, and navigating society as a minority".[15] Akio Chiba is known for his manga work related to sports. Two of his series- Captain (on baseball) and Play-ball ran simultaneously for years and received wide popularity.

Xu Wei

A Ming Chinese artist who lived in the 16th century Xu Wei finds a lot of mention for his creations as well as life with a difficult mental state with bipolar features. He is believed to kill his wife in a state of paranoia and tried to kill himself nine times. Due to his contribution in painting, poetry, and drama, he is known as a pioneer on modern Chinese art. Known for his dramatic pseudo names like 'the mountain man of the heavenly pond', 'Daoist of the green vine house', 'the water and moon of the Bureau's farm' etc., he was devastated by early deaths of loved ones and repetitive failures in life. His suicide methods included axing skull and drilling both ears.

As a playwright, he explored adventures and achievements of female protagonists in his plays- 'the heroine Mulan goes to war in her father's place', 'a female degree holder', 'the adventures of the intelligent Huang Chongjia' etc. His expressiveness in paintings was obtained by the method called 'splattered ink' where ink is poured on painting surface and then worked on. "In his paintings he used broad, dramatic washes of ink and dynamic, cursory lines, suggesting an emotional confrontation between the artist and his materials".[16] His paintings chiefly of flowers, plants, and bamboo magic of brush and ink was evident.[17]

"The sadness will last forever"[18-20]

One of the most influential figures in the history of Western art, Vincent van Gogh was diagnosed with "acute mania with generalised delirium" after he had severed his left ear with a razor before wrapping the ear in paper following an altercation. Ravaged by yet another severe relapse two years later, van Gogh shot himself in the chest with a seven mm revolver. He succumbed to his injury two days later. He was 37. His use of bold colours and dramatic, expressive brushwork in his prolific volume of artwork offers a subtle ingress into the workings of his creative mind. As a post-Impressionist, his emphasis on abstract qualities and symbolic content is a departure from the concern for the accurate depiction of light and colour that characterised the preceding tradition of Impressionism. His enduring portraits exhibit a full range of both painting styles- from the restrained to the frenetic. His self-portraits, mostly created during introspective periods, are fascinating insights into the artist's varying mental and physical health, his gaze seldom directed at the viewer. He also appears bandaged in the portraits that he created after his self-mutilation. His landscapes have an abundance of flowers and orchards- a hint at his special interest in

the language of colours. The optimism and yet delicate nature of these works with recurring themes of change of seasons conjure up a sense of impermanence and cyclicity akin to the course of bipolar disorders. His paintings of wheat fields and rural landmarks that capture his views from outside his window are largely sombre; yet the rich use of an array of colours and palettes creates a sense of picturesque idyll-seemingly reflecting a desire to return to lucidity. Van Gogh captures public imagination as a "misunderstood genius" and a "tortured artist". His works have been among the most expensive paintings to be auctioned and his legend is perpetuated by the millions of visitors who throng the Van Gogh Museum in Amsterdam every year. That the artist's suicide weapon, the seven mm Lefauchex, was auctioned in June 2019 for an impressive 162,000 euros is testimony to Van Gogh's timeless charm.

"The sadness will last forever" were known as the last words by Vincent van Gogh in the early hours of 29 July 1890, the day of his death.

Rise of bipolar superheroes

Twenty-first century is an era of superhero dominance in popular culture magnetising young and the old alike. Another recent phenomenon on the rise is that of web-series. Characters in both these mediums are increasingly exploring 'flaws' and 'abnormalities' of human nature. Portrayal of such characters help in popularising and building awareness and acceptance of the human imperfections.

Lorna Dane aka Polaris aka the Magnet Girl- one of the main characters from the marvel spin off series The Gifted is one example. Polaris owns her imperfections as gracefully as her special abilities. She often refers to her past as 'the unpopular bipolar kid in the neighborhood with green hair who made regular trips to rehab'

who went on destruction spree in her phases. Another marvel character 'the unstoppable wasp' or Nadia from the comics version is affected with bipolar disorder. But she is yet to gain acceptance or popularity among the marvel fans.

Blurred boundaries, mysterious overlaps

The understanding of mental health is embedded and inseparable from the socio-cultural and religious traditions of any time or place. In countries like India, China, and Japan, this historical delay and socio-cultural difference in recognising mental health conditions is reflected in popular culture too. Creative fields are a platform for bipolar affected people to receive due recognition as well as protest against the social exclusion. There is immense scope for research to understand how opinions are still affected by the spatial differences.

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AFFECT

CHAPTER V

Bipolar disorders and sexuality

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Bipolar disorder (BD) is a chronic mood disorder characterised by recurrent depressive episodes and manic/ hypomanic episodes that negatively affect social and professional functionality.[1] Various studies have shown that most patients with BD also experience subsyndromal symptoms in euthymic periods and that those symptoms are associated with decreased functionality in many areas.[2-4] The literature on sexual functionality in BD is quite limited. A negative association have been reported between BD and sexual functioning.[5,6] One of the study reported that patients with BD in remission experienced more sexual problems than did healthy controls.[7] Likewise, studies which focused on both genders found that the sexual distress level was higher in female patients with BD than in controls.[8]

Sexual dysfunctions

When compared to DSM-IV-TR, DSM-5[9] has fewer categories describing sexual dysfunction and continues to classify sexual dysfunction based on gender. Minimum duration required to make a

diagnosis of sexual dysfunction in DSM-5 is six months with frequency ranging from 75-100%. In females, sexual desire and arousal disorders have been combined into one disorder; vaginismus and dyspareunia come under genito-pelvic pain/ penetration disorder. DSM-5 has done away with sexual aversion disorder. Various types of sexual dysfunctions have been categorised based on onset and context. DSM-5 includes lifelong versus acquired subtypes and situational versus generalised subtypes. Psychological versus combined subtypes have been dropped; medical versus other non-medical correlates have been added; cultural and religious factors has been significantly highlighted. Culture related diagnostic issues have been mentioned separately for each diagnosis.

According to ICD-10,[10] sexual dysfunction refers to a person's inability to "participate in a sexual relationship as he or she would wish". Compared to DSM-IV-TR, ICD-10 does not try to describe various sexual dysfunctions.

ICD-10 describes following categories of sexual dysfunction: (1) sexual dysfunction not caused by organic disorder or disease, (2) sexual aversion and lack of sexual enjoyment, (3) failure of genital response, (4) orgasmic dysfunction, (5) premature ejaculation, (6) nonorganic vaginismus, (7) nonorganic dyspareunia, and (8) excessive sexual drive.

ICD-10 classification have been criticised widely for not being sexual response cycle specific. Both the classifications have been criticised for not reflecting sexual dysfunctions as encountered in clinical settings.

Hypomania/mania and sexuality

BD can involve sexual disturbances directly related to the illness phase. Male and female patients in manic or hypomanic episodes often experience hypersexuality, with an increased incidence of risky sexual behaviours.[11] By contrast, in depressive episodes, reduction of sexual desire is common Overall, sexual dissatisfaction is often associated with BD.[12] Patients with BD tend to have more stable sexual partners and a more intense sexual activity than those with schizophrenia.[12,13] When compared to females, males with BD tend to have more sexual partners and are more likely to have sexual intercourse with strangers.[14] Sexual dysfunction is a common residual symptom in euthymic patients with BD, and has a significant negative impact on quality of life.[15] Impact of the disorder on all phases of sexual response cycle leads to, suicidal plans and worthlessness.[5] In addition, sexual dysfunction has been identified as a predictor of poor medication adherence.[16] A meta-analysis indicated statistically significant association between a history of sexual abuse and a lifetime diagnosis of anxiety disorder, depression, eating disorders, sleep disorders, and suicide attempts.[17] Unfortunately, no longitudinal studies assessing patients with BD are available in this respect. Sexual aggression is common in youth with BD, particularly in those with a lifetime history of comorbid post-traumatic stress disorder.[18] Prompt identification and treatment of these youths is the need of the hour. Addressing and psycho-educating regarding the sexual issues in manic episodes will go a long way in preventing promiscuous activities and negative consequences.

There are many controlled and uncontrolled studies which show that sexuality is often increased in adults with BD.[1] The DSM-IV-TR description of mania listed hypersexuality in criteria B #6 and #7 as

"increased goal driven behaviour. . .sexually" and/or "excess involvement in pleasurable activities that have a high potential for painful consequences: for example, sexual indiscretions".[2] The DSM-5 criteria for mania include:[9]

1. Elevated, expansive, or irritable mood
2. Abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day
3. Three (or more) of the following symptoms

a. Inflated self-esteem or grandiosity
b. Decreased need for sleep
c. More talkative than usual or pressure to keep talking
d. Flight of ideas or subjective experience that thoughts are racing
e. Distractibility
f. Increase in goal-directed activity or psychomotor agitation
g. Excessive involvement in activities that have a high potential for painful consequences

4. Marked impairment in social or occupational functioning or necessitating hospitalization or there are psychotic features
5. Not attributable to the physiological effects of a substance

The first three DSM-5 criteria for hypomania are same as mania. The only difference lies in the socio-occupational functioning or disruption. Those criteria are as follows:[9]

1. Unequivocal change in functioning that is uncharacteristic of the individual
2. Observable by others
3. Not severe enough to cause marked impairment in social or occupational functioning nor necessitating hospitalization nor are there any psychotic symptoms

4. Not attributable to the physiological effects of a substance

Bipolar disorder and sexuality (controlled studies)

Diagnostic criteria and clinical treatment have changed dramatically over the past years. Studies which addressed sexual functioning were not uniform in terms of the questions asked or instruments used to acquire information. Most of the studies did not have information on the medication status of patients and the phase of illness. There were mixed results about sexuality in bipolar patients.[5]

Positive studies

Multiple studies found increased sexuality in manic and hypomanic patients as compared to depressed patients.[19,20] These studies found that 40 percent of the Bipolar I and II patients reported elevated sexuality as an enduring inter-episodic trait. Another study found that when compared to schizophrenic patients, bipolar patients had stable sexual relations, stable marriages, more frequent intercourse.[13] Studies which compared BD with unipolar depression showed that change of sexual partners was more common in BD.[5] A study which compared different types of BD, found that bipolar I patients had more sexual interest, desire, placed more value on sex, and engaged in intercourse more frequently than bipolar II patients.[21]

Negative studies

There are few studies which reported period of celibacy to be higher in bipolar that unipolar patients.[22] Another study found that bipolar patients were less sexually active than unipolar patients.[23] A study which compared bipolar patients with normal controls found that sexual interest was less among bipolar patients.[24] A

study comparing couples in which one partner was bipolar to non-psychiatrically disordered control couples done by Frank *et al.*[25] found no difference in satisfaction.

Uncontrolled studies on bipolar disorder and sexuality

One of the studies which tried to understand the sexual behaviour in manic or hypomanic patients found that more than 50% of the women in the group had increased sexual display and seductive behaviour.[26] In the same study, marked increase in libido in an elevated mood state was found in 7/12 men and 10/12 women. An Indian study found that 65 percent of manic episodes were characterised by increased sexuality.[27] Out of 20 unmedicated manic patients admitted for four months, an observational study found hypersexuality in 80% of them.[28] However, another study in which medications were started by the third day of admission found sexual preoccupation in only 25% of 16 manic inpatients.[29] A retrospective chart review study of 1,000 bipolar II patients, found 40% of cyclothymic patients to have had "episodic or unexplained promiscuity or extramarital affairs" and bipolar II patients manifested diverse types of sexual excess including sexual infidelity, overt bisexuality, and sexual activity many times per day. Of the uncontrolled studies, Jamison *et al.*'s study,[20] addressed "aspects of sexuality in bipolar individuals who were in the euthymic state, conceptualised sexuality in terms of the whole person, highlighted sex differences between men and women in sexual experience, and directed attention to state versus trait sexual phenomena."

A unique study conducted in 2016, focusing on sexuality as part of the person's temperamental trait behaviour, sought to assess whether sexuality was different among individuals with BD even when they are euthymic compared to those without affective

disorder and found that bipolar patients had more sexual partners than the comparison patients and increased frequency of risky sexual behaviour. In addition, bipolar males had more sexual partners during the past year than bipolar females and more bipolar males had engaged in homosexual activity. Bipolar males were also somewhat more likely than comparison males to have engaged in receptive intercourse without condoms during the past year.

The above mentioned studies found diverse aspects of sexuality in relatively stable bipolar individuals.

Sexual dissatisfaction can not only affect functionality and the course of BD, but also be a source of stress triggering an episode. Patients with psychiatric illnesses have a low rate of self-reporting of sexual dysfunctions and it is mostly disregarded by clinicians.[30,31] However, sexual dissatisfaction can lead to decline in quality of life, increased interpersonal relationship problems, impairments in marital adjustment, and treatment non-adherence.[8,32,33]

In a small sized study which assessed bipolar I patients, bipolar II patients, and healthy controls, using some items of section I of the Sexual Interest and Sexual Performance Questionnaire, "Actual Value of Sexuality" and "Implicit Sexual Interest", found an increase of sexual interest in patients with bipolar I as compared both with bipolar II patients and healthy controls. They also observed a higher desired frequency of intercourse higher occurrence of repeated sexual intercourse in women with bipolar I than bipolar II.[21]

Depression and sexuality

It is recommended that all patients reporting sexual dysfunction should be screened for depression and vice-versa.[34] A study comparing depressed patients with normal controls found that

depressed patients were twice as likely to have sexual dysfunction as controls.[35]

Recurrent depressive disorder was found to be more associated with sexual problems. The US Study of Women's Health Across the Nation found that sexual arousal, physical pleasure, and emotional satisfaction problems were more reported by women with recurrent depressive episodes.[36] Surveys done in the Netherlands found that the presence of mood disorders was associated with a lesser chance of reporting sexual satisfaction.[6] Depression, especially among young adults, lowers sexual interest and satisfaction expression.[37] Anxiety symptoms present along with depressive symptoms can worsen sexual difficulties and dissatisfaction.[38,39] Depression can exert adverse effects on all aspects of the sexual response in both males and females,[40] Hence, depression and sexual dysfunction have a bidirectional relationship. Although most antidepressants have side-effects on sexual function and satisfaction, but the adverse effects of depression itself warrant treatment of these patients.

The embarrassment felt by patients and health professionals can lower consultation and recognition rates in primary medical care.[36,41,42] Most depressed patients do not spontaneously report of sexual adverse events leading to a substantial underestimation of sexual problems in depressed patients.[43,44] Screening and severity questionnaires can facilitate recognition and assessment, but cannot fully substitute for a comprehensive but sensitive assessment. The Arizona Sexual Experiences Scale (ASEX),[45] the Changes in Sexual Functioning Questionnaire (CSFQ),[46] the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ-SALSEX),[47] and the Sex Effects Scale (SexFX)[48] have been recommended for assessing sexual function and satisfaction in depressed patients before and during antidepressant treatment.[44]

Table 1: Studies comparing sexual dysfunction between controls and depressed subjects					
Study	Subjects with depression	Control subjects	Dysfunctions assessed	Prevalence in depression, %	Prevalence in control, %
Casper *et al.*[24]	Hospitalised for major depressive disorder (unipolar: n=85; bipolar n=47)	Age and gender matched (n=80)	Loss of sexual interest (derived from scores on items 14 of HAMD, 32 of VIBES, 5 of HSCL, and 230 of SDAS-C)	72 (unipolar) 77 (bipolar)	5
Mathew and Weinman [49]	Drug-free patients with depression (n=51)	Drug-free patients with depression (n=51)	Loss of libido (libido is defined as desire to have sex)	31	6
			Excessive libido	22	0
			Impotence	35	0
			Premature ejaculation	38	0
			Delayed ejaculation	47	6
			Lack of orgasm	34	11
Angst [35]	Random selection from population scoring above the 85th percentile on SCL-90-R; includes major depressive disorder, dysthymia and recurrent brief depression (n=126)	Randomly selected from a population scoring below the 85th percentile on SCL-90-R (n=365)	Males (n=16)		
			Increased libido	23	7
			Decreased libido	26	11
			Sexual dysfunction	11	7
			Emotional problems	16	7
			Any sexual problem	48	18
			Females (n=35)		
			Increased libido	9	2
			Decreased libido	35	32
			Sexual dysfunction	26	18
			Emotional problems	19	15
			Any sexual problem	51	32
HAMD- Hamilton Rating Scale for Depression, VIBES -Video Interview Behaviour Evaluation Scale, HSCL- Hopkins Symptom Checklist, SADS-C- Schedule for Affective disorder and Schizophrenia Change form					

Table 2: Western studies in female sexual dysfunction in depressed patients			
Study	Prevalence	Scale Used	Findings
Bonierbale and Jean[50]	65% (untreated) 71% (treated)	ASEX	The prevalence of sexual dysfunction in patients with major depression is high. Antidepressant drugs appear to aggravate such problems, with certain classes of drug better tolerated than others. Sexual dysfunction in depressed patients is often not optimally treated.
Lin *et al.*[38]		ASEX	The severity of sexual dysfunction among patients with MDD was most correlated with the severity of the depressive dimension, but not the severity of the somatic dimension.
Ishak *et al.*[51]	64.3%	Quality of life enjoyment & satisfaction questionnaire	Despite the sexual side effects of the citalopram, treating depression to full remission was associated with improvements in sexual satisfaction and QOL
Yazdanpanahi *et al.*[52]	The mean scores of stress, anxiety, and depression in the sexual dysfunction Stress: 6.43±4.68, Anxiety: 6.19±4.5, Depression: 4.07±4.03	FSFI	Depression has significant all domains except sexual pain; and between Anxiety and all domains of sexual function. Stress, anxiety and depression have a significant inverse relationship with the total score of sexual function

Table 3: Indian studies on female sexual dysfunction in affective disorders				
Studies	Prevalence	Scale used	Sexual dysfunction	Findings
Abhivant *et al.*[53]	67.34%	FSFI, ASEX	Desire: 45%, Arousal: 45%, Lubrication: 53%, Orgasm: 51%, Pain: 49%, Satisfaction: 45%	Study reported high prevalence of sexual dysfunctions in depressed females. All domains of sexual functioning were affected and there was significant association between sexual dysfunction and depression.
Roy *et al.*[54]	70.3% 73.3%	FSFI, ASEX	Desire: 83.35%, Arousal: 90%, Lubrication: 86.7%, Orgasm: 76.7%, Pain: 23.3%, Satisfaction: 76.7% (as per FSFI)	Study found that there was a severe sexual dysfunction of sexual activity in depression in all domains of female sexual cycle.
Sreelakshmy *et al.*[55]	90%	FSFI		The study showed a high prevalence of female sexual dysfunction in depressed females regardless of type and severity of depression. Depressionwith medical comorbidities was associated with a significant decrease in desire.

In an early study, loss of sexual interest was reported by 72% of patients with unipolar disorder and 77% of those with bipolar disorder out of 132 depressed patients.[56] Loss or lowering of sexual desire may be the presenting complaint or pre-date other features of depression in some patients with significant depressive symptoms, but they were reported only after direct questioning.[57]

Comparative studies indicate higher levels of sexual dysfunction in patients with depression than in controls (Table 1). Although the incidence of specific types of sexual dysfunction varies across

studies, loss of sexual desire may be more common than disorders of arousal and orgasm. In a comparative study, changes in libido were significantly more common in patients with depression when compared to controls.[49] As shown by a prospective cohort study done in Zurich, young subjects (28-35 years old) with depressive disorders had almost double as much prevalence of sexual problems as compared to controls.[58] These included emotional problems, sexual dysfunction, and both decreased and increased libido.

The same study also compared the effect of medication (50% benzodiazepines, 50% antidepressants) or psychotherapy on sexual problems and showed that 62% of patients who received treatment had sexual problems as compared to 45% of those who did not and 26% of the controls. So, a higher prevalence was found among patients as compared to controls, with sexual problems being more common among those on medication. No statistically significant differences were found in the prevalence of sexual dysfunction based on the mode of treatment, medication or psychotherapy alone.[35]

A number of brain regions like the hypothalamus, limbic system, and cerebral cortex control the various factors involved in the sexual response cycle.[59] Various neurotransmitters and neuropeptides like increased serotonin, decreased dopamine, blockade of cholinergic and increase in α1-adrenergic receptors, inhibition of nitric oxide synthetase, and elevation of prolactin levels have been implicated in sexual problems.[60]

Increased availability of serotonin inhibits all phases of the sexual response cycle, mainly via 5-hydroxytryptamines 2 and 3 (5-HT2 and 5-HT3) receptor agonism, whereas dopamine release enhances sexual function. Many mechanisms have been proposed for

antidepressant induced sexual dysfunction.[61] The four mechanisms commonly implicated include: nonspecific sedation (e.g. sedation resulting in impaired arousal), hormonal effects (e.g. prolactin elevation associated with use of a typical neuroleptic, resulting in erectile dysfunction), central neurotransmitter effects (e.g. increased central nervous system [CNS] serotonergic levels associated with selective serotonin reuptake inhibitor [SSRI] use, resulting in delayed orgasm), or a peripheral neurotransmitter effects (e.g. peripheral blockade of noradrenergic receptors associated with trazodone use, resulting in priapism). The effects of antidepressants on sexual functioning are hypothesised to be dose dependent and mediated by alterations in the activity of serotonin, dopamine, norepinephrine, histamine, and acetylcholine.[62,63]

Conclusion

Sexual dysfunction is more common in BD. Factors like phase of the illness, medications used, affects all the phases of sexual response cycle. Sexual dysfunctions not only affects quality of life, also have effect on compliance of medicine, which leads to relapse. Being aware of sexual dysfunctions and addressing them appropriately by therapist, will help patients with BD in significant way.

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AFFECT

CHAPTER VI

Treatment emergent sexual dysfunction in bipolar disorders

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Psychiatric illnesses often have underlying sexual dysfunction. This can be due to the illness itself or even because of the use of psychotropics. As the patient improves symptomatically, many of these sexual problems resolve, but not always the ones that are related to the treatment given. These often persist for longer, and are commonly not recognised by clinicians and are seldomly researched in trials. Sexual dysfunction can unfavourably affect quality of life and can be one of the reasons for poor treatment adherence. Depending upon the mechanism of action, the incidences of sexual dysfunction due to different compounds vary. While antidepressants have a prevalent serotonergic action, and antipsychotics can cause hyperprolactinaemia, mood stabilisers may induce hormonal changes. In all of these cases, moderate to severe sexual dysfunction may occur in the form of decreased libido, delayed orgasm, anorgasmia, and sexual arousal difficulties. A previously existing

satisfactory sexual activity may be hampered by severe mental disorders. When compared to the general population, mentally ill patients can have unsatisfactory sexual life or more frequent risky sexual behaviour owing to absence of intimacy in relationships and poor mental and physical health.[1]

Treatment of hypomanic/manic disorders and sexuality

Pharmacological management of bipolar disorder involves the use of mood stabilisers, antipsychotics, anticonvulsants, antidepressants, and benzodiazepines, either as monotherapy or in combination. One of the most common adverse effects of these medications are sexual symptoms, which effects the quality of life in patients and their medication compliance in long-term treatment.[1]

Mood stabilisers and sexuality

Lithium

Lithium has long been accepted and used as the first-line drug in treatment of bipolar disorder. Approximately one-third of both male and female patients treated with lithium experience sexual dysfunction, usually more than a single domain.[2] Several studies have shown a significant negative impact of lithium on sexual functioning, as it was seen to reduce libido, worsen erectile function, and reduce sexual satisfaction.[3,4] Patients are less likely to experience sexual fantasies, have sexual desires, engage in sexual intercourse, and report satisfaction, and 30% of these patients attributed the above problems to lithium treatment.[5] Despite this, when compared to other options of pharmacological treatments in bipolar disorder it seems that lithium has a less pronounced side effect profile on sexual functions,[6] especially to antipsychotics.[7] The concomitant use of benzodiazepines with lithium seems to be

associated with an increased incidence of sexual dysfunction, while this dysfunction does not appear to be related to serum lithium levels.[8]

Labbate[9] opined that "if benzodiazepines cause sexual problems, it remains unclear if this effect is independent of lithium or due to a combined effect of benzodiazepine and lithium". Also, concluded that the extent of sexual dysfunction was not a source of distress to patients and did not lead to poor medication compliance.[10] Zuncheddu and Carpiniello[5] performed a comparison study on 51 patients diagnosed with bipolar disorder who were on lithium monotherapy and compared them to a control group of 176 healthy individuals, using a questionnaire (self-administered) designed by the researchers themselves. "The questionnaire consisted of 6 items investigating: presence of sexual intercourse activity, sexual pleasure, sexual satisfaction, frequency of sexual intercourse, sexual fantasies and desires."[5] Authors found that subjects on lithium had significantly lower scores on all of the questionnaire items compared to controls, and concluded that lithium has negatively impacted sexual desire and sexual arousal. Unfortunately, the study had several limitations regarding the validity of the tools used.

Valproate

Valproate is known to elevate serum testosterone levels, androstenedione and dehydroepiandrosterone sulfate (DHEAS) concentrations, while prolactin levels typically remain within normal limits.[11] In women receiving valproate for bipolar disorders and in epilepsy, increase in androgen levels was associated with a greater risk of menstrual disorders and polycystic ovarian syndrome (high serum testosterone levels).[12,13] In men, valproate treatment was shown to cause erectile dysfunction.[14] Schneck *et al.*[15]

hypothesised that the sexual dysfunction in women treated with valproate was as a result of increased serotonergic transmission, frequently associated with the use of selective serotonin reuptake inhibitors (SSRIs) leading to severely decreased libido and anorgasmia. There are reports of endocrine disorders (possibly related to the presence of ovarian cysts in women, and reduced testicular volume in men), among those taking valproate.[16] However, in the study by de Vries *et al.*,[17] long-term treatment with valproate in girls with epilepsy was associated with increased testosterone levels after menarche, and not with clinical hyperandrogenism or polycystic ovary syndrome.

Carbamazepine

Carbamazepine is often associated with reduced levels of oestradiol, progesterone, and testosterone, and may cause hypogonadism, amenorrhoea, and decreased sexual function and sexual desire.[18] It may also increase sexual hormone-binding globulin (SHBG) concentration, resulting in reduced bioactivity of testosterone and oestradiol, and consequently diminishing sexual desire and leading to erectile problems.[19] There are not many studies to implicate oxcarbazepine with hormonal changes and sexual dysfunction,[3] but some researchers have occasional reported anorgasmia women and retrograde ejaculation in men.[20,21]

Lamotrigine

Lamotrigine is one molecule that has been widely studied and shown to have least sexual adverse effects in bipolar patients.[22,23] Lamotrigine does not seem to cause any alteration to SHBG levels, probably due to its non-involvement in hepatic enzyme induction. In a study comparing sexual activity by addition of the sexual function scores, bioactive testosterone (BAT) and bioactive

oestradiol (BAE) levels, hormone ratios (BAT/BAE), and gonadal efficiency (BAT/luteinising hormone) were found to be higher in the lamotrigine group when compared to the carbamazepine and the phenytoin-treated groups.[24,25] Lamotrigine prescribed three case reports in men showed improvement in sexual function.[26] In an open-label, observational trial on 141 patients, lamotrigine was reported to be associated with improved sexual function in both men and women.[27] Patients were assessed using the "changes in sexual functioning questionnaire (CSFQ)". Women in the study on lamotrigine, had significant improvement with their CSFQ total score and in each of the five dimensions of the scale (desire/frequency desire/interest, pleasure, arousal/excitement and orgasm), whereas pleasure dimension was observed to have improved significantly in men. Two case reports of "hypersexuality" have been reported during treatment with lamotrigine; however, the mechanism is unclear.[28]

There is little evidence about management of sexual dysfunction associated with mood stabilisers. Using the lowest effective dose of the drug, switching to alternatives, or some add-on strategies may be useful.[29]

Adjunct therapy

"There is currently no information on the potential utility of phosphodiesterase type 5 (PDE-5) inhibitors such as sildenafil, but it seems reasonable to consider them based on clinical experience in other patients. There is some evidence that switching from enzyme-inducing (valproate, carbamazepine) to non-enzyme-inducing (oxcarbamazepine, lamotrigine) anticonvulsants can be beneficial."[12] A small randomised placebo-controlled trial observed an improvement in erectile dysfunction in patients

undergoing lithium treatment when given adjunctive aspirin (240 mg/day).[30]

Anticonvulsants in mood disorder and sexuality

Anticonvulsant medications have been widely used for decades as mood stabilisers in bipolar patients. They are often associated with sexual dysfunction in people with epilepsy (35-55% of patients),[31] but there is limited evidence of these adverse effects in patients with bipolar disorder.[25,32,33] Studies on epileptic patients, have shown that switching to lamotrigine was associated with an improvement in desire, pleasure, excitement, and orgasm in women, but only in the pleasure dimension in men.[27] Addition of lamotrigine to carbamazepine or valproate can ameliorate sexual dysfunction in male patients.[26]

Several studies suggested that old anticonvulsants, i.e. carbamazepine, phenytoin, and phenobarbital may cause sexual dysfunction[34-37] by reducing blood levels of free testosterone. The results of a study by Herzog *et al.*[25] seem to confirm this finding (particularly for carbamazepine) which has also been identified in previous studies. Circulating testosterone is highly bound to a specific transport protein (SHBG), whose production is increased by drugs such as carbamazepine, that induce hepatic metabolism. The increase in plasma concentrations of SHBG results in a decrease in levels of free testosterone, partly contributing to hypogonadism.[38]

Oxcarbazepine

In an observational, open-label study, that lacked a control group, 673 adult male patients with partial epilepsy who were prescribed oxcarbazepine monotherapy, were questioned about their sexual

function at baseline and after 12 weeks of treatment. Two hundred and twenty eight patients (33.9 %) complained of pre-existing sexual dysfunction prior to treatment: among whom 181 patients (79.4%) reported an improvement in sexual function after three months of treatment with oxcarbazepine and 23 patients (10.1%) experienced no sexual impairment at the final 12 week visit.[39] In contrast to the findings of this study, some case reports of dose-dependent oxcarbazepine-related anorgasmia and retrograde ejaculation have been published.[20,21,40] The pathophysiology underlying oxcarbazepine-induced anorgasmia is not fully understood.[12]

Gabapentin

Gabapentin use was linked to anorgasmia in both men and women.[41-43] In a case report by Kaufman and Struck,[44] men treated with gabapentin at a total daily dose of only 300 mg in addition to anorgasmia, also reported anejaculation, decreased desire, and erectile dysfunction. Similar findings were reported by Labbate and Rubey,[45] Calabrò,[46] suggesting that gabapentin-induced sexual dysfunction is most likely secondary to a central inhibitory effect on neurotransmission: the inhibition of calcium currents induced by gabapentin could lead to a decrease in neurotransmitter release and attenuation of postsynaptic excitability. However, we did not find evidence to support this hypothesis.[12]

Pregabalin

Some case studies examining the sexual side effects of pregabalin reported erectile dysfunction, anorgasmia and delayed ejaculation in men.[47,48] The aetiology of sexual dysfunction associated with anticonvulsant drugs in context of bipolar disorder is unclear: changes in sex hormone levels induced by anticonvulsants may be a possible cause, however, other mechanisms similar to those

described for antidepressant drugs cannot be excluded, e.g. mechanisms involving the numerous central and peripheral neurotransmitters (especially serotonin, dopamine, acetylcholine, norepinephrine) and vasodilatory substances (such as nitric oxide, which plays a key role in increased blood flow in the genitals) which can influence the phases of the sexual response cycle (desire, arousal, and orgasm).[12]

In this section of the review, we have looked at anticonvulsants used as mood stabilisers and have not described the actions of anticonvulsants prescribed for non-psychiatric disorders (e.g. phenytoin, topiramate).

Antipsychotic in mood disorder and sexuality

Antipsychotics as first line agents have a significant impact on patients' sexuality during short- and long-term management of bipolar disorders, and is commonly associated with negative impact on quality of life in adult and adolescent patients.[49] Wide range of studies depending on the methodology used have reported the prevalence to be between 38% and 86%,[50,51] both when symptomatic and in remission. Sexual dysfunction profile includes reduced libido, difficulties in sexual arousal; erection difficulties, reduced vaginal lubrication, and orgasmic dysfunction; and reduced sexual satisfaction. The most commonly reported complaints in clinical practice include orgasm dysfunction and erectile difficulties in the short-term and decreased desire in the longer-term treatment. The most frequent pattern in male patients is the combination of reduced desire with erectile dysfunction, which is poorly studied.[52,53] Wide range of factors contributing to these symptoms include disrupted dopaminergic activity, hyperprolactinaemia, and alpha-1 receptor blockade.[54]

Hyperprolactinaemia and related hypogonadism have been strongly implicated in sexual dysfunction, occasionally accompanied with infertility, amenorrhoea, gynaecomastia, and galactorrhoea.[55,56] Elevated plasma prolactin levels are associated with higher rates of erectile and ejaculatory problems attributed to dopamine-blocking and hyperprolactinaemia-inducing antipsychotics such as haloperidol, risperidone, paliperidone, and amisulpride. They are more likely to be associated with decreased libido and/or arousal difficulties. On the contrary aripiprazole, quetiapine, olanzapine, and ziprasidone have shown to have reduced risk of developing sexual dysfunction (16-27%) in open studies,[49,57] and in meta-analyses.[58] A lower risk for prolactin elevation and sexual dysfunction was found with aripiprazole once-monthly when compared to long-acting paliperidone; this difference being associated with a greater improvement in quality of life.[59] Erectile problems with antipsychotic drugs may be specifically related to endothelial dysfunction linked to decreased nitric oxide production due to inhibition of endothelial nitric oxide synthetase,[60] and vasoconstriction from beta 2-adrenergic effects.

Young men with psychosis consider impairment of sexual function as the most important adverse effect of antipsychotic medication affecting treatment adherence.[61] Management strategies for treatment emergent sexual dysfunction in psychotic patients involve any of the following: dosage reduction, switching the antipsychotic, add-on strategies with a dopamine agonist, addition of aripiprazole, or use of a PDE-5 inhibitor; all have shown some beneficial effects. However, reducing antipsychotic dosage increases the risk of relapse; so, switching to another antipsychotic medication may be preferable in managing treatment-induced sexual dysfunction in psychotic patients. Several studies on aripiprazole, found improvement in delayed ejaculation/orgasm in some naturalistic

settings in men.[62] Psychosocial interventions, i.e. psychoeducation, supportive psychotherapy, and psychiatric rehabilitation, also play a critical role, for restoring previous sexual functioning. Medications with a lower frequency of sexual side effects should be considered as potential first line options in psychotic patients with an active and satisfactory sexual life.

Treatment of depression and sexuality

The extent and frequency of treatment-emergent sexual dysfunction due to antidepressants has so far been challenging. This includes both the deterioration of already existing problems and emergence of newer issues in patients that had previously never had any sexual dysfunction. Two international studies that attempted to assess the prevalence of sexual dysfunction in depressed patients that were on either an SSRI or an serotonin norepinephrine reuptake inhibitor (SNRI), considered both, the sexual problems (self-reported) before treatment was started, as well as the possible side-effects of the medication, found that 27-65% of female and 26-57% of male patients reported a further increase in already present sexual dysfunction or new sexual difficulties in the initial weeks of treatment.[63,64]

A meta-analysis in which various differently designed studies (double blind, open label, retrospective, and cross-sectional) showed that treatment emergent sexual dysfunction was only as common in the antidepressants agomelatine, amineptine, bupropion, moclobemide, mirtazapine, or nefazodone as it was with placebo. The other antidepressants were found to have a significantly more likely chance of causing sexual dysfunction, including higher association of dysfunction in each individual phase of sexual response.[65] When compared with SSRIs like escitalopram, fluoxetine, paroxetine, or

sertraline, it was seen that bupropion had a significantly lower chance of amounting to treatment emergent sexual dysfunction,[66] which could be attributed to its predominant mechanism of action being related to the noradrenergic dopaminergic system.[67]

Another meta-analysis, that included 58 radomised controlled trails (RCTs) and five observational studies, found only minor variation between most antidepressants, although paroxetine and venlafaxine were shown to have comparatively worse results, and bupropion had better ones.[68] A systemic review that compared mirtazapine with other antidepressants in terms of tolerability and efficacy found that mirtazapine was less likely to lead to sexual dysfunction,[69] possibly because of its antagonist effects at alpha-2 adrenergic and 5-hydroxy tryptamine 2C (5-HT2C) receptors.[70]

Some other antidepressants possibly have a lesser chance of causing detrimental effects on sexual function.[71] RCTs have shown that when compared with other antidepressants, agomelatine has relatively fewer side effects on sexual functioning, which could be attributed to its antagonist effects at the 5-HT2C receptor, and not the agonist effects at melatonin receptors,[72-74] keeping in mind that the lack of effects on the nitrergic relaxation of the corpus cavernosum smooth muscle may also play a role.[75] Vilazodone because of its partial agonist effects at the 5HT1A receptor seems to have a lesser chance of causing sexual dysfunctions when compared to placebo. It appears to not have any advantages in the improvement of sexual functioning during the treatment of major depressive disorder and the "number needed to harm" was seven in men and 13 in women.[76-78] Vortioxetine is another antidepressant that showed a low rate of causing sexual dysfunction in men (three to five per cent) and women (one to two per cent) possibly due to its antagonist effects on the 5HT3 receptors and indirectly causing

increase in noradrenaline and dopamine.[79] Some risk factors have been identified in the development sexual problems while undergoing treatment with antidepressants which include- male gender, poor academic achievements, lack of stable employment, chronic comorbid physical illnesses, multi-drug treatment, older age, poor family support, and strained interpersonal relationships.[80,81]

Behavioural approaches to premature ejaculation have been found to be most effective in male patients.[82] Many men (including those without depression) suffering from persistent problems benefit from treatment with either the tricyclic antidepressant clomipramine or SSRIs.[83] The short-acting SSRI dapoxetine is efficacious in treating premature ejaculation, with either daily dosing or "on demand" dosage.[84] A systematic review of randomised placebo-controlled trials with trazodone, at higher daily doses (150-200 mg) was efficacious in treating "psychogenic" erectile dysfunction.[85] The exact number of patients who stop or discontinue treatment because of sexual side effects is not well established,[86,87] nor is the time course of sexual dysfunction in patients who continue with antidepressant treatment.[88]

Agents with primarily serotonergic actions

Initially, in trials that needed unprompted reporting of sexual dysfunctions, it was seen that with fluoxetine the incidence was as low as two per cent.[89] Subsequent studies however, that used specific questionnaires revealed that preponderance of treatment emergent sexual dysfunction ranged from 40-80%.[90-93] SSRIs were compared to placebos in double-blind placebo-controlled trials,[92,94-98,] which employed straight questioning and these studies systematically found a considerably higher preponderance of sexual dysfunction in SSRIs as compared to that of placebo.

When compared in double blind studies[99-102] and open level trials,[103,104] SSRIs have shown to have sexual side effects. A survey including 502 adults in France and UK showed sexual side effects due to SSRIs/SNRIs in 39.2% of the sample in UK and in 26.6% of French sample.[63] Around 25.8-80.3% of patients on antidepressants had sexual dysfunction as found by a metanalysis.[65] The order of magnitude of antidepressants causing sexual side effects was seen to be sertraline, venlafaxine, citalopram, paroxatine, fluoxatine, imipramine, phenelzine, duloxetine, escitalopram, and fluvoxamine. There was less association seen between sexual dysfunction and bupropion, nefazodone, and mirtazapine. All SSRIs have been found to cause absent/delayed orgasm/ejaculation and at times reduction in desire and arousal.[105,106]

A study[107] evaluated sexual dysfunction in depressed patients using sexual dysfunction questionnaire. These patients were prescribed fluoxetine, sertraline, or paroxetine. It was seen that in up to 60% of men, there was emergence of sexual dysfunction with delayed orgasm as the most common dysfunction (35%). This was followed by an inability to achieve orgasm and increase in stimulation threshold needed to maintain erection (30%) and decreased intensity of orgasm (24%) in a quarter of the subjects. There are also studies[86,108] that show SSRI's eminent effect in anorgasmia and delayed ejaculation/orgasm. There is persisting ambiguity regarding the significant differences among SSRIs/SNRIs in the incidence of sexual dysfunction they produce. Sexual dysfunction is more likely to occur with the use of paroxetine than other SSRIs, meanwhile there might be noticeable advantages to the use of fluvoxamine.[109] A comparative study done on men with premature ejaculation, evaluating the effects of fluvoxamine, fluoxetine, paroxetine, and sertraline showed that men taking

paroxetine found greater delay in ejaculation while men on fluvoxamine found the least delay.[110,111] How the SSRIs cause their sexual side-effects is probably multi-faceted; but, evidence points towards their serotonergic effect through 5HT2C receptors being chiefly responsible while antagonism of cholinergic receptors and attenuation of effects of nitric oxide[111] too may play a part. This could point towards the reason treatment with paroxetine shows a higher occurrence of erectile dysfunction in men and reduced vaginal lubrication in women.[109]

Agents with dual actions on serotonin and norepinephrine

Evidence exists that noradrenergic effects may counter the serotonergic effects on sexual function; however, the studies on SNRIs (duloxetine, milnacipran, venlafaxine, and desvenlafaxine) have provided uncertain results. Duloxetine[112] proved to have much lower chances of causing sexual dysfunction than paroxetine or escitalopram; however, the contrast was not present after 12 weeks of treatment, which would suggest that duloxetine may just have an edge over SSRIs for a short term.[93]

Kennedy *et al.*[103] compared sexual side effects of venlafaxine to those of paroxetine and sertraline in men and women, and found that women had lesser sexual dysfunction than men. Further studies[63,90,113] since then have not been able to get similar results and show that up to 60% on treatment with venlafaxine showed decreased desire and delayed orgasms which would bring it on par with SSRIs. Studies utilising unprompted self-reporting have shown that desvenlafaxine causes lesser sexual dysfunction in women as compared to men.[114-116] Clayton *et al.*[117] conducted a unified analysis of all randomised, double-blinded, placebo-controlled studies for depression (four flexible and six fixed dose studies). It

showed that erectile dysfunction was the most likely sexual side effect linked to desvenlafaxine treatment in men (seven per cent vs one per cent in placebo) and anorgasmia was the most common side effect in women (one per cent vs zero per cent). Milnacipran, an SNRI with marked antagonism of norepinephrine transport, has been asserted to have lower rates of causing sexual dysfunction than SSRIs.[118] A collective study that assessed sexual functionality first at six and then at 12 weeks of treatment with milnacipran reported enhancement in desire in 56% of the sample along with 60% decrease in depressive symptoms.[119]

Mirtazapine supports noradrenergic and serotonergic activity by its agonistic effect on post-synaptic HT1A receptors as well as its antagonistic effects on 5HT2 and 5HT3 receptors.[120] It is the 5HT2 antagonism mechanism that is believed to reduce serotonergic mediated sexual side effects. It is on this basis that it has been asserted that when pitted against SSRIs and venlafaxine, mirtazapine has a much lesser chance of causing sexual dysfunction.[86,109] A systematic assessment of sexual functionality among outpatients suffering from depression revealed that mirtazapine may in fact increase functioning of some of the phases in both men as well as women.[120] Ozmenler *et al.*[121] found that in case of patients who were already in remission and developed SSRI-induced sexual dysfunction, switching to mirtazapine led to only less than half of them reporting sexual dysfunction at the end of the eight weeks treatment. Sexual dysfunction that occurred while on treatment with duloxetine also seemed to improve when the patient was switched to mirtazapine according to initial evidence.[122] However, when the rates of sexual dysfunction were compared between mirtazapine and serotonergic antidepressants, studies showed irregular findings as some of the studies[123-125] showed greater rates of sexual dysfunctions while on SSRI treatment and other studies[126-128]

showed almost no differences. Some studies report that when mirtazapine does cause sexual dysfunction, the intensity is substantially lower.[109] Clayton *et al.*[90] assessed more than 6000 patients who were started on newer antidepressants. Patients on SSRIs, mirtazapine, or venlafaxine had significantly higher sexual dysfunction while patients on nefazodone and bupropion had the lowest.

Treatment-emergent sexual dysfunction in depression

Various methods have been proposed for the management of patients with antidepressants induced sexual dysfunction but there are few randomised controlled data that assess the efficacy and acceptability of various pharmacological and psychological modes of management[129] and no intervention can be labelled as "ideal".[130]

When priority is preservation of usual sexual functioning, antidepressants with lower rates of sexual side effects could be preferred. However, many of these could have alternative side effects, constrained availability, or debatable efficacy. As sexual dysfunction caused by antidepressants may be dose related, diminution of dosage is often adopted as a first line approach to treatment,[131] which however could lead to a relapse of the depressive symptoms and thus should only be an option once patients have gone into full remission. Periodic withholding of treatment (drug holidays) have been considered but this would be beneficial only a proportion of patients on some particular antidepressants, furthermore there may be worsening of the depressive symptoms and withdrawal symptoms can occur.[132] Various adjuvant interventions have been suggested for management of sexual dysfunction but the evidence for them is currently lacking.

Randomised placebo-controlled trials have shown evidence of effectiveness of bupropion and olanzapine,[133] testosterone gel,[134] and the PDE-5 inhibitor sildenafil (both in male as well as female patients),[135,136] and tadalafil.[137] There are few comparative studies, but a placebo-controlled study suggested no efficacy in using mirtazapine or yohimbine in female patients as augmentation drugs.[138] When aripiprazole was used as an augmentation agent with antidepressants, improvement was seen in desire and satisfaction in depressed women, and this was independent of any change in depressive symptoms.[139] Changing of antidepressant agent seems reasonable and is often done but placebo-controlled evidence of effectiveness has been shown only in a single study of moving from sertraline to (now withdrawn) nefazodone.[129] Switching drugs may also lead to SSRI withdrawal symptoms and the new drug may not be as effective in treatment of depression. That regular exercise done before sexual activity improves desire and overall sexual functioning in depressed females on treatment with antidepressants was shown by a single study.[140] There is involvement of nitric oxide in the male and female sexual functioning. In men, by bonding to the guanylate cyclase receptors in the corpus cavernosa of the penis, nitric oxide leads to increased levels of cyclic guanosine monophosphate (cGMP), which causes relaxation of the smooth muscles (vasodilation), increase in the flow of blood into the spongy tissue of the penis, and subsequently erection. By strongly inhibiting cGMP specific PDE-5, sildenafil, tadalafil, and vardenafil cause increase in cGMP and thus facilitation of erection.[141] The interaction of nitric oxide and estrogen in women is less understood but the PDE-5 inhibitor enhancement of cGMP in non-adrenergic non-cholinergic signaling for women appears to have same effect as in men, as the release of nitric oxide causes vasodilation in clitoral and vaginal tissues.[142] The

effectiveness of PDE-5 inhibitors in improving sexual dysfunction caused by antidepressants was shown by randomised placebo-controlled trails. In depressed men with erectile dysfunction who were not on any antidepressant treatment, starting PDE-5 inhibitors showed a decrease in depressive symptoms, a better quality of life, and improvement of interpersonal relationships.[143-145] In the Flinders rat depressive phenotype,[146] nitric oxide activity was shown to be a significant vulnerability factor. It was also shown that PDE-5 inhibitors can pass through the blood brain barrier[147] and that sildenafil through central inhibition of muscarinic receptors, showed some antidepressant properties.[148] Some limitations for the use of PDE-5 inhibitors for the treatment of sexual dysfunction includes side effects like headache, dyspepsia, visual disturbances as well as the need for careful use in patient with cardiovascular conditions.

Conclusions

Sexual dysfunction can be caused by various mental illnesses and psychotropic drugs. A thorough enquiry in every patient about their earlier and current sexual life are required to evaluate potential sexual dysfunction, and to treat it aiming for maintaining quality of life and emotional experiences as well as preserving partner relationships. Management options with lesser sexual side effects should be preferred in patients with mental illnesses who prioritise preserving a sexual life. For achievement of best possible results and to ensure compliance, management of treatment-emergent side effects is imperative.

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AFFECT

CHAPTER VII

Treatment resistant depression: a penumbra for review?

Chayanika Choudhury

"But when the melancholy fit shall fall
Sudden from heaven like a weeping cloud,
That fosters the droop-headed flowers all,
And hides the green hill in an April shroud;
Then glut thy sorrow on a morning rose,"
- John Keats

Depression is a debilitating illness that can wither anyone suffering from it, from the tender age to the winter of one's life.

According to noted reports, World Health Organization (WHO)[1] hands out an alarming number of 300 million people suffering from depression worldwide. Depression saps out the social life of a person and also cripples the occupational aspects of one's life. Studies have shown light on the deleterious effects of it on cognition. Dotson *et al.*[2] studied the risk of cognitive impairment

and dementia with depression, and found that episodes of depression elevates the risk of dementia by 14%.

New era has witnessed more number of people coming out of their dark pit and approaching a medical desk for depression. This scenario is a two sided coin. We can applause the rising awareness and breaking of the taboo hinged with obtaining medical help for it. Also, raising concerns for the mental health professionals is the extent of response one can expect.

Antidepressants have come a long way from the serendipitous discovery of monoamine oxidase inhibitors to the newer molecules. Brain stimulation techniques have also been tested and advocated by many reliable studies worldwide. Despite the progressive advances in treatment of depression, there has been minimal researches for specific antidepressants for the patients with recurrent depression or treatment resistant depression (TRD).

The burden of depression is only over-burdened by the increasing number of non-remitters. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial of antidepressants showed that only one-third patients remit on their first antidepressant treatment and even after a year of treatment with four different antidepressants given for adequate duration (12 weeks), only two-third achieve remission of their symptoms. Even in remitters, there lies a risk of relapse. The likelihood of relapse increases with the number of treatment a person needs to remit. The trial states that the relapse rate for non-remitters ranges from 60% at 12 months and 33% for remitters at 12 months after one treatment, respectively. However, the protective nature of remission disappears once it takes four treatments to achieve remission.

Souery *et al.*[3] conducted a multicentre European study (Group for the Study of Resistant Depression [GSRD]) which found that 50.7% of depressed patients recruited from specialist referral centres were labelled as treatment resistant after two consecutive courses of antidepressants.

The intricacies of every illness have been clearing up ever since our resolute to re-evaluate the existing paradigms of it. TRD is defined as no response to two adequate courses of treatment.[4] Interestingly, albeit newer antidepressants, there has been a rise in the number of so labelled TRD. This scenario undermines the existing paradigms of the diagnostic system and questions the validity of it. We are faced with the perplexity of the paradigms of the diagnostic criteria and the apt choice of medication for the individual. Several debates have been going on to reach a consensus on a renewed definition of 'treatment resistant depression', 'treatment resistant bipolar depression' and 'multi drug resistant bipolar depression'. Re-evaluation of the adequacy of treatment duration with monotherapy has called for several studies across the globe. Hence, a re-examination of the diagnostic system followed by choice of medication are of paramount importance so that the loopholes do not create avenues for misdiagnosis and non-remission.

First and foremost trouble occurs due to the mismatch of nature of illness and that of diagnostic system. Illness is longitudinal in nature, while our diagnostic paradigms are cross-sectional in nature. A simple example like one getting treated for major depressive disorder or recurrent depression unless a polarity of mania comes up. The bipolarity of the illness taken into consideration far later in the course of it is a disadvantage to us as it could have spared us the lag time of early use of mood stabilisers.

The disparity of symptom observation and self-reported symptoms is another grey area of diagnostic confusion due to overlap of symptoms. There is no crystal clear demarcation of symptom criteria for bipolar II, recurrent depression which can be easily confused with a patient of borderline personality disorder in the first setting.

Diagnostic heterogeneity in psychiatric taxonomy is another cause of concern. DSM-5 and ICD-10 have a dichotomous view on the same illness. DSM-5 needs five out of nine symptoms whereas ICD-10 needs four out of ten symptoms with one from the three primary symptoms. Also, criteria for 'mixed feature specifier', according to DSM-5, does not include irritability, distractibility, and psychomotor agitation which means that many cases with mixed features are missed.[5]

The criterions are based on clinical researches and epidemiological surveys which operates on the symptoms rather than the underlying pathophysiology. Age of onset as well as cause of onset plays a pivotal role. Anxiety may be perceived as depression by the adolescents, whereas hereditary load definitely makes them vulnerable for further episodes of depression or bipolar disorder. Depression can occur after significant life events like childbirth, loss of loved ones which may be the only episode in entire lifetime. Also, some might suffer seasonal variations. It is then we must address the underlying cause. Basically, it is the combination of symptoms, patterns, cause, and heredity that must be borne in mind before reaching out for optimum treatment options.

The issues surface up when one tries to 'fit in' the symptoms into the rigid framework of the available diagnostic system. The presentation of real-world symptoms may not align with the existing

paradigms which may lead to over diagnosis or under diagnosis of the patients.

The failure in treatment has more to do with the labels of 'response', 'remitters', and 'non-remitters' than with the antidepressants per se. Fifty per cent reduction in the symptoms is considered as response. Here, we need to be sceptical about the improvement in terms of specific symptoms. An improvement in sleep and appetite with intact suicidal ideation in a person cannot be weighed as same in another with reduction in suicidal thoughts with sleep and appetite disturbance. A more specific definition of response is needed. The kernel of TRD should include those who fail to show response even after third strategy of treatment for depression. Some may not respond to treatment from the initiation of the treatment who are also labelled as treatment resistant which only puts out our inability to diagnose and treat, and our lack of patience.

de Vries YA *et al.*[6] conducted 30 trials and concluded that non-response till six weeks does not rule out remission as it can take up to 12 weeks. In 2012, a European multicentre project conducted by GSRD, "Patterns of treatment resistance and switching strategies in affective disorder", challenged the notion that prescribing the same antidepressant with same mechanism of action for longer time is more beneficial than switching. Adding to it was the observation that switching between classes had no added advantage over switching between the same class.[7]

The onus of responsibility of the patient outcome lies on the shoulders of clinicians as well as researchers. Researchers should endeavour to revise the diagnostic paradigms comprehensively. They must elaborate the validity of the diagnostic system on heterogeneous groups of population with genetic and geographical

variability. The clinicians must be alert about the subtypes and varied presentations of the illness and must learn to read between the fine lines of the overlapping manifestations. The specific symptoms improvement must be weighed more over an overall improvement in a rating scale. TRD need not be helpless entity in our hands. A mere change of viewing glasses could alter our approach and be a game changer for us.

Let not the depressed be compressed by our rigidity.

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CHAPTER VIII

Bipolar disorder and neurosyphilis

Suresh Chakravarty, Bobby Hmar, Priyam Sharma, Siddhartha Nandi

Introduction

Syphilis is also called "the great imitator" of a lot other diseases. It is associated with neuropsychiatric manifestations sometimes. Neurosyphilis (NS) develops in four to ten per cent of untreated syphilis. NS can occur at any stage but commonly seen as a late manifestation of syphilis.[1] In human immunodeficiency virus (HIV) patients, NS has a rapid course and illness is severe. However, in patients with immunity intact, the disease is very insidious and largely unsymptomatic.[2] A lot of neurological and psychiatric manifestations are seen in NS. We describe in this case study, a female patient of bipolar affective disorder (BPAD) with psychotic symptoms having NS who is non-HIV infected.

Case report

A 70-year-old Hindu female, mother of one son and known hypertensive for last 15 years was brought and was consequently

admitted in psychiatry ward of Gauhati Medical College and Hospital (GMCH) in the month of July 2019. She had symptoms of talkativeness, tall claims, singing songs, decreased sleep, muttering, hearing voices not heard by others, decreased appetite, religiosity, and aggressiveness with features of delirium like fluctuating orientation and confused behaviour for last two months and the illness presented episodically for last 25 years. The onset of the illness was insidious.

The first episode occurred in 1994 (with similar symptoms except features of delirium) and was admitted in a hospital for two months. She also received electroconvulsive therapy (ECT) with medications (details not known). The patient reached premorbid level in four months. She discontinued medications following two check-ups and only used to take tablet clonazepam 0.5 mg as and when she had decreased sleep.

The second episode occurred in 2009 when the symptoms were less severe with no delirium and present for around four days. There was a stress factor during that time as her nephew did not agree to marry a girl whom she liked. She was taken to a psychiatrist and took medications continuously for one month. Then she reached premorbid level and took medications off and on.

The third (current) episode occurred from May 2019 and symptoms were severe along with symptoms of delirium and dyselectrolytaemia. This time the stress factor was increased tension regarding her granddaughter using mobile excessively and making new friends. She first had symptoms of decreased sleep along with talkativeness and after ten days, she was found to be disoriented and confused. She was admitted in a hospital for around one week and was detected with hyponatraemia. After correction, she regained

consciousness and responded to verbal commands. But, irrelevant talk and manic symptoms persisted. When her symptoms were not improving any further, she was admitted in the Department of Psychiatry, GMCH.

It was found that her father and sister had similar psychiatric illnesses (BPAD symptoms) and there was also history of suicide in her eldest sister's son by hanging. She was married for last 40 years and attained menopause at 45 years of age. She completed Bachelor of Arts degree and worked as a high school teacher (currently retired). Premorbidly she was introvert and anankastic. Her hobbies included writing poems and singing old folk songs.

In mental status examination, her psychomotor activity was raised, eye to eye contact was partially maintained, speech was coherent, relevant, but at times irrelevant, productivity of speech was increased and reaction time was decreased. Her orientation was fluctuating.

The diagnosis of BPAD currently in mania with psychotic symptoms was made according to ICD-10.[3]

We did all routine blood investigations and also did cerebrospinal fluid (CSF) study in which her haemoglobin came out to be 7.2 gm/dl, white blood cell (WBC) count 13,490/ microlitre and CSF-VDRL (Venereal Disease Research Laboratory) test came out to be positive. Her mini-mental state examination (MMSE)[4] score revealed 19/30 which suggested that there was mild cognitive impairment. Integrated Counselling and Testing Centre (ICTC) testing for HIV came out to be negative.

She was prescribed injection benzathine penicillin 1.2 million unit deep intramuscular (IM) in each buttock once every three weeks. She was also given tablet risperidone 1 mg twice daily and tablet

donepezil 5 mg + memantine 5 mg at bedtime. She was hypertensive for last 15 years and continued tablet telmisartan 40 mg once daily in the morning.

Magnetic resonance imaging (MRI) of brain revealed cerebral atrophic changes with Fazekas grade 1 white matter changes (Figure 1). It also revealed disease T2 and Fluid-Attenuated Inversion Recovery (FLAIR) hyper-intensities in bilateral fronto-parietal lobes in periventricular and subcortical locations. Basal ganglia calcification was noted bilaterally (Figure 2).

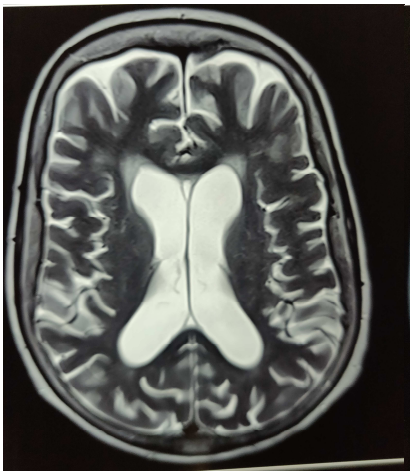

Figure 1: Magnetic resonance imaging (MRI) showing cerebral atrophic changes.

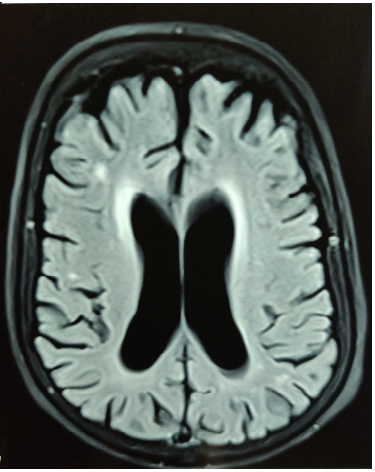

Figure 2: Magnetic resonance imaging (MRI) showing basal ganglia calcifications.

With benzathine penicillin and other medicines, there was drastic improvement in the symptoms of the patient. Patient did not give history of any sexual exposure with others apart from her husband. Husband's serum VDRL was negative and according to her, he had

no exposure with sex worker. She was discharged after two months of hospital stay. She came for two follow-ups. The first one was after two weeks of discharge and the second one was one month after first follow-up. In both the follow-ups, her symptoms had improved and she was maintaining well.

Discussion

NS has various ways of presentation. NS can present as meningeal syphilis, meningovascular syphilis, and neuropsychiatric group in the form of general paresis.[1] Mesodermal structures (example-meninges) are affected first. Brain and spinal cord are affected in late NS. At times there is overlap of diseases too.

In late manifestation of syphilis, tabes dorsalis occurs due to demyelination of dorsal roots and posterior columns.[1] In NS, neurological symptoms include foot drop, bladder disturbances, impotence, headache, and dizziness.

According to various literature, psychiatric manifestations are seen frequently with NS and ranges from 30 to 85%.[2,5] Psychiatric manifestation seen most commonly include personality changes, delusions, and hallucinations. NS may also present with dementia, schizophrenia-like disorder, and also with mood disorder, both bipolar and depressive symptoms.[2]

If CSF VDRL is reactive then diagnosis of NS is confirmed.[2,6] CSF-VDRL is highly specific but 50% samples with NS is negative.[6] So, negative VDRL does not rule out NS.

Finding in MRI include diffuse cerebral atrophication, and changes in parenchyma of the temporal and frontal region are observed. Infarcts and white matter changes are observed.[7] In our patient,

MRI shows cerebral atrophic changes along with hyper-intensities in bilateral fronto-parietal in periventricular and subcortival areas. However, normal MRI at this age may also reveal these finding. Dose of medication given in the form of injection benzathine penicillin is the first choice for treatment of NS.[8]

Conclusion

We have to be careful and think about psychiatric symptoms in NS. In differential diagnosis for mood disorder, we should keep NS as a probability.

In this article, early diagnosis of NS along with mood disorder with psychosis and proper treatment changed the outcome of patient drastically.

Declaration of patient consent

All appropriate consent forms were signed by patient and her relative to the author. The patient and her relative have given permission for her investigation images and other information to be published in book. The patient knows that the name and initials will be kept secret and not be published, but anonymity cannot be guaranteed.

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CHAPTER IX

Challenges of psychosocial management in bipolar affective disorder

Mythili Hazarika, Puja Bora

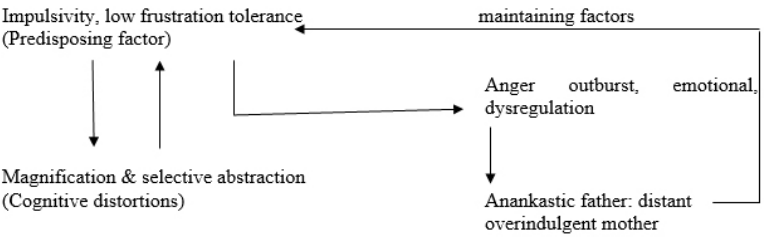
Bipolar affective disorder (BPAD) is a challenge for any clinician to treat because of the bipolarity nature of the illness. As switching from one polarity to the other is a challenge, a holistic psychosocial management becomes imperative. This enigma of bipolarity becomes more accentuated due to the comorbidities such as anxiety disorders, substance abuse, obsessive compulsive disorder (OCD), axis II disorders, personality disorders, family pathology, etc. This case report focuses on early onset BPAD with an evolving borderline personality disorder (BPD) where a comprehensive psychosocial management was planned.

Authors present a case of early onset bipolar disorder to highlight the challenges in management. Master X, aged 16 years reported to a tertiary centre who was evaluated in the inpatient setting for chief complaints of insidious onset, continuous illness for two years duration characterised by substance use, demanding behaviour,

novelty seeking, anger outbursts, feeling lonely, low mood, feeling restless, inability to concentrate, feeling of boredom, deliberate self-harm, aggressive outburst in trivial matters bringing chaos to family atmosphere. Frequent feelings of boredom and emptiness was reported and subsequent intent to commit suicide was present. Considering the suicidal thoughts, Master X was admitted for assessment and management.

On mental state examination (MSE), mood was anxious and low with ideas of helplessness and worthlessness. As he had syndrome composed of primarily emotional dysregulation, and a number of true personality traits like inordinate anger, impulsivity, and a tendency to break down in cycles of irritability and depression, a diagnosis of BPAD with an evolving BPD and substance use was made.

Past treatment of electroconvulsive therapy (ECT), mood stabilisers, and rehabilitation for substance use (tobacco, alcohol, and dendrite inhalation) was present and there was very minimal improvement in his aggressive behaviour, demanding nature, and excessive mobile use with significant family conflicts. Father had an anankastic personality and the client's communication with him is closed while there was switchboard pattern through the mother. Physical examination was normal. The psychotherapeutic formulation was:



The psychotherapeutic components look into the holistic approach of cognitive style, affective component, motivation, and capacity for introspection as these determine whether an expressive (psychoanalytically oriented) technique is preferable or a cognitive behavioural one would be necessary. In a case where nearly all the axis are involved then flexibility is beneficial. In emotional crisis supportive work, in demanding situations limit setting, in cognitive distortions cognitive behavioural therapy (CBT), in anxiety mindfulness based, in emotional dysregulations dialectical behaviour therapy (DBT) techniques, in maintaining social and interpersonal rhythms interpersonal and social rhythm therapy (IPSRT), in family conflicts a structured family therapy approaches were used. Hence, the eclectic model of psychosocial care was undertaken to address the issues of the individual and the family. The client was motivated, psychological minded, support system was adequate, emotional insight was present which were favourable for therapy and prognosis. Though literature suggests specific DBT for BPD and IPSRT for BPAD, we had to take an eclectic approach which is a combination of various principles of psychotherapy, tailor made to the client and his family.

Initial sessions (three sessions) focused on psychoeducation about BPAD and the comorbidities, i.e. evolving BPD, substance use, and the dysfunctional communication styles. Family sessions were held and the need for open communication and direct interaction was initiated among all family members. Homework assignments and activity scheduling was done in the inpatient setting with standard instructions to mother not to be indulgent and put limits to his mobile use as it was a cause of his sleep deprivation. Thought diary was asked to be maintained and how each situation made him feel and how he reacted to those were discussed in subsequent sessions. The antecedents, behaviour, and consequences were written by him

and those were replaced by various positive options which were generated by the client with therapist guidance.

The circadian basis of IPSRT where the significance of stable daily routines in the maintenance of the euthymic state was introduced. The vicious cycle of disturbed circadian rhythm precipitating BPAD was put forward, and the client and the family were made aware of proper sleep hygiene. Our DBT individual therapy had a focus on enhancing the client's motivation and helping him to apply the skills to specific challenges and events in his life in the future.

Middle phase (three sessions) of therapy focused on his failures in relationships and the feeling of emptiness. The rejection sensitivity was discussed in detail and the cognitive distortions of magnification of the failed relationships and subsequently thinking that he was a complete failure in interpersonal relationships was addressed with a rational emotive therapy approach. His beliefs were asked to be written down and the core belief of "must's" and "should's" in life were made flexible. The stage of adolescence and the inherent need for identity was addressed with various CBT strategies. The negative implications of taking substances were discussed and thereby establishing a contract of "no substance use". Mindfulness-based stress reduction (MBSR) was initiated as he was found to do things impulsively.

There were crisis situations in between as the client resisted and demanded to allow him to go out and drive his car to which the therapist had to put limits and this was asked to be practiced at home. He was taught to tolerate frustration by the mode of habituation which is another behaviour therapy technique. Jacobson's progressive muscle relaxation (JPMR) was initiated as anxiety was found to be significant which are cues for relapse in

BPAD. The rationale for each approach was discussed and after consensus they were asked to be applied during the hospital stay. The acceptance of the client by the therapist with an approach to modify his behaviour continued keeping the DBT approach in mind. Homework assignments were done regularly and his demands had decreased.

In the termination phase (three sessions), along with family therapy (structural and behavioural) and concurrent individual sessions, the client was positively reinforced for writing his diary and doing his tasks and for his motivation to apply the therapeutic principles after discharge.

He gave positive feedback about the sessions where he could understand himself better and his illness which were causing hindrance in his academic pursuits. Post discharge plan was made with an activity schedule for his daily activities, mood charting for medication adherence was focused as he was put to lithium, olanzapine, and fluoxetine; so, monitoring of mood was essential if switch to mania or hypomania takes place, limit setting in car driving was proposed as he was under-aged and had no license, restrictions in mobile use with a regular sleep time, family rituals of eating together, meeting and discussing about newspaper headlines, general topics and no critical comments and hostile remarks, and focus on positive communication were suggested. JPMR and MBSR was asked to be practiced at home.

In the subsequent follow-up on an outpatient basis, when the client was reviewed, he and his parents reported that his mobile use was less, frustration tolerance had increased as he did not express his desire to drive the car whereas his demand to drive the car was a major conflict before therapy, and he slept well on regular time.

His anger outburst and demanding behaviour still persisted. When this was reflected upon, the therapist found that his mother continued to be indulgent which was a negative prognostic factor. The biggest challenge was their place of stay which was quite far from the tertiary centre; so, the treating team advised them to see a therapist locally in their hometown once a week for his conduct problems which was personality related. This is again a challenge in our part of the state where trained clinical psychologists are negligible and, in his hometown, there is none. But, a local psychiatrist was contacted and he was guided for necessary psychosocial interventions with the client and the family.

Discussion

There is a debate over the issue of BPD belonging to bipolar spectrum.[1] Comorbidities are so common between the two that approaches to treatment requires meticulous history taking and tailor-made interventions. The biological, psychodynamic, psychosocial, and childhood experiences with parents are aetiological factors in BPAD with BPD. In the last several years, BPAD and BPD were considered to be biological diseases with genetic bases and possibly triggered by stress factors.[2] There is also evidence that stressful life events influence the course of this disease; hence, the "kindling" effect. Literature suggests that some cases of BPD are linked genetically to or are in the "border" of BPAD.[3] But, the conditions can also arise due to adverse postnatal environment like parental neglect and childhood trauma.

In some patients, both risk genes for BPAD and adverse family conditions are present but, in our client, the genetic loading was absent though his father had an anankastic personality, it was not in the range of a disorder. Hence, with pharmacotherapy, the

psychosocial management was imperative for relapse prevention and to resolve the characteristics in his personality which had signs to develop into an emotionally unstable personality (mixed). Our clinical case raises the question of the possible stress factors like parents' psychopathology, parenting style, childhood trauma, and environmental variables that may have influenced the onset and the course of BPD and further developing BPAD. This early onset bipolar disorders usually have patho-plastic effect on the personality development and has lifelong impact on the course of the illness. Hence, the psychosocial management was challenging but proved to be beneficial in managing the risky behaviour that would have been detrimental for an adolescent's holistic care and rehabilitation.

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AFFECT

CHAPTER X

Delirious mania in elderly

Sansanka Kumar Kakati, Porimita Chutia

Introduction

Delirious mania is one of the rare psychiatric syndromes, characterised by acute onset mania or hypomania, along with signs and symptoms of delirium, with past and family history of affective disorder, and with positive response to treatment for mania.[1] Calmeil, in 1832 was the first to identify this.[2] After Bell described it as a separate clinical entity in 1849, it came to be known as Bells mania.[3] Kraepelin in 1921, differentiated it from hypomania and acute mania and described it as most severe form of mania.[4] Since then it has been reported only in case reports as secondary to some underlying cause.[5] Here, we are going to discuss one such case of an elderly female who presented with symptoms of delirious mania.

Case report

Mrs. X was a 55 years old, married, female homemaker, studied up to class ten, from rural origin who presented to the psychiatry outpatient department (OPD) with symptoms of decreased sleep, restlessness, trying to wander out, forgetfulness, talkativeness, and irritability. She was admitted with these symptoms for further

evaluation and appropriate management from Gauhati Medical College Hospital (GMCH) OPD on 22/10/18.

On further probing, history revealed that she had shouting spells and an altercation with some neighbourhood boys playing carom, around eight to nine days ago. Thereafter, she developed confusion and showed signs of forgetfulness (for last three to four days). There was also one episode of passage of urine in clothes.

The attendant gave history of similar kind of symptoms around seven years back for which she was admitted in GMCH and received three sessions of electroconvulsive therapy (ECT). After treatment, symptoms gradually decreased and the patient reached the premorbid level after around three to four months. However, medical documents of that period was not shown. There was no significant past history of any known major physical illness. There was no history of any substance abuse/use; so, the possibility of substance withdrawal or intoxication was ruled out. The family members did not notice any deterioration in memory prior to the onset of these symptoms and she was carrying out her daily activities with no difficulty. There was no known family history of any psychiatric illness. Mini-Mental State Examination (MMSE) score was done and it came out to be 8/30 in the OPD and 12/30 after admission on the evening of the same day. She showed deficits in domains of orientation, attention, recall, calculation, and language. Thus, possibility of delirium was considered. The lower score in OPD might be due to the patient being very anxious about her illness and by evening, anxiousness had decreased after receiving benzodiazepine.

On hospitalisation, all routine investigations were done and routine blood parameters, blood sugar, liver and kidney function tests were

normal except serum sodium which was marginally low. The patient was given adequate intravenous (IV) fluids (normal saline) and salt capsule for correction. But despite this correction, the symptoms of confusion continued. Hence, further investigations were done to rule out any metabolic causes of delirium. Vitamin-B12 level came low and injectable methylcobalamin was added to the treatment regimen.

Initially, she received injectables (haloperidol and promethazine) but later when restlessness decreased, she was started on tablet olanzapine (10 mg) and tablet divalproex (500 mg) at bedtime while injectables were gradually tapered and stopped. She showed improvements with the above medications, MMSE score was found to be 19/30, and was discharged.

Written informed consent was obtained from the attendant.

Discussion

Delirious mania is a rare presentation of bipolar disorder. It is essential in clinical practise to identify and differentiate delirious mania from delirium for proper management of the patient. Weintraub and Lippmann[6] reported two cases of elderly individuals with mania who initially had symptoms of delirium. Lee *et al.*[7] reported five cases, of which one was elderly and presented with manic symptoms and later developed delirium. This is very much similar to our case as discussed above and hence, it fits in to the diagnosis of delirious mania.

There is a chance in our case that old age was a predisposing factor for delirious symptoms. Old age is considered as an independent risk factor for developing delirium in the elderly.[8] Hence, physical

assessment along with current and past psychiatric histories are important for appropriate diagnosis and treatment.

Delirious symptoms might also be due to some underlying medical conditions; but, past history and routine investigations revealed no major physical illness in the form of diabetes, hypertension, or thyroid abnormalities except slightly low level of vitamin-B12 for which she was already receiving supplements.

Another probability for the above manifestation of mania and delirium might be cerebrovascular phenomenon. However, the absence of any neurological signs and negative brain imaging study ruled out this possibility too.[9]

Limitations

1. Lack of appropriate diagnostic criteria for accurate diagnosis in ICD or DSM.
2. Low vitamin-B12 might be contributory factor for confusion.
3. Reports of delirious mania are very few in elderly population.

Conclusion

Our case shows that delirious mania, although has not found a place in the psychiatric classification yet, is still valid as elderly people can have atypical presentations of psychiatric syndromes. On this, we hope that delirious mania is considered as a differential diagnosis in elderly with history of affective disorder presenting with delirious symptoms in the absence of acute medical condition.

There is also a need for inclusion of this condition in the classification of psychiatric conditions for better diagnosis and appropriate management.

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CHAPTER XI

Caregiver testimonial from Ashadeep

Experiences of working with persons affected by bipolar disorders

Anjana Goswami

The burden on caregivers of patients with bipolar is multifaceted. The caregivers need to have a proper understanding of the symptoms, intervention method, and sign of relapse. As the bipolar cases tend to be chronic, the burden on caregiver is significantly higher than other types of mental illness. The task of care giving for person with bipolar disorders become more challenging as the obvious fluctuation of mood from manic to normal to depression creates a negative impression on the family as well as in the community. As families are the major caregivers, they have to be under tremendous pressure and stress, which sometimes affect in their mental health. I am citing here the case of Maya (name changed) a beautiful young girl, diagnosed with bipolar. She was married off to a young businessman at a very young age. After a few months of her marriage, she started showing off the symptoms. When her manic phase started, her in-laws as well as her husband

were quite confused and they decided to send her back to her parents. One fine day she was brought to her home by her husband with the promise that he will take her back after a few days, but have never returned. Maya's parents were at the height of helplessness. Their unlimited rounds to the psychiatrist, hospitals, and medication seemed to be unending. But despite all these she used to have relapses. She attempted suicide twice in between her depressive episodes. At that stage she was referred to Ashadeep day rehabilitation centre by a psychiatric social worker. Presently Maya is engaged in the vocational unit of Ashadeep and she is showing good progress of recovery. The interval periods of relapse which were quite frequent earlier, has now been subsided and for the last two years she is maintaining quite a balanced condition. She continues to have her medication regularly.

During the episodes, Maya's parents and siblings had to face many challenges. The whole family was emotionally most affected by the negative judgement of people and they were socially isolated. Maya's parents were almost on the verge of burnout. But it is heartening to see that their experiences have taught them to cope with the problem of their daughter and they learned to develop a positive attitude towards the illness.

In most cases, it is seen that caregivers' burden and their traumatic experience goes unnoticed. Very often they feel distressed, which ultimately affects in their care giving process. Therefore, clinically effective, well targeted, and practically viable intervention methods should be designed towards the psychiatric needs of families of bipolar persons, which may result in improved caregiver and patient outcome.

My journey in Ashadeep

Lisali Humtsoe

One particular day, I was sitting at my desk with the laptop in front, trying hard to focus on my incomplete assignment. But, for some reason I was feeling low and demotivated. And then, a young man comes in and greets me with a smile, "Hi, how are you?" I smiled back and said I was fine, but I was not actually fine. He stood near me for some time staring at what I was doing in my laptop.

He is Mr. Lohit (name changed). Presently, he is a resident of Udayan- rehabilitation home for homeless mentally ill men.

As he chose to sit with me for some time, we talked about our interests, likes and dislikes, and I asked few questions which he responded with ease. We continued talking and towards the end of our conversation, I asked if he would be comfortable to share some of his experiences while he had his episodes. I was curious to know whether he remembers or not. He did not hesitate or feel shy but he courageously spoke about the worst days of his life. He goes on.....

"Feeling of hopelessness, worthlessness, meaningless life, suicidal thoughts, and suicidal tendencies are some of the worst feeling I have experienced during my episodes…

When I lost my mother in 2014, I thought I was all alone in this whole wide world. I felt very lonely and depressed…

In 2016, I was diagnosed with a severe mental disorder called bipolar disorder. It was more than just an illness for me. It destroyed my relationships, and affected my work performance. Having pursued

Diploma in automobile engineering, I worked in few telecom sectors, and work was my passion.

One day, I decided to give up my life and I jumped into the mighty Brahmaputra but luckily police found and rescued me and brought me to Ashadeep".

Today, despite the pain and suffering he had been through, he still fights to regain new life. Having vast experience in telecom sector, today he still lives with confidence and throughout our conversation he repeatedly said, "I believe in myself that I can do it again". He continues to live with hope to retain his identity by doing what he loved to do. He knows he will have to live with his illness for the rest of his life, but he does not want to let his illness defeat him.

He continues to fight every day to find meaning and purpose of life. And he is confident that he would find himself a job soon. He believes that it was god who gave him second chance to live, which is his main motivation to keep going.

Then, I suddenly questioned to my inner self; why I was complaining about my small problems. Why not I look at them and learn from their struggle and the battles of everyday life. Their problem is not just a problem, because they have to live with the stigma and discrimination which is an inerasable mark that makes them vulnerable. Besides all these pain, they still smile at you, greet you warmly, and treats you with trust and admiration.

My four years of journey in Ashadeep as a social worker, was not quite an easy one. To be working with mentally ill people, every day is challenging for me. But I take every challenge as a lesson to develop myself. There were situations where I found myself demotivated and discouraged especially when they do not respond

to the interventions despite the hard efforts put towards recovery; or we are unable to reunite them with their families. But with that being said, I also feel happy and satisfied working in this field. Had I not worked in this field, I would not have been as strong, positive, and dedicated as I am today. I see them as my source of motivation, and I love and enjoy being around them as much as they enjoy my presence. Today I have embraced mental health as my favourite subject and I am not afraid to speak or discuss about it openly. It has taught me a lot about life and to see things positively from every aspect.

A glance from caregiver perspective of bipolar disorder

Nilima Rabha

Caring for someone with bipolar disorder was not that easy. In my nine years of experience as a caregiver in Ashadeep rehabilitation home, I have come across few cases and it was very challenging treating a bipolar person for many reasons. For instance, when a person is in manic phase, they often refuse to take their medicines and they become very dominating, uncooperative which becomes even more difficult to manage. From my keen observation I found that, a person with bipolar disorder generally has good intellectual capacity. They remain disorientated to their surroundings while insights and memory remains adequate even during their episodes. They become abusive, aggressive, and uncooperative, and at times, they become too suspicious. The only method of bringing them to control is through medications and proper management skills.

Despite the few challenges and difficulties I enjoy working in this field and love being around them. I feel some kind of incompleteness when I am not around them as they are now like a

part of my family. I always try not to lose my patience while dealing with difficult cases but at the same time I have learnt to tackle those situations because at the end of the day I realise I am here for them, to make a difference in their life.

From my experience I feel that to be an effective caretaker one should have patience and an adequate understanding of their mental condition, be an effective communicator and a good listener, be empathetic and maintain a good relationship with the patients.

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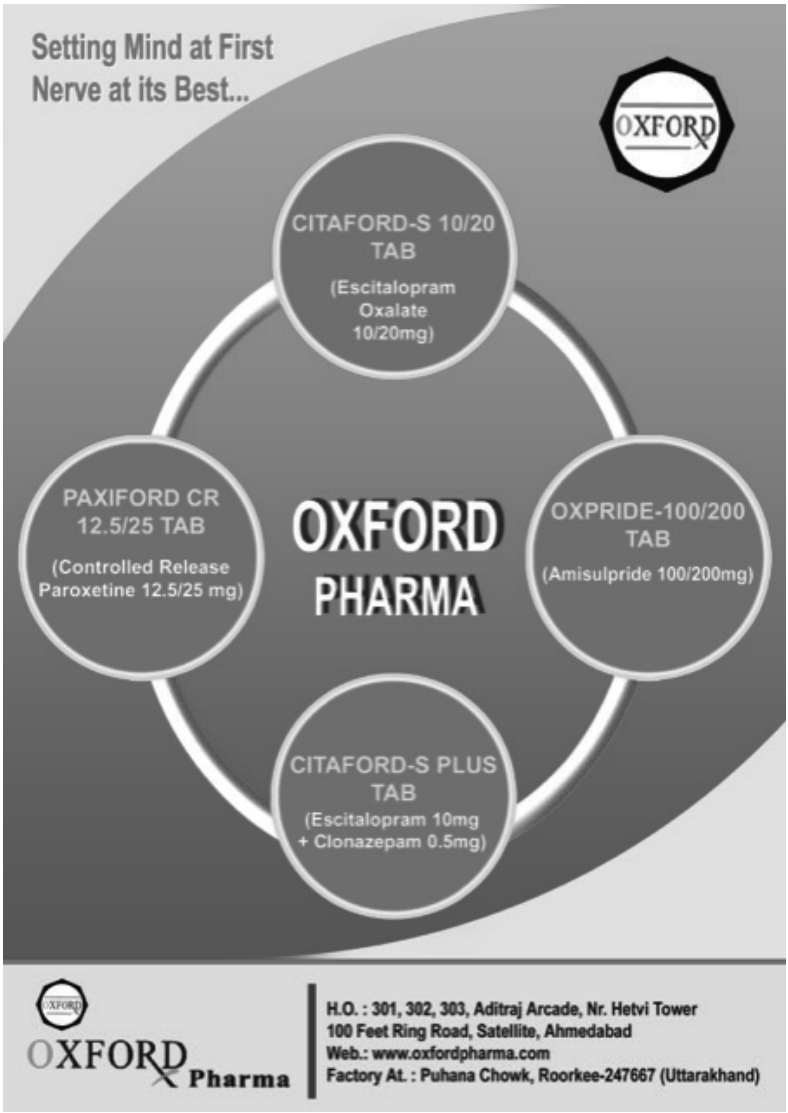
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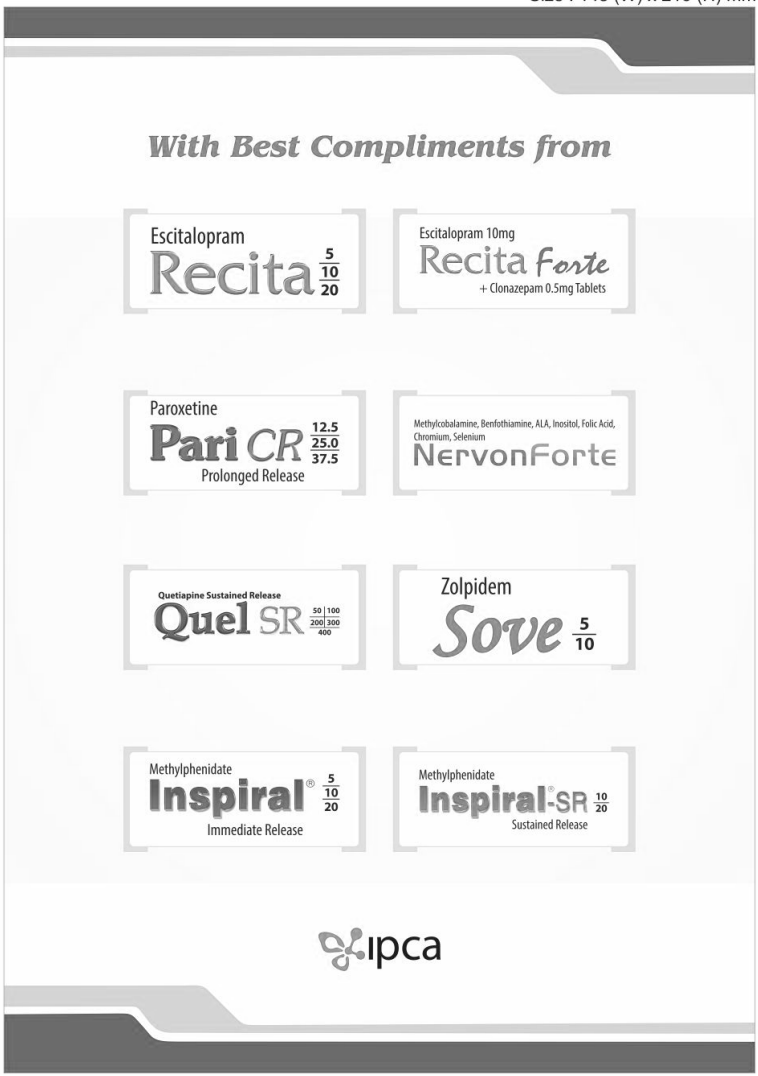


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