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Compliance, cognition and comorbidity in bipolar disorder

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Summary

Background: Bipolar disorder (BD) causes unusual shifts in mood and energy levels which can have life-long adverse effects on the patient's mental and physical health.

Aim: To identify and address the unmet clinical needs in diagnostic assessment and therapeutic intervention on compliance, cognitive impairment, comorbid substance use and obsessive compulsive disorder in BD among Indian clinical practice.

Method: A total of eighty-five expert psychiatrists reviewed specific areas of uncertainty and formulate the consensus pertaining to bipolar disorder through focused group discussion sessions (FGDs) conducted across seven cities in India. Themes were used to generate research questions which were thoroughly discussed with the psychiatrists.

Results: Bipolar disorder identification of at-risk populations has been difficult. According to psychiatrists, mania is diagnostic of BD. When patients present with alarming symptoms, psychiatrists consider the condition as BD and were of the opinion that patients should be fully well-versed with manic and depressive symptoms. Further BD has exhibited high rates of treatment non-adherence and in clinical practice psychiatrists observed that personality of patient, medication dose, influence of patient's family member, and stigma are the key factors influencing treatment adherence. Psychiatrists opined that assessment of cognitive impairment is needed during follow-up to plan personalized cognitive remediation in case of definite cognitive deficiency.

Conclusion: In conclusion, BD is a major public health problem complicated by high comorbidity and poor health outcomes leading to significant mortality risk. Patients and family care givers awareness about disease burden, diagnosis and management can reduce complications and enhance outcomes.

Key words: bipolar disorder, compliance, cognition, substance use, obsessive compulsive disorder

Introduction

Bipolar disorder (BD), also known as manic-depressive illness, is a brain disorder that causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks. The four basic types of BD are: Bipolar I, Bipolar II, Cyclothymia, other specified and unspecified bipolar disorder [1]. BD typically begins in adolescence or early adulthood and can have life-long adverse effects on the patient's mental and physical health,

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educational and occupational functioning, and interpersonal relationships [2].

The prevalence of BD across the world varies from 0.4 to 1.5 percent by country. Globally, an estimated 40 million people in the world had bipolar disorder in 2016, with 0.55 and 0.65 percent being male and female, respectively [3]. According to the 2015-2016 report of the National Mental Health Survey (NMHS), the current and lifetime prevalence of mood disorders including bipolar and depressive disorder in India is 2.84% (95% CI: 2.81-2.87) and 5.61% (95% CI: 5.57-5.65) respectively, while that of BD alone (including single mania and hypomania episodes) is 0.30% (95% CI: 0.29-0.31) and 0.50% (95% CI: 0.49-0.51) respectively [4].

Literature reports that patients with BD often present with depression, mixed state (i.e., depressed mood combined with increased energy, restlessness and racing thoughts), psychosis, manic or hypomanic episodes with rapid cycling between such episodes [5]. Studies report that 50% or more of patients initially present with depression and since MDD and BD have similar symptoms it is very common for BD to be misdiagnosed as MDD [6]. One study reported that over 60% of patients who were eventually diagnosed with BD had previously been misdiagnosed with MDD [7]. Further, patients vary greatly in severity of symptoms and duration of episodes. As a result of diverse symptoms and misdiagnosis, the condition remains unrecognized in many patients for several years often leading to delay in diagnosis.

Even with a successful diagnosis, management of BD is challenging due to wide range of phenotypic expressions and responses to treatment. Although the number of treatments has increased, full recovery is rarely observed as substantial proportion of patients do not respond adequately to drug monotherapy, and combinations of drugs are often required to achieve stability and reduce relapses [8]. In addition to pharmacotherapy, adjunctive psychosocial interventions are also considered in order to improve social functioning, reduce the need for- pharmacotherapy, number of hospitalization and relapse rates [9-12]. Given the demographic, geographical and cultural diversity in India, it becomes essential to understand principles and practice of managing BD among Indian population. Therefore, the objective of the expert consensus document was to identify and address the unmet clinical needs in diagnostic assessment and therapeutic intervention on compliance, cognitive impairment and comorbid substance use and obsessive compulsive disorder (OCD) in bipolar disorder among Indian clinical practice through detailed focus group discussions, involving experts in bipolar disorder so as to aid clinical decision making for practitioners in the complex decision-making process.

Method

An expert panel groups were constituted comprising 85 leading psychiatrists' experts in India who thoroughly reviewed the up to date literature and developed the consensus document.

Results

General considerations

This clinical scientific statement represents the consensus of panel experts who focused on to understand the unmet need and challenges faced during the treatment of BD.

Uncertainties & unmet needs in bipolar disorder

For psychiatric disorders in general, and for BD in particular, identification of at-risk populations has been difficult as there is considerable uncertainty about how to identify high-risk groups and no effective preventive measures are available [8]. The most promising approach so far observed is to follow up children and adolescents who have parents with bipolar disorders [13,14]. To identify at-risk BD population, expert panel were of opinion that mania is diagnostic of BD and when patients present with alarming symptoms they consider the condition as BD and were of the opinion that patients should be fully well-versed with manic and depressive symptoms. Further, expert panel were of the opinion that every patient followed a set pattern of individualized symptoms such as BD episodes and relapse. Moreover, BD has genetic inheritance and runs in the families and thus genetic loading and predisposition is quite high. Behavioral disorder, childhood depression, personality disorder with substance abuse should be screened in patients suspected with BD. ADHD is associated with small children who struggle to pay proper attention in school due to high stress level. Attention deficit is present during inter episodal phase i.e., euthymic phase and thus it should be noted that the symptoms of ADHD often carry on into adulthood merging with symptoms typically associated with adults with bipolar spectrum disorder. Since bipolar is a progressive condition, no specific brain imaging biomarkers are available for identification of at risk population and thus it remains a grey area. However, the clinical benefit of identifying at-risk population needs to be seen.

Further, expert panel were of opinion that diagnosing BD, compliance, polytherapy, patient insight and cultural beliefs are few challenges encountered by them. Compliance is an issue as it takes seven days' time for a medication to work making patients poorly adhere to the treatment. Diagnosing BD particularly misdiagnosis is a challenge. BD is sometimes misdiagnosed as schizophrenia and patients are put on long term antipsychotics which later cause depression in patients. This depression is again seen as negative symptom of schizophrenia and psychiatrist prescribe another medication to treat it ultimately leaving patients with no improvement at all. Thus, it is important to diagnose mania. Also, longitudinal and family history becomes important to diagnose BD. Along with patient's less

knowledge, convincing patient's caregivers/parents is also a practical challenge.
Early intervention aiming to stop or delay the course of BD is appealing. Expert panel opined that diagnosing and initiating BD intervention early results in fewer relapse rate and overall better clinical prognosis of BD which is in line with the published literature. Opinion from expert panel is as mentioned in below box.

Recommendations for unmet need

- Start treatment with low dose and continuous monitoring. In case where patient's RFT is normal, clinical dose must be according to the patient's weight
- Monotherapy is advisable as polypharmacy leads to subclinical dose treatment
- In case of normal SGPT and creatinine levels sodium valproate at a dose of 20 mg/kg should be administered
- Lithium as nutritional supplement in small doses is being used for the prevention of dementia
- Maintenance treatment with lithium monotherapy was superior to quetiapine for clinical secondary outcome measures of depression, quality of life, work functioning
- The depressive phase of bipolar disorder is associated with suicide attempts and unsuccessful treatment of bipolar depression can cause unnecessary suffering and morbidity like substance abuse
- Quetiapine recommended in bipolar type I and type II depression
- Lurasidone recommended in bipolar type I depression
- Lamotrigine alone recommended in bipolar type II depression, while lamotrigine in combination with lithium recommended in bipolar type I depression

Expert panel opined that bipolar disorders are leading causes of disability in young people as they can lead to cognitive and functional impairment and increased mortality, particularly from suicide and cardiovascular disease.
Further, patients with first-episode of BD present with increased psychosocial function compared with patients with multiple episodes [15]. Expert panel were in favor about the combined clinical and psychosocial interventions on symptomatic and functional recovery, including cognitive functioning. They opined that in acute phase mania and depression, psycho education and psychosocial intervention is very helpful. Expert panel were of opinion that delay of correct diagnosis impacts clinical practice. They opined that in most cases when symptoms are observed, parents or family members do not take it seriously and do not come for regular follow-ups. However, when there are severe manic episodes family members considers the seriousness of the condition. Diagnosis delay is particularly observed with younger age of onset. Expert panel were of the opinion that substance use is one of the comorbidity in BD in younger age group. Younger age patients via surfing internet usually concludes what they are suffering from i.e., they have social anxiety or low mood and treat themselves using cannabis where monitoring dose becomes difficult.

Compliance in bipolar disorder

Treatment adherence is an important factor for managing patients with BD in order to prevent relapses, hospitalizations, and other negative consequences. However, BD is expected to be characterized by high rates of treatment non-adherence [16]. Available evidence suggests that 20-60% of the patients with BD become non-compliant with medication and drop out of treatment [17].
Table I enlists determinants of medication non-adherence in BD [16,18]. In addition to these determinants, in clinical practice expert panel have observed that personality of patient, medication dose, influence of patient's family member or relative, and stigma are the key factors influencing treatment adherence. If the patient presents with a break-through episode, the initial strategy is to check the medication compliance and ensure adequate compliance. If compliance is not an issue, initial strategy is to optimize the mood stabilizer which the patient is already getting.

Recommendations for compliance

- Simple dose regimen increase compliance
- Administration of single dose regimen than multiple dose to increase compliance.
- Psychoeducation is the most important parameter to improve compliance.
- Small size of the tablet preferred for long term compliance
- To reduce misconception, explain the cycle of mania and depression to patients and family
- CBT - 8 to 10 sessions required to improve compliance
- Explain patient about importance of medication with examples

Strategies that have been adopted to improve medication adherence include pharmacological and psychological. Adherence in BD often is difficult when patients require a complex medication regimen to control their illness. Literature reports that patients and clinicians may prefer to use once-daily dosing drug formulations, which can pro-

Table I. Determinants of medication non-adherence in BD.

Factors determining medication non-adherence	
Demographic factors	Age, gender, race, education level
Clinical factors	Duration and severity of illness, BD subtype, comorbidity
Treatment related factors	Duration and intensity of treatment, medication side effects
Clinician related factors	Influence of clinician-patient interactions
System related factors	Health system barriers to gaining access to appropriate care
Patient centered factors	Attitudes and beliefs regarding medications, knowledge about the illness and its treatment, role of family members, patient satisfaction

vide consistent serum levels and fewer adverse effects e.g., divalproex extended-release (ER) which showed that 62% patients preferred divalproex ER who were switched from divalproex delayed-release [19]. This is in line with the expert's opinion to use single dose regimen than multiple dose to increase compliance. Similarly, long-acting injectable formulations (LAIs) may be used as maintenance treatment if nonadherence is an issue e.g., risperidone-FDA approved for maintenance treatment of BD-I [20]. However, according to Expert panel, LAIs can be given to prevent relapse of BD. Moreover, if one drug is continuously administered it may create insight in illness, which may lead patient to consume mood stabilizers improving compliance. Thus, with LAIs compliance is increased however further literature search is needed.

Psychosocial strategies such as individual and family psychoeducation, cognitive behavioral therapy (CBT), interpersonal and social rhythm therapy (IPSRT), and family focused therapy are used in BD. Expert panel were of opinion that psychoeducation is the most important parameter to improve compliance apart from medication. Furthermore, tablet-related characteristics such as difficulty in swallowing tablets due to shape and size is one well-known problem among patients which negatively affects their treatment acceptance and preference. Data indicate that less than a quarter of people who have difficulty swallowing their pills discuss the problem with a health professional [21]. To this point Expert panel agreed that the size of the tablet plays a vital role in improving the long-term adherence in BD patients.

However, according to the Expert panel usually adherence to treatment is seen when patients follow-up regularly and based on their symptoms checked. According to Expert panel treatment adherence scales are time consuming and hence not preferred by them. Moreover, they were of opinion that a structured group (including patients and their care givers) is more beneficial than individual CBT.

Cognitive impairment in bipolar disorder

Cognition refers to thinking skills which includes mental processing speed, attention, learning and memory, and executive skills- known as cognitive domains. Problems in lower cognitive domain such as mental processing speed will impair higher cognitive domains such as attention and executive skills. Cognition is impaired during both mania and depression [22]. Expert group opined that during a Depressive episode, people often experience problems related to paying attention, concentrating, remembering things and solving problems, and during a Manic episode cognition is also affected thoughts may be racing and often change content, while the abilities to judge a situation, pay attention and inhibit impulses are limited.

Recommendations for cognitive impairment

- Clinically mifepristone and lamotrigine have been the best medication as they improve working memory and have cognitive enhancing effects
- Limited use of scales such as SCIP and COBRA for screening cognitive impairment in BD patients in clinical practice
- Implementing functional and remediation techniques for better promising results along with pharmacological treatments

Several investigative techniques are available for diagnosing cognition in BD such as neuropsychological assessment, laboratory assessment, structural neuroimaging and functional neuroimaging. Cognitive functions can be assessed by asking certain questions to patients pertaining to their cognitive problems in daily life. However, it has been observed that in many cases neurological screening is required as patients with cognitive impairment fails to accurately self-report their impairments [22]. Further, Expert panel opined that assessment of cognitive impairment is needed during follow-up to plan personalized cognitive remediation in case of definite cognitive deficiency. There are several cognitive screening tools available such as DSST (Digital Symbol Substation Test), Screen for Cognitive Impairment in Psychiatry (SCIP) and Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) which are of limited use in clinical practice. Several lifestyle factors such as poor sleep and diet, physical inactivity, medical illness, consumption of alcohol and recreational drugs and stress have negative impact on cognition and play a key role in identifying and addressing ways to improve cognition in BD patients [22].

Drugs have dopaminergic & glutamate mechanism will have better for cognition impairment in bipolar disorder. Different drugs with potential beneficial effects for the treatment of neurocognitive impairment have been examined such as mifepristone, lamotrigine, lithium and divalproex, venlafaxine and olanzapine. The following are the opinions from the expert group for different drugs: mifepristone (helpful in visual memory not in executive function); galantamine (helpful in verbal only not in executive function); donepezil (not preferred molecule for cognitive impairment treatment and is not used much in clinical practice); vortioxetine (may be used in mood disorder); modafinil (used in clinical practice, but not much experience in terms of its clinical improvement, and often the improvement in attendance is sustaining); lurasidone & pramipexole (have less effect on cognition impairment); and neuroprotective agents (seems promising, but need more substantial data for their usage in clinical practice).

Of all these, according to expert panel clinically mifepristone and lamotrigine have been the best medication as they improve working memory and have cognitive enhancing effects. Further, expert panel believed that lithium and divalproex are also good drugs however; lithium in higher dose can lead to cognitive impairment. Similarly, carbamazepine also exerts difficulty in remembering short and long-term memory in higher dose. According to expert panel' venlafaxine may improve attention; however, nowadays, it is hardly being used in BD. However, there are different strategies used to prevent cognitive impairment

such as memory exercise, no multiple activities at time (only need to focus on one activity at a time), omit drugs which can cause cognition impairment, yoga and mindfulness therapy, identification of comorbidity, gamification for 20 minutes to 1 hour to improves cognition, mobile games may improve cognition and cognition enhancing drug.

In addition to pharmacological treatments, psychological treatments also play an integral part for treating cognitive impairment. Functional remediation and cognitive remediation are two remediation techniques used popularly and have shown promising results. Expert panel believed that remediation techniques help in memory exercise and stimulating brain. Expert panel opined that noninvasive brain stimulation techniques such as transcranial magnetic stimulation (TMS), deep transcranial magnetic stimulation (DTMS) and transcranial direct current stimulation (tDCS) have been neglected in the studies and were in the favor of using them. Further, according to Expert panel repetitive TMS has shown few side effects in BD patients however, it is very much useful in patients with resistant depression. Also, when rTMS is used with mood stabilizers it acts as a temporary cognitive enhancing agent.

Expert panel opines that the clinical benefit of mindfulness based cognitive therapy (MBCT), particularly through increasing the ability to maintain focus over longer periods of time, in cognitive impairment is not clear and needs further research. Further, psychiatrist believe that along with medication, physical exercise, adequate rest, avoiding concomitant medications that interfere with cognitive function, and promoting healthy habits helps managing cognitive impairment in BD patients.

Substance use disorder in bipolar disorder

Lifetime prevalence of substance use disorders (SUDs) is higher in BD than in any other psychiatric disorder, including unipolar depression. Prevalence rate of SUDs in literature ranges from 20%- 70% in patients with BD and contribute to high rates of disability, morbidity, and treatment non-adherence [23]. Various types of SUDs associated with BD includes alcohol, cannabis, tobacco, opioids and benzodiazepines. Across few studies reviewed, alcohol use is associated with a prevalence rate of 42%, cannabis 20%, and other illicit drug associated with a prevalence rate of 17% [24]. According to Expert panel, clinically around 30-60% of SUD is observed in BD patients in India and it depends on the type of substance used. Also rates of SUD ranges from 14% to 65% in inpatient and outpatient treatment setting among Indian patients. The Expert panel observed that excessive cannabis use was associated with an earlier onset of BD after adjusting for possible confounders while excessive alcohol users had a later onset of BD. Further, panel opined that if patient experiences mania he may start drinking beer for alerting his mind. Expert panel believe that BD and substance abuse is bidirectional, sometimes it may be that substance itself may precipitate BD symptom or because of bipolarity, substance use increases.

The expert panel opined that BD in SUD exhibited significantly poorer performance than BD without SUD in visual memory and conceptual reasoning/set-shifting. Expert panel were of opinion that there is dire need to treat SUD in BD as misuse of substance concurrently with serious mental illness like BD can give manic or depressive episode and opined that both the conditions need to be treated simultaneously. Further, in manic episode, patients have tendency for high risk behaviors, like performing unpredicted sex and sharing of needles while using heroine. Therefore, a normal or depressed person will not do unpredicted sex but under the influence of drugs they may indulge in unpredicted sexual activities, whereas the fact is it's not.

Moreover as reported in literature, comorbid alcohol and substance use can precipitate an episode, increase the frequency of episode, may be associated with rapid cycling affective disorder (RCAD), higher risk for suicide, poor response to treatment, longer time to achieve remission, can influence the choice of medication, and can lead to higher vulnerability for side effects [17].

Pharmacotherapy along with psychological interventions may be helpful in management of comorbidity. The sequential selection of drug for SUD in BD is usually oxcarbazepine in higher doses, valproate and topiramate (given after evaluation of RFT in patient). The number of episodes can be managed by administering the patient with mood stabilizers such as valproate, carbamazepine, withdrawal management, psychoeducation, family involvement and CBT. The stable phase of BD can be managed with the aid of life charts, motivational interviewing, integrated therapy, self-help groups, IPSRT, mood stabilizers and relapse prevention medications. Expert panel were of the opinion that first choice would be lithium followed by sodium valproate (if liver function test is normal) and oxcarbazepine (if liver function test is not normal). Drugs such as naltrexone hydrochloride, acamprosate, citicoline are used in case of alcohol use disorder. The other pharmacological therapy preferred for treatment includes antipsychotics, quetiapine, lurasidone, olanzapine + fluoxetine, active withdrawal drugs such as benzodiazepines, baclofen, carbamazepines, drugs for relapse prevention such as naltrexone, acamporosate and antidepressants. Expert panel opined that fear of the consequences of combining alcohol/illicit substances with mood stabilizers may lead some bipolar patients to be nonadherent to pharmacotherapy.

Recommendations for SUD

- Prevalence of substance use disorder in BD patients depends on the type of substance used
- Same diagnostic criteria must be developed for BD and SUD
- Both SUD and BD should be treated simultaneously
- First choice of drug is lithium followed by sodium valproate and oxcarbazepine

Obsessive compulsive disorder in bipolar disorder

Obsessive-compulsive disorder (OCD) is one of the most frequently associated comorbidities in bipolar disorder. The real challenge lies in managing patients with BD-OCD because both mood stabilizing and management of OCD should go hand in hand. Prevalence of OCD may be masked by the presence of manic or depressive symptoms in BD, impact of OCD in BD disability, quality of life, poor functioning, and higher unemployment, episodic course, rapid cycling, frequent hospitalizations [25]. The panel opined that "stepwise" approach should be used when selecting primary mood-stabilizer treatments as well as when considering concomitant use of pharmacological or psychological treatment. Highest prevalence of OCD in BD is documented in studies of remitted patients.

The first line agents preferred for treatment of OCD-BD are combinations of lithium/divalproex+ risperidone, lithium or divalproex + olanzapine, lithium/divalproex + quetiapine. The second line agents preferred are carbamazepine, ECT, lithium or divalproex/asenapine [25]. Valproate is useful in the treating an SRI intolerant OCD and clozapine-induced OCS. In remitted cases of BD, clinicians will be hesitant to start a SSRI because of high propensity of SSRI to induce mood instability. Mood stabilizer along with olanzapine - SSRI/clomipramine combination is also helpful [25]. Lithium though used in management of OCD, evidence has been not yet established. Psychological interventions have become an integral part of treatment in OCD. Meta analyses of cognitive behavioral therapy (CBT) in OCD have shown it to be effective.

Discussion

Given that BD is a major psychiatric illness and about 0.5% of patients suffer from it in India, there is a need to understand clinical practice pattern of expert panel across India with regards to diagnostic assessment and therapeutic intervention on compliance, cognitive impairment and comorbid substance use disorder in bipolar disorder to meet with unmet clinical needs. The long-term course of bipolar disorder is highly variable, associated with both interindividual variation and heterogeneity between patients [8].

Early intervention in bipolar disorders has not received comparable attention, despite a need for early intervention treatment strategies. Very little attention has been paid to studying the effects of early intervention in patients with either a genetic susceptibility to BD or with attenuated symptoms of this disorder. Further, patients often experience several years of depressive symptoms or full-blown depressive episodes before their first episode of mania or hypomania [26]. Many patients experience a significant delay between the onset of their first symptoms and their diagnosis with bipolar disorder. One study indicated that only 53% of patients were correctly diagnosed with bipolar disorder in the first year, while in the remaining patients it took an average of 7.5 years until a correct diagnosis was made [27]. This delay in diagnosis leads to delay in treatment. It has been observed that delayed treatment initiation is linked with an adverse impact on many clinical variables, including poorer social adjustment, more hospitalizations, increased risk of suicide, increased rates of comorbidities (particularly, substance abuse), forensic complications resulting from committing felonies while unwell, and impairment in age-specific developmental task [28].Therefore early intervention for BD is potentially useful strategy however, it warrants further investigation.

Neurocognitive deficits seem to be present not only in the early course of the illness but also in premorbid stages before illness onset [29]. Although the cognitive impairments found in persons with BD are often subtle, improving neuropsychological processing may dramatically improve psychosocial functioning in these patients. It would seem beneficial to consider neuropsychological functioning when developing long-term care plans for individuals with bipolar disorder [30].

Effect of SUDs on bipolar disorder is substantial with a negative impact on symptom presentation, manifestations, course, and treatment adherence and thus SUD and BD need to be treated concurrently.

In conclusion, BD is a major public health problem complicated by high comorbidity and poor health outcomes leading to significant mortality risk, thereby making the primary care physicians and psychiatrist's role vital in improving quality of life. Early recognition and treatment improves outcome. A number of pharmacological treatments such as mood stabilizers, antidepressants, antipsychotics and non-pharmacological treatments such psychotherapy and psycho education are available as acute and maintenance treatments, with the idea of achieving reduced symptoms and enhanced functioning in BD patients. Awareness of patients and family caregivers about disease burden, diagnostic issues, manage ment choices, treatment non-adherence and effectiveness of early intervention can reduce complications and enhance outcomes in substantial proportion of patients.

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Appendix 1. Research Questions Discussed During Focus Group Sessions

Uncertainties & unmet needs in bipolar disorder
How do we improve identification of at-risk bipolar disorder populations?
What are the clinical benefits of early intervention?
What are the effects of combined clinical and psychosocial interventions on symptomatic and functional recovery, including cognitive functioning?
Do you feel that delay of correct diagnosis impact clinical practice?
Is delay in diagnosis a particular problem in patients with younger age of onset?
Digital Platforms for BPD?
Compliance
What are the brief interventions which can increase treatment adherence?
Cognitive impairment in bipolar disorder
In your clinical practice, how do you diagnose the patients with cognitive impairment in bipolar disorder (BD)?
What are the factors influencing cognitive function?
In your clinical practice, how do you manage patients with cognitive impairment in bipolar disorder?
How does medication affect patient's cognition?
Different ways to overcome cognitive difficulties
What are the promising pharmacological treatments?
What are the promising psychological treatments?
What are the non-pharmacological treatments?
What can be other approaches to prevent cognitive impairment in bipolar disorder?
Substance use disorder (SUD) in bipolar disorder
Is there any clinical significance of substance use disorder in bipolar disorder?
Do you feel there is a need to treat substance use disorder in bipolar disorder patients?
In your clinical practice, what are the diagnostic criteria that you follow to identify patients with substance use disorder in bipolar disorder?
In your clinical practice, how do you manage patients with substance use disorder in bipolar disorder?
What do you believe are the medications which can treat different aspects of the treatment process?