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Assessing and addressing cognitive impairment in bipolar disorder: the International Society for Bipolar Disorders Targeting Cognition Task Force recommendations for clinicians.

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Title: Assessing and Addressing Cognitive Impairment in Bipolar Disorder: The International Society for Bipolar Disorders Targeting Cognition Task Force Recommendations for Clinicians

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Abstract

Objectives

Cognition is a new treatment target to aid functional recovery and enhance quality of life for patients with bipolar disorder. The International Society for Bipolar Disorders (ISBD) Targeting Cognition Task Force aimed to develop consensus-based clinical recommendations on whether, when and how to assess and address cognitive impairment.

Methods

The task force, consisting of 19 international experts from nine countries, discussed the challenges and recommendations in a face-to-face meeting, telephone conference call and email exchanges. Consensus-based recommendations were achieved through these exchanges with no need for formal consensus methods.

Results

The identified questions were: (I) Should cognitive screening assessments be routinely conducted in clinical settings? (II) What are the most feasible screening tools? (III) What are the implications if cognitive impairment is detected? (IV) What are the treatment perspectives? Key recommendations are that clinicians: (I) formally screen cognition in partially or fully remitted patients whenever possible, (II) use brief, easy-to-administer tools such as the Screen for Cognitive Impairment in Psychiatry and Cognitive Complaints in Bipolar Disorder Rating Assessment, (III) evaluate the impact of medication and comorbidity, refer patients for comprehensive neuropsychological evaluation when clinically indicated, and encourage patients to build cognitive reserve. Regarding question (IV), there is limited evidence for current evidence-based treatments but intense research efforts are underway to identify new pharmacological and/or psychological cognition treatments.

Conclusions

This task force paper provides the first consensus-based recommendations for clinicians on whether, when, and how to assess and address cognition, which may aid patients' functional recovery and quality of life.

Key words: Cognitive impairment, bipolar disorder, screening, neuropsychological, recommendations

1. Introduction

Functional recovery and quality of life are important new treatment targets for patients with bipolar disorder (BD). While sustained symptomatic remission is an achievable goal with current pharmacological and psychological treatments, patients often do not recover full functional capacity, including work and social life. Indeed, quality of life is not merely the inverse of affective symptoms but also involves patients' perceptions of their position in life in the context of their culture, values and personal aspirations (1). Poor life quality in BD is therefore closely linked to patients' lower academic attainment and vocational function (2-4), high unemployment rates (5;6), and problems with household and community functioning (7). This has led to growing consensus that clinical remission ─ i.e., *feeling well* ─ is not a sufficient treatment goal: Patients also need to *do well* and recover functionally to achieve good quality of life (8).

Persistent cognitive impairments across memory, attention, processing speed and executive function during periods of remission are directly related to poor quality of life (9) and socio-occupational outcome in BD (10-13). In fact, meta-analytic evidence indicates that memory and executive function are among the strongest contributors to occupational outcome in BD with greater impact than residual mood symptoms (13;14). According to meta-analytic evidence, cognitive impairment in the remitted phase of BD is on average of a moderate effect size (15). However, recent studies revealed substantial cognitive heterogeneity in remitted BD patients: 12-40% of patients present global cognitive impairments across several domains, 29-40% show selective deficits in attention and psychomotor speed, and 32-48% are relatively 'cognitively intact' in comparison with norms (16-18). Importantly, patients with either global or selective cognitive impairments reported poorer quality of life, more perceived stress and lower vocational function than patients who were cognitively intact despite comparable levels of residual mood symptoms (18;19). It is therefore imperative to identify patients with persistent cognitive impairment, to characterize the pattern of their impairments, and to implement

strategies for remediating these deficits to improve the clinical management of BD. To this end, there is a need for consensus on whether and how to screen for and treat cognitive impairment in clinical practice.

The International Society for Bipolar Disorders (ISBD) convened an expert task force in September 2016 under the lead of Dr. Miskowiak with the aim of developing (I) a consensus-based guidance paper for the methodology and design of cognition trials in bipolar disorder for pharmacological and non-pharmacological interventions, (II) a clinical recommendations paper for clinicians on how to address cognitive impairments in their patients, and (III) an educational patient booklet with information about cognitive impairment and pragmatic strategies for compensating for these in daily life. A paper addressing goal (I) was recently published in Bipolar Disorders (20). This specific paper addresses goal (II), developing consensus-based clinical recommendations by this ISBD task force that can be used by clinicians to guide their choices on whether, when and how to assess and address cognition in their patients.

2. Methods

The ISBD Targeting Cognition Task Force was initiated by Dr. Miskowiak in collaboration with Drs. Kessing and Vieta. It consists of 19 international experts in the field of cognition in mood disorders from the following nine countries (in alphabetical order): Brazil, Canada, Colombia, Denmark, Japan, New Zealand, Spain, United Kingdom, and United States of America. Members of the task force were selected based upon their expertise and include several members of a previous ISBD Cognition Task Force (21).

The process of the task force

The task force work on goal (II) was initiated with a face-to-face meeting between task force members during the ISBD Congress in Washington DC in May 2017. During the meeting, the task force reviewed, expanded and agreed upon a series of key questions and tentative recommendations to be addressed in the clinical guidance paper. This was followed up by a telephone conference in May 2017 for the task force members who had been unable to attend the ISBD congress. During the conference call, task force members discussed the identified clinical questions identified by Dr Miskowiak and associated recommendations. Consensus on the recommendations was reached through subsequent email exchanges between the task force members. The use of formal consensus methods was deemed unnecessary given high agreement amongst the task force members.

3. Results: task force recommendations

(I) Should cognitive screening assessments be implemented in the clinical management of bipolar disorder?

Objective and subjective cognitive impairment

The first questions addressed by the task force were: Should *objective* cognitive screening assessments with a short cognitive screening battery be recommended in addition to assessment of patients' self-reported cognitive difficulties? If so, should objective assessments be conducted for all patients, or only for those with either subjective cognitive complaints and/or occupational difficulties?

There was strong agreement among task force members that qualified mental health professionals trained in cognitive screening assessment should conduct formal assessment of cognition for all **adult** patients in partial or full remission (e.g., a Hamilton Depression Rating Scale [HDRS] Score <14),

whenever possible. Assessment of cognition in clinically stable, at least partially remitted patients ─ ideally not before 2-3 months after a mood episode ─ enables detection of 'trait-related' cognitive deficits; i.e., deficits that do not result from acute mood symptoms but persist long-term and hamper patients' work capacity and social life (10;12;13). The recommendation to screen and track cognition in all (partially) remitted patients is based on the evidence for poor correlation between subjective and objective cognitive impairment (22-25). This implies that it is not always the patients with the most *subjective* complaints who show greatest *objective* impairments and vice versa. Indeed, patients' insight into their own cognitive abilities relies on several factors, including metacognitive capacity and severity of mood symptoms (26). Since 30-50% remitted patients are objectively cognitively intact in comparison with norms despite subjective cognitive complaints (16;18;19), relying purely on subjectively reported difficulties could lead to a high false positive rate. At the same time, subjective assessments would also miss a considerable group of patients with unreported objective cognitive impairments due to poor insight or limited metacognitive capacity (27). Specifically, patients with BD may underreport difficulties within processing speed, attention and executive function domains (26). This is in keeping with emerging evidence that deficits in processing speed and attention domains are often mistaken for memory problems because failure to pay attention to and process information hampers subsequent recall of this information (28). Objective assessment of cognition is therefore necessary for correct identification of patients with cognitive impairment.

Notwithstanding the importance of objective cognition assessments, it is also essential to evaluate patients' subjectively experienced cognitive problems and/or work difficulties that may originate from objective cognitive deficits. Specifically, patient-reported cognitive difficulties in daily life situations and/ or decreased work capacity are crucial for the clinical meaningfulness of implementing strategies to compensate for or treat cognitive impairment. Consequently, cognition assessments should include both objective and subjective measures. Finally, patients with cognitive performance in the normal

range, but who had high premorbid function, may be experiencing impairment relative to their true abilities even if this cannot be detected with a cognitive screening tool (where cut-offs for impairment are based on norms). Therefore, clinicians should also take into consideration patients' educational and occupational attainment as a proxy for their premorbid function. Without this consideration, clinicians may erroneously relay the idea to patients that they are not experiencing cognitive challenges and not adjusting their treatment given unobserved decline.

Brief cognitive screening

Brief cognitive screening is valuable for three key reasons: (i) to detect cognitive impairment, (ii) to identify those who are relatively cognitively intact in comparison with norms, and (iii) to track cognition over time. First, screening for objective cognitive impairment is clinically important for patients with symptoms of depression or mania close to clinical threshold, since these patients tend to display greater subjective problems than objective impairment (26). Objective neurocognitive screening assessment can clarify whether their subjective cognitive difficulties and/or socio-occupational problems are a consequence of objective cognitive impairment or secondary to other factors, such as residual mood symptoms or difficulties applying cognitive skills in complex daily life. This information can guide treatment selection to target either residual mood symptoms or cognition. Further, objective cognitive screening in patients with poor insight due to executive dysfunction (29) may clarify the extent to which objective cognitive deficits are contributing to any observed socio-occupational problems. Since the mean age of BD onset is in the late teens to early twenties (30), persistent cognitive impairments can be detrimental for academic achievement, early occupational function and interpersonal relations. Hence, detection of cognitive impairment after (partial) remission in newly diagnosed patients may help patients identify and compensate for cognitive difficulties to maintain their educational or occupational functions, thus leading to better prognosis and quality of life (see discussion of cognitive reserve under point III). In patients later in the course of illness with more

substantial functional impairments, cognitive screening assessments are also valuable as they clarify if their functional issues are at least partially rooted in cognitive deficits. This may inform compensation strategies and cognitive/ functional rehabilitation interventions (see clinical implications and treatment perspectives under points III and IV).

Second, objective cognition assessments may be useful in the management of patients presenting with concerns over 'neuroprogression' or dementia. A cognition assessment will enable clinicians to identify the 30-50% of patients who despite such potential concerns are objectively cognitively intact. Objective 'proof' that their cognitive capacity is within the normal range can provide great relief and comfort for these patients and their relatives. Nevertheless, the results of a brief cognitive screening test should always be interpreted with caution and be considered in the context of the particular clinical presentation.

Third, implementation of cognition assessments enables clinicians to track patients' cognition over time in response to new treatments or new illness episodes. In particular, assessment of whether there is an objective change in cognition when patients have achieved (partial) remission after a medication switch may be particularly useful in cases where patients experience cognitive side-effects of their medication. If objective assessments reveal no cognitive change over time, this would provide an objective reference point for patients that reduces patients' concerns about cognitive side-effects. In this way, cognitive screening assessments may aid treatment adherence (31) and thus indirectly improve patients' prognosis. On the other hand, if cognition assessments do reveal cognitive decline in response to a new treatment, this could inform a change of the treatment plan to reduce the cognitive side-effects. For elderly patients, tracking cognition may be particularly useful in determining whether cognitive decline could be indicative of dementia onset. In such cases, patients should be referred to a complete diagnostic assessment. The frequency should be individualized, but ideally assessments should be made at least every 5 years or whenever there is a reason to anticipate the assessment (a

change in functioning or increased cognitive complaints, for example). However, major impediments for the detection of cognitive change are the uncertain reliability of test results and practice effects (32). Several psychometric approaches have been developed to determine 'true' or clinically significant change at the level of the individual patient (32). However, at this point, normative 'cognitive change data' are limited or unavailable for the SCIP (35) or other potential prospective cognitive screening tools in BD. This is an area of growing research and more specific guidelines are likely to become available to guide clinicians in their assessment of cognitive change within the next few years.

(II) What are the most feasible cognition screening tools in bipolar disorder?

A cognitive screening tool should be brief, easy and cost-effective for clinicians given time constraints and resource restrictions that make referral to a neuropsychologist untenable in most cases. There was consensus among task force members that the optimal way would be to have a simple, freely available "online package" which clinicians could use for all clinically stable adult patients in partial or full remission. Such a tool should include a few neurocognitive tests combined with questions about cognitive difficulties in daily life and mood status. Since there is currently no such validated online cognition screener for bipolar disorder, the Task Force agreed to explore the possibility of developing such a tool as a next goal. Until such a tool is available, the recommendations are to use available paper-and-pencil tools that are validated for detection of cognitive impairment in bipolar disorder. Two particularly feasible, easy-to-administer tools are the Screen for Cognitive Impairment in Psychiatry (SCIP; (33)) and the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA; (34)). Both tools are short and feasible and have been shown in several studies to have high internal consistency, retest reliability and concurrent validity (24;34-37).

Screen for Cognitive Impairment in Psychiatry

The SCIP is a brief cognitive screening tool consisting of five short objective tests of cognition that can be administered bedside in approximately 10-15 minutes and exists in three parallel versions to allow for repeated testing. It provides a quick quantification of significant difficulties with verbal working memory, verbal learning and memory, verbal fluency, and psychomotor speed and has high decision validity in patients with bipolar disorder (i.e., high sensitivity and specificity for cognitive impairment). The SCIP exists in several languages (in alphabetical order): Chinese (Mandarin), Danish, English, French, German, Italian, Japanese, Persian, Portuguese, Russian, and Spanish. The Danish, English, French, and German versions have been validated to detect cognitive impairment and exist with their respective norm data sets and respective cut-offs for cognitive impairment, whereas the Chinese, Italian, Japanese, Persian, Portuguese, and Russian versions exist in beta-versions (i.e., translations in need of further beta testing). These versions of SCIP (including beta-versions) can be obtained free of charge by clinicians who treat patients with bipolar disorder from the ISBD website (URL). Notably, the Spanish version of the SCIP is only commercially available via TEA Ediciones (web.teaediciones.com).

Cognitive Complaints in Bipolar Disorder Rating Assessment

The COBRA is a subjective cognitive impairment rating scale for patients with bipolar disorder that consists of 16 questions about cognitive difficulties in daily life scenarios (e.g., 'Do you find it hard to concentrate when reading a book or a newspaper?', 'Do you have difficulties to find objects of daily use (keys, glasses, wristwatch…)?', 'Do you have the feeling that you do not finish what you begin?'). Despite general poor correlation between subjective and objective measures of cognition (22-25), the COBRA has shown some correlation with objective memory and executive function (24;34;36;37). However, when used alone, the sensitivity and specificity of the COBRA for objective cognitive impairment is suboptimal (i.e., below 70%) (24) and the instrument should therefore ideally be used in combination with an objective cognition measure such as the SCIP. The COBRA ─ and suggested cut-

offs for cognitive impairment ─ is available from the ISBD website in the following languages (in alphabetical order): Chinese, Danish, English, Japanese and Spanish. An alternative to the COBRA is the Lithium Battery-Clinical (38), a list of recommendations for clinical assessment of subjective cognitive difficulties. For example, clinicians are encouraged to ask patients about their cognitive function if patients do not present spontaneous complaints, to discuss the multifactorial influences on perceived impairment, including the influence of mood symptoms, and to track subjective cognitive function over time (38).

Cut-offs for impairment

Importantly, cut-offs for impairment on the SCIP and the COBRA should only be used as 'rough guides' and should always be considered in the context of patient demographics, mood state and external outcome, such as ability to work, drive, and live independently. For the SCIP, it may be advisable to use a somewhat more conservative cut-off (i.e., lower SCIP total score) for cognitive impairment in older age patients than the published norm material (24;35) given the age-related cognitive decline (39), which is potentially accelerated in mood disorders (40). Further, bipolar disorder in older age is associated with greater prevalence of dementia compared with the general population (41;42). An international expert group within the ISBD therefore recently recommended that clinicians screen cognition in older age patients using dementia sensitive instruments, such as the Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) (43). Other dementia sensitive screening tests may also be used, such as the Addenbrooke's Cognitive Examination (ACE-R) and the Short Cognitive Performance Test (SKT). These instruments may be particularly suitable in cases where dementia is suspected because of ceiling effects in better functioning and/or younger patients. In addition, given the potential complexity of differentiating the cognitive deficits in late-life BD from those associated with various types of dementia, referral for full neuropsychological evaluation would be recommended in some of these cases.

While the current norm material in some studies is based on age-, gender- and IQ-matched healthy control groups, it is not age-corrected *per se*, which reflects a current limitation that may be overcome with further normative data collection. Ongoing research aims to determine the optimal SCIP and COBRA cut-offs for cognitive impairment across a range of age-groups including older age patients. Another issue with using the published SCIP norms is that cognitive impairment may be difficult to detect in patients with substantial above-normal premorbid function. Thus, is logistically feasible, clinicians may consider cognitive impairment with reference to patients' cognitive reserve as reflected by their educational level or general IQ. Since higher COBRA scores correlated with greater symptom severity (24), a more conservative cut-off (i.e. a higher COBRA score) for impairment may therefore be considered for patients with substantial subsyndromal symptoms. Finally, linking cognitive impairment to external outcomes is also important for guiding treatment steps when cognitive impairment is detected (see implications and treatment perspectives under points III and IV).

Minimum tools

In situations where it is not possible for clinicians to conduct the full SCIP and COBRA, or where these instruments are not available in the local language, the recommendation for 'minimal assessments' would be to talk with the patient about their cognitive abilities in daily life, asking them to give specific examples, and combine this interview with one or two SCIP subtests, such as the verbal fluency and coding tests (which can be easily administered in any language and require minimal time/ training). In particular, the SCIP coding test has shown sensitivity to cognitive change in response to medication effects and aging, and is therefore the recommended 'minimum tool' to track cognition over time. However, for screening purposes, cutting down the SCIP to 1-2 subtests would be at the expense of assessment validity, since the tool is already short (<15 minutes) and constitutes a minimum of what can be considered a valid cognition assessment.

Limitations of cognitive screeners

While brief cognitive screening tools can be administered by qualified mental health professionals after minimal training, take little time to administer, and are thus feasible in the clinical management of BD, these tools also have important limitations: They do not measure real life functions and cannot replace a comprehensive neuropsychological evaluation, which would give more detailed insight into which specific cognitive deficits may be related to the patients' particular psychosocial difficulties (44). The SCIP is therefore not a substitute for a comprehensive neuropsychological examination, but is merely a useful initial tool to screen patients who may benefit from a more thorough assessment to rule out cerebral pathology. For example, in cases where rapid declines in cognitive function occur (and/or accompanied by other symptoms such as confusion, headache etc.) or when function is highly discordant with current mood state/function, brief screening would *not* be adequate. Brief cognitive screening therefore cannot replace such full diagnostic evaluations, and if they show some clear deficits, this may also trigger a referral for a more comprehensive specialist assessment.

(III) What are the implications if cognitive impairment is detected on a brief tool?

It may be argued that clinicians should not screen for something if they do not have management options for the condition. While there are several promising candidate cognition treatments currently under evaluation, we currently do not have any clinically available treatment with direct pro-cognitive effects (20;45). Nevertheless, cognitive screening assessments can still improve the clinical management of BD in three important ways.

Referral to a thorough neuropsychological evaluation

First, detection of marked cognitive impairment with a cognitive screener provides a basis for referral to a thorough neuropsychological evaluation by trained neuropsychologists in certain cases. Specifically, circumstances that could warrant such a referral in the face of a 'positive screen' may include: (i) when there is a substantial impairment in the screening, (ii) when there is a perception of worsening in either cognition or functioning in patients assessed in the past, (iii) when there is a query about the potential organic brain illness due to a comorbid condition (e.g. substance abuse, traumatic brain illness, or dementing process), (iv) when there is a desire to evaluate multiple cognitive domains implicated in bipolar disorder (e.g. sustained attention, verbal and nonverbal declarative memory, multiple executive functions including response inhibition, fluency, working memory, attentional shifting, mental flexibility, organization, and planning) for treatment or rehabilitative purposes, (v) when there are concerns about the patient's motivation or effort during cognitive screening and thus the validity of test results, or (vi) when there are likely premorbid/developmental/learning problems that may complicate the cognitive picture.

Evaluation of 'secondary' causes of cognitive deficits

Second, cognitive screening during partial or full remission can provide a basis for evaluation of the potential impact of medical or psychiatric comorbidity, and medication on cognition. Clinicians could be prompted by a positive screen to ascertain for potential 'secondary' causes of cognitive deficits due to psychiatric comorbidity (e.g., alcohol use disorder or ADHD), medical comorbidity (e.g., cerebrovascular disease, diabetes, elevated ammonia levels or uncontrolled hypothyroidism), substantial subthreshold depressive symptoms and medications (e.g., antipsychotics, elevated serum levels of lithium or anticonvulsants, and benzodiazepines). This can be useful for optimization of patients' treatments to reduce cognitive impairments; for example, reducing antipsychotic medication and benzodiazepine use or ensuring that serum mood stabilizer levels are within the recommended range. It is important to consider and address these common causes of secondary or pseudo-specific

cognitive deficits before a 'true' illness-associated cognitive impairment can be assumed. In many cases, addressing such secondary causes of cognitive deficits will result in significant cognitive improvement.

Patient recommendations

Detection of persistent cognitive impairments can provide a basis for recommendation of compensational strategies, adjustment of work responsibilities or rehabilitative interventions to improve functioning. Specifically, the assessments can be used to inform patients and their relatives about the nature and consequences of cognitive impairment which may help patients tackle and compensate for these difficulties in daily life. By increasing patients' and their families' insight into the nature and impact of residual cognitive impairments, the assessments may encourage patients to implement compensation strategies and reduce potential interpersonal problems (for example, family members' irritation or disappointment when patients forget daily chores or anniversaries). When patients wish to resume work, brief assessment of their cognitive status can become an important basis for adjustment of work demands and reduce expectations so they are realistic. Finally, cognitive screening assessment can also provide impetus for good habits including getting regular and sufficient sleep and physical exercise, restricting alcohol intake, and adhering to treatment.

Another important way of reducing cognitive impairment in bipolar disorder is implementation of strategies to boost patients' cognitive reserve, the capacity of the brain to tolerate neuropathology, reduce symptom manifestations and manage cognitive challenges (46). Specifically, high cognitive reserve – which is estimated by patients' premorbid IQ, educational level and occupational attainment(47) – is thought to slow down the clinical presentation of neurocognitive decline whereas low cognitive reserve may exacerbate cognitive decline (46;48). Cognitive screening assessments can

motivate patients to build up their cognitive reserve to prevent further cognitive decline and even improve their cognitive outcome.

(IV) What are the treatment perspectives?

There are no available treatments with documented direct pro-cognitive effects in bipolar disorder despite the pressing need for such treatments to enhance functional recovery and reduce societal costs (20). The unmet clinical need is partially due to several major methodological challenges in cognition trials in bipolar disorder, which have been addressed and discussed by the task force in a recently published methodological guidance paper (20). However, current research effort is likely to reveal effective pharmacological and psychological treatments within the next few years.

Promising pharmacological treatments

Among the most promising candidate pharmacological treatments are the corticosteroid receptor antagonist mifepristone, the atypical antipsychotic lurasidone, the multifunctional neurotrophic growth factor erythropoietin (EPO), the antidepressant vortioxetine and non-amphetamine stimulant modafinil. In particular, two studies of mifepristone (a one-week cross-over study and a three-week parallel study) in moderately depressed patients with bipolar disorder found beneficial effects on spatial working memory (but not on other cognitive domains) (49;50). Further, a recent randomized, open-label study recently found beneficial effects of six weeks treatment with lurasidone on a global measure of cognition in euthymic patients with bipolar disorder type I (51). A large multicenter RCT of six weeks lurasidone treatment for cognitive impairment in bipolar disorder is underway (https://clinicaltrials.gov/ct2/show/NCT02731612). Finally, two parallel RCTs investigating the effects of EPO trials in partially remitted patients with bipolar disorder and in treatment-resistant unipolar

depression revealed beneficial effects across several cognitive domains (52-54). Based on this, two new parallel RCTs have recently been initiated to examine the effects of 12-weeks EPO treatment of cognitively impaired patients with bipolar disorder and their first-degree relatives, respectively (Petersen et al, in prep.). In addition to the above mentioned candidate treatments with preliminary evidence for efficacy on cognition in bipolar disorder, there are several compounds that have shown promising effects in unipolar disorder. Modafinil – which was originally intended to treat narcolepsy – is a promising candidate treatment based on findings from a recent RCT in remitted patients with unipolar disorder. Specifically, beneficial effects of a single dose (200 mg) modafinil over placebo were observed on episodic memory and working memory (but not on executive function or sustained attention) in these remitted patients (55). Further, the antidepressant vortioxetine was found in several RCTs to improve some aspects of cognition in unipolar disorder, which seems to be partially independent of its antidepressant actions and was also recently shown in remitted patients (56;57). Studies are therefore warranted to investigate the ability of these compounds to improve cognitive function in bipolar disorder.

Promising psychological treatments

Promising psychological treatments for cognitive and functional impairments in bipolar disorder are functional remediation (FR) and certain cognitive remediation (CR) programs including action-based cognitive remediation (ABCR). Functional remediation and ABCR both involve cognitive training, compensation techniques and coping strategies to overcome cognitive difficulties in daily life situations. However, while FR focuses primarily on the training of neurocognitive strategies and psychosocial skills (58), ABCR emphasizes computerized cognitive training and transfer of the learned skills to daily life challenges by practical in-session exercises and actively seeking cognitive challenges in daily life. Functional remediation seems a viable option for patients presenting cognitive and psychosocial impairments because it has shown to be effective at improving functioning in patients in

late states of illness (58;59). While a large RCT did not show significant benefits of 21 weeks FR on cognition, this may be because of the study design that involved enrichment for functional impairment but not for cognitive deficits (58). Indeed, exclusion of the patients who were cognitively intact revealed a significant treatment benefit on verbal memory function (60). In addition, several naturalistic or quasi-experimental studies of different CR programs for bipolar disorder have been investigated over the past decade with encouraging preliminary results (61-65), although the only published RCT of 12-weeks group-based CR showed no efficacy on objective cognition (66). Notably, a non-randomized controlled trial of 10 weeks of ABCR was recently found to improve not only cognition but also vocational function in a mixed group of patients with severe mental illnesses (schizophrenia, unipolar and bipolar disorder) (67). Based on this evidence, two parallel RCTs were recently set up to investigate the effects of 10 weeks ABCR in cognitively impaired patient with bipolar disorder in remission and their first-degree relatives (68). Other ongoing RCTs investigate the effects of 12 weeks of cognitive-behavioral rehabilitation (69), 12 weeks of cognitive remediation (70) and 24 weeks internet-based cognitive remediation for BD I (71).

A highly promising treatment perspective is the combination of pharmacological and psychological interventions (e.g., (72)). This is likely to produce synergistic effects on brain function that may translate into more robust efficacy on cognition and functional outcome than either treatment modality alone. Multimodal treatment approaches are therefore considered a key next step for cognition trials in bipolar disorder that is likely to reveal new effective treatment options.

4. Conclusions

Cognition is a new key treatment target in bipolar disorder but there has been a lack of consensus on how cognitive impairment should be assessed and managed. This ISBD Targeting Cognition Task

Force paper provides the first consensus-based recommendations for clinicians on whether and how to assess and address cognition in their patients. The task force addressed questions about (I) whether and when to conduct cognitive screening assessments, (II) what screening tools are most feasible, (III) what the implications are if impairment is detected, and (IV) which treatment perspectives there are for improving cognition and functioning in BD. The recommendations are summarized in Table 1 and displayed in Figure 1. Key recommendations are that clinicians: (I) conduct formal assessment of cognition for all patients in partial or full remission whenever possible, (II) use brief, feasible tools that include objective and subjective cognition measures such as the SCIP and COBRA, which exist in multiple languages and are freely available through the ISBD website, (III) evaluate the potential impact of medication, comorbidity and symptoms when impairment is detected, refer for more comprehensive neuropsychological evaluation when clinically indicated, use the assessments to encourage patients to build up their cognitive reserve. Regarding (IV), there is currently no clinically available treatment with efficacy on cognition but intense research effort is likely to reveal new effective pharmacological, psychological and multimodal treatments in the near future.

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Table 1: Quick guide with a summary of the ISBD task force recommendations.

Clinical Recommendations for Assessment of Cognition in Bipolar Disorder by the International Society for Bipolar Disorders Targeting Cognition Task Force **Quick guide**
(I) Should cognitive screening assessments be conducted?
• Conduct formal screening assessment of cognition for *all patients in partial or full remission* whenever possible since subjective and objective cognition measures correlate poorly
• Assess objective and subjective cognition to: (i) detect cognitive impairment that should be addressed and in some cases may require referral for comprehensive neuropsychological evaluation, (ii) identify those who are cognitively intact, and (iii) track cognition, ideally at least every 5 years or whenever there is a reason to anticipate the assessment
(II) What are the most feasible tools?
• Use brief, feasible tools that include objective and subjective cognition measures such as the Screen for Cognitive Impairment in Psychiatry (SCIP) and Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA)
• Obtain the SCIP and COBRA- which exist in multiple languages and are freely available - through the ISBD website at (URL)
(III) What are the implications if cognitive impairment is detected?
• Evaluate the potential impact of medication, comorbidity and symptoms when impairment is detected to discriminate between 'secondary' and 'primary' causes of cognitive impairments – and adjust medication if necessary to reduce cognitive side-effects
• Consider referral for more comprehensive neuropsychological evaluation when there is a substantial impairment in the screening, when there is concern of organic brain illness, comorbidity, or cognitive decline, when there is a need to evaluate multiple cognitive domains in greater detail, when there is a question of poor effort affecting validity of test results, or when premorbid/developmental/learning problems may be complicating the cognitive picture. • Inform patients and relatives about the nature and possible consequences of patients' cognitive impairments and encourage compensation strategies, support and adjustment of expectations
• Encourage patients to implement good habits, including regular sleep and exercise and to build up their cognitive reserve by engaging in education and vocational activities
(IV) What are the treatment perspectives?
• There is currently no clinically available treatment with efficacy on cognition but intense research effort is likely to reveal effective treatments within the next few years
• Promising pharmacological candidate treatments are: mifepristone, lurasidone, erythropoietin (EPO), vortioxetine and modafinil
• Promising psychological interventions are functional remediation and cognitive remediation programs including action-based cognitive remediation