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The Management of Cognitive Impairment in Bipolar Disorder: Current Status and Perspectives

Marsal Sanches, MD, PhD[*], **Isabelle E. Bauer, PhD**, **Juan F. Galvez, MD**, **Giovana B. Zunta-Soares, MD**, and **Jair C. Soares, MD, PhD**

UT Center of Excellence on Mood Disorders, Department of Psychiatry and Behavioral Sciences, UT Houston Medical School, The University of Texas Health Science Center at Houston, Houston, TX

Abstract

Bipolar disorder (BD) is associated with important cognitive deficits that persist during the periods of remission. Although these deficits seem to play an important role in the functional impairment experienced by bipolar patients, evidence regarding their clinical management is scant. We revised the databases PubMed, MEDLINE, and clinicaltrials.gov, searching for studies focusing on the pharmacological and nonpharmacological treatment of cognitive deficits among bipolar patients. In addition, a manual search of bibliographical cross-references was performed. Currently, there is no Food and Drug Administration–approved pharmacological agent for the management of cognitive deficits in BD. A number of agents have been tested in the treatment of cognitive deficits in BD, with mixed results. Nonpharmacological interventions, such as cognitive remediation and noninvasive brain stimulation techniques, seem promising, but their role has not yet been properly explored among bipolar patients. Additional studies, aiming at evaluating the efficacy of interventions combining cognitive rehabilitation and biological treatments, are highly desirable.

Keywords

bipolar disorder; cognitive impairment; neuropsychology; cognition

Introduction

Bipolar disorder (BD) is among the most severe and potentially disabling mental disorders. In addition to its association with important psychological suffering, BD is implicated in elevated rates of suicide. Epidemiological studies point to a lifetime prevalence of bipolar spectrum disorders as high as 2.4%[1] and describe a substantial long-term psychosocial risk associated with this condition.[2]

[*]Address for correspondence: UT Center of Excellence on Mood Disorders, Department of Psychiatry and Behavioral Sciences, UT Houston Medical School, The University of Texas Health Science Center at Houston, 1541 East Road, Houston, TX 77054. marsal.sanches@uth.tmc.edu.

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For many decades, BD was considered a condition characterized by full recovery between the mood episodes, in contrast with schizophrenia, where residual symptoms are expected even during remission. More recently, however, this proposition has been brought into question.[3] It has been demonstrated that bipolar patients show important cognitive impairment during mood states, and this impairment is observed even during euthymia.[4,5] Moreover, these cognitive deficits play an important role in the functional impairment observed among bipolar patients.[6] Despite the heavy impact/burden of cognitive impairment in the life of BD patients, research on pharmacological and nonpharmacological treatments of cognitive impairment in BD is still in its early stages.

In the present article, we performed a comprehensive review on the therapeutic strategies for cognitive impairment in BD. The database MEDLINE (1990–2014) was searched using the key words “bipolar disorder,” “cognition,” “cognitive impairment,” and “treatment.” In addition, a manual search of bibliographical crossreferences and the database clinicaltrials.gov was also carried out.[7]

Cognitive Impairment in BP: General Aspects

Cognitive profile of bipolar patients

The finding of cognitive impairment in BD has been well demonstrated by several cross-sectional studies.[8] Among the different cognitive domains, bipolar patients exhibit psychomotor retardation and impaired declarative memory, executive function, and, to a lesser extent, visual memory and attention when compared with healthy controls.[9] These abnormalities do not seem to be state-dependent and are therefore present across all phases of BD, including euthymia.[4,5,10–15] Cognitive deficits have considerable implications in the life of bipolar patients because they limit the patients' abilities to set goals, monitor their behavior, and plan activities. As a result, patients may encounter difficulties in conciliating work and family responsibilities, as well as in coping with life stressors.[12]

Although the majority of cognitive studies in BD focused on heterogeneous BD populations, a small number of cross-sectional studies compared cognitive functioning across the acute and euthymic phases of BD.[16–18] Overall, manic patients display poorer verbal memory, verbal fluency, and cognitive estimation skills when compared with depressed and remitted patients.[16] By comparison, patients with bipolar depression present primarily with verbal memory deficits.[11,12,18–20] In one study,[21] manic patients were found to have a worse cognitive profile than depressed patients in terms of psychomotor retardation and selective attention at the time of their discharge from an inpatient unit. Notably, the evaluation of the same group of participants 6 to 8 weeks after discharge revealed that manic patients had maintained the same pattern of reduced psychomotor speed and high propensity to perseverative behaviors that they presented at discharge. By comparison, depressed patients showed improvement on measures of inhibition (eg, fewer perseverative errors on the Modified Card Sorting Test) and conflict resolution (attentional network task).

Another study comparing manic, hypomanic, depressive, and euthymic BD patients showed that manic patients had the weakest cognitive profile of all treatment groups and presented deficits in immediate and delayed verbal memory [eg, California Verbal Learning Test

(CVLT), Wechsler Memory Scale, logical memory, and visual reproduction subtests] and executive functioning like verbal fluency [Stroop task and Wisconsin Card Sorting test (WCST)].[22] At a functional level, verbal fluency and verbal memory scores were found to be positively correlated with occupational and psychosocial functioning.[18]

Similar results were found in a study comparing first-time BD patients and healthy controls whereby reduced performance on executive functioning tasks such as the Stroop test and verbal fluency predicted duration of remission among patients.[23] Furthermore, there is evidence indicating that duration of illness and symptom severity have a negative impact on memory performance and executive functioning.[12,13,24] Moreover, a high number of mood episodes has been linked to poor performance across cognitive domains.[25–27]

In summary, manic BD patients show widespread deficits across cognitive domains when compared with patients with bipolar depression. Cognitive deficits persist during euthymia and may represent markers of chronic progression and unfavorable prognosis. An important limitation of these findings is related to the impact of psychotropic drugs on cognition and brain structure. This issue will be discussed in the next section.

Medication effect on cognition in BD

Lithium—The literature findings regarding the effects of lithium, one of the most widely used pharmacological treatments in BD, on cognition are equivocal. Although some studies reported cognitive deficits in attention and memory within 14 days of the beginning of lithium treatment, others failed to detect any short-term impact of lithium treatment on cognitive performance.[28–30] Furthermore, 2 studies did not find any cognitive difference between bipolar patients medicated with different agents (including lithium) and drug-naive BD subjects.[31,32] In contrast, a large meta-analysis of cognitive studies in BD reported that lithium-treated patients are more likely to present with learning and encoding difficulties and poor cognitive flexibility when compared with unmedicated patients.[33] The interpretation of these findings is, however, limited by the heterogeneous medication regimen across studies.

However, long-term lithium use has few cognitive side effects. A 6-year follow-up study on lithiumtreated BD patients concluded that lithium did not have detrimental effects on memory performance.[34] Similarly a 4-year follow-up study did not find any difference in attention, verbal and visual memory, and executive functioning among treated and untreated BD patients and healthy individuals.[35] In contrast, a study following lithium-treated BD patients and healthy controls for a period of 2 years found that psychomotor retardation and executive dysfunction (eg, WCST, Stroop and Continuous Performance Task) persisted over the full follow-up period.[36]

Anticonvulsants—Anticonvulsant medications, such as valproic acid, lamotrigine, and carbamazepine, have well-established mood stabilizing and cognitive enhancing properties. A 6-month follow-up study found that lamotriginetreated BD patients obtained better scores on phonemic verbal fluency and, to a lesser extent, verbal memory tasks (eg, immediate cued recall of the CVLT) compared with patients treated with valproic acid and carbamazepine.[37]

Similarly, children with BD showed improvements in working memory (eg, verbal and spatial span), verbal memory (eg, CVLT), and executive functions (eg, Trail Making Test) within 14 weeks of starting lamotrigine. It is worth mentioning that the memory performance of BD patients was comparable with that of healthy individuals at follow-up.[38] A cross-sectional study comparing psychomotor speed, memory, attention and executive functioning in BD patients taking valproic acid, lamotrigine, carbamazepine, or lithium showed that lamotrigine-treated patients had a more functional cognitive profile compared with that of the other 3 medication groups.[39] In particular, lamotrigine-treated BD patients had the highest performance, followed by patients treated with lithium, valproic acid, and carbamazepine. Little is known about the neurocognitive effects of valproic acid and carbamazepine in BD, but studies in healthy volunteers and epileptic patients have shown that anticonvulsants generally lead to psychomotor retardation and memory and attentional decline.[39–41]

Antipsychotics—A randomized, double-blind crossover study using the second-generation antipsychotics risperidone and quetiapine in euthymic BD patients showed that quetiapine had adverse effects on psychomotor speed, attention, and working memory.[42] In a larger study on 119 euthymic BD patients, risperidone- and olanzapine-treated BD patients performed poorly on memory (eg, CVLT), attention (eg, TMT Part A), and verbal fluency tasks when compared with healthy individuals. Further, relative to olanzapine- and quetiapine-treated patients, the risperidone-treated group performed poorly on the WCST and CVLT tasks. In contrast, the quetiapine group obtained higher scores than the other treatment groups on the cued short-term recall of the CVLT and made fewer mistakes on the recognition task of the CVLT when compared with the olanzapine group. However, the statistical significance of these findings disappeared when results were adjusted for the variable “history of psychotic symptoms.”[43] Further analyses revealed that the quetiapine-treated group performed worse on executive functioning and working memory measures such as the semantic fluency and backward digit tasks when compared with healthy controls.[43] The lack of proper randomization limits the generalization of these findings.

Compared with lithium and anticonvulsants, findings on the cognitive effects of antipsychotics in the treatment of BD are limited. Additional controlled studies evaluating pretreatment and posttreatment effects of this class of medications on the neuropsychological performance of bipolar patients are therefore needed to substantiate current findings.

Cognitive impairment as an endophenotype for BD

BD has a substantial genetic component, with heritability estimates ranging from 70% to 80%.[44–46] Unaffected relatives and offspring of BD patients exhibit mild deficits in the memory, visuospatial, and executive function domains. A meta-analysis detected executive function and verbal memory deficits of small effect size in first-degree relatives of BD patients.[47] By comparison, relatives of BD patients were more prone to commit perseverative errors on the CANTAB Intradimensional/Extradimensional Shift task (this task assesses attention and cognitive flexibility) when compared with healthy individuals.[48] In another study, first-degree relatives of BD patients exhibited slow reaction times on the

Digit Symbol test and performed poorly on tasks of divided attention (eg, low accuracy on the TMT Part B).[49] Similarly, Daban et al[50] observed sensorimotor speed deficits of large effect size (Cohen $d = 0.89$) in BD patients and of medium effect size (Cohen $d = 0.52$) in unaffected first-degree relatives of bipolar patients. Alongside psychomotor retardation, unaffected first-degree relatives of BD patients perform worse on verbal and spatial memory tasks (eg, letter number span, object delayed response, immediate and delayed facial memory tests).[51] Unaffected relatives of BD patients and BD patients also exhibited visuoconstructional deficits, as measured by the Block Design Test of the Wechsler Adult Intelligence Scale.[52] Likewise, 2 studies showed that the accuracy on the WCST and on a sustained attention task was reduced in first-degree BD relatives compared with healthy patients.[53,54] Studies on twins discordant for BD concluded that non-BD co-twins had poorer working memory capacity (eg, Brown Peterson test) and learning and episodic memory (eg, Wechsler Memory Scale and CVLT) when compared with control twins.[45,55,56]

Unaffected offspring of BD patients present a similar cognitive profile as relatives of BD patients. In one study, both BD offspring and unaffected relatives of bipolar patients were found to have a lower IQ[57] and reduced literacy (as measured by the Wide Range Achievement Test 4)[58] when compared with healthy controls.

In conclusion, verbal memory, psychomotor speed, and response inhibition are consistently observed in unaffected relatives of BD patients and may serve as cognitive indicators of genetic vulnerability to BD. However, the characterization of cognitive markers of illness vulnerability in high-risk individuals is still a work in progress.

Therapeutic Approach for Cognitive Impairment in BD

Pharmacological interventions

Cholinesterase inhibitors—Cholinesterase inhibitors, commonly used in the management of Alzheimer disease and other dementias, were among the first drugs tested for the treatment of cognitive impairment in BD. As illustrated in Table 1, several of these studies (Table 1) adopted open-label designs, with no placebo group.

In one of the few randomized, double-blind studies on the topic, Ghaemi et al[62] observed improvements in episodic memory (measured by the CVLT) among galantamine-treated BD patients compared with placebo. However, the small sample size and the high rate of dropouts limit the generalization of the findings.

Similarly, an open-label, non–placebo-controlled study[63] found that BD patients scored higher on the CVLT and on a (objective) test of sustained attention (Connor continuous performance test) following administration of extended-release galantamine. In this study, patients underwent magnetic resonance spectroscopy at baseline and after 4 months of treatment. Analyses showed an increase in N-acetyl-aspartate (a marker of neuronal viability) and a decrease in choline (Cho) in the left hippocampus associated with treatment.

Studies on donepezil have produced less favorable evidence. In a naturalistic case series,[61] 58 patients with BD were treated with donepezil. In total, 67% of the donepezil-treated BD

patients reported subjective improvement in cognition. Positive results seemed restricted to patients with BD type II and BD NOS, and no objective cognitive measure was performed. In contrast, another study[60] failed to find any positive impact of donepezil on the cognitive performance of late-onset BD patients. Shortcomings of this study were the open-label design, the absence of a placebo group, and the small sample size.

Overall, the evidence supporting a possible role of cholinesterase inhibitors in the treatment of BD-related cognitive impairment is very limited. Although the lack of well-designed studies limits the interpretation of available results, it is possible that the pathophysiological mechanisms involved in the cognitive deficits found among bipolar patients result from disruptions in noncholinergic neurotransmitter systems. If substantiated in future studies, this hypothesis would explain the reason that BD patients are less likely to respond to this class of medications.

Memantine—Memantine is an N-methyl-D-aspartate glutamate receptor antagonist, approved for the treatment of Alzheimer disease. Preclinical and clinical evidence suggests that this agent may have a beneficial role in the treatment of acute mania.[69] In addition, anecdotal reports indicate that it may also have positive effects on the cognition of bipolar patients.[70,71] It is yet unclear whether the cognition-enhancing properties of memantine are independent of its effects on mood symptomatology. A recently completed randomized, placebo-controlled trial specifically addressed the possible role of memantine in the management of cognitive impairment in BD, but, to our knowledge, there are no currently published findings from this study.

Mifepristone—Given the findings of abnormal allostatic load with consequent hypercortisolemia in affective disorders and its potential deleterious effects on the hippocampus, medications targeting the HPA pathophysiological pathway may be promising in the management of cognitive symptoms in BD. Mifepristone is a glucocorticoid receptor antagonist that has been tested in the management of these symptoms. In a double-blind, placebo-controlled study,[59] 20 bipolar patients received mifepristone for 7 days, at the dose of 600 mg/d. Cognitive function was assessed at baseline and 2 weeks after completing treatment. The authors found significant improvements in spatial working memory, spatial recognition memory, and verbal fluency in the medication group. Notably, no effects on verbal memory were displayed. This finding suggests that this improvement, if present, could not be detected at the time points established by the investigators for revaluation.

In a more recent study by the same group,[66] 60 patients with bipolar depression were treated with mifepristone (at 600 mg/d for 7 days) and experienced improvements in their performance in a spatial working memory task. It is noteworthy that the effects were found to be independent from improvements in mood.

Although the results above suggest that mifepristone may have a potential role in the treatment of cognitive deficits in BD, the side-effect profile of this medication limits its clinical routine use in the clinical setting. Moreover, a complementary analysis in one of the studies above[59] found that the improvements in spatial recognition memory were directly

correlated to baseline cortisol levels. This finding indicates that a subgroup of bipolar patients, with elevated HPA activity, may benefit from treatment with mifepristone.

Intranasal insulin—Growing evidence points to a possible role of insulin on neuroplasticity regulation, and the presence of insulin receptors in the hippocampus suggest that insulin is involved in processes associated with memory consolidation. Moreover, exogen insulin has been shown to enhance the cognitive function of controls and elderly patients with memory impairment.

A randomized, placebo-controlled study[66] tested the effect of intranasal insulin (at the dose for 40 IU/d for 8 weeks) on the cognitive performance of bipolar patients. The analyses revealed improvements in executive functioning (measured by the TMT Part B) in the medication-treated group compared with the placebo group. With respect to other cognitive functions, improvement was similar in both groups. The authors hypothesized that the positive impact of insulin on cognition may result from putative regional effects on neuroplasticity in the dorsolateral prefrontal cortex.

Pramipexole—The putative involvement of the dopaminergic system in the cognitive deficits observed in BD points to a possible role of dopaminergic agonists in the treatment of these symptoms. In a preliminary study, improvements in attention and visual search efficiency were observed among patients with bipolar depression who received pramipexole (a D2, D3, and D4 agonist) as an augmentation strategy for 6 weeks.[72]

Similarly, a more recent randomized study conducted by the same group[64] evaluated the impact of pramipexole (given for 8 weeks at a dosage ranging from 0.125 mg to 0.75 mg twice a day) on the cognitive performance of euthymic bipolar patients. Results were basically negative, although the authors noticed some degree of association between residual mood symptoms and lack of response to the medication. When the analyses were restricted to the sample of treated patients without residual mood symptoms, the authors found improvements in the digit span backward and the Stroop color interference effect associated with pramipexole treatment.

Herbal agents—In preclinical studies, *Withania somnifera*, an herbal agent, has been found to have antioxidant and neuroprotective properties, in addition to procholinergic and anticholinesterase effects. It has been used for centuries in India to increase resistance to stress and disease. A recent double-blind, randomized clinical trial[68] showed that an 8-week treatment with *W. somnifera* extract (at the dosage of 50 mg/d) in a sample of bipolar patients led to better selective attention (measured by the digit span test), faster reaction times on the neutral items of the Eriksen Flanker task, and higher scores on the facial emotion recognition rating scale of the Penn Emotional Acuity Test.

Antioxidants—N-acetyl cysteine is a precursor of glutathione, an endogenous antioxidant, and displays marked antiinflammatory and neuroprotective properties, in addition to modulatory effects on the dopaminergic and glutamatergic systems.[73] A recent randomized, doubleblind study analyzed the effect of N-acetyl cysteine (given at the dose of 2000 mg/d for 6 months) on the cognitive function of patients with BP.[65] No significant differences

were observed between groups in regard to changes in any of the cognitive domains evaluated, after 6 months of treatment. The authors argued that the duration of the treatment was probably insufficient to induce cognitive improvement in the treatment group.

Likewise, omega 3 polyunsaturated fatty acids have well-demonstrated antioxidant properties, in addition to possible neuroprotective effects secondary to inhibition of the enzyme protein kinase C.[74] Studies have demonstrated its effect as an adjunctive treatment strategy in the treatment of bipolar depression, but it is still unclear if they might play a role in the management of cognitive impairment in BD. To date, we are not aware of any controlled studies specifically addressing the impact of omega 3 fatty acids on the cognitive performance of bipolar subjects.

Moreover, L-carnosine, a dipeptide, has well-demonstrated antioxidant properties and has been found to have a role in the treatment and prevention of several chronic conditions.[75] A clinical trial is currently evaluating its possible effect on the cognitive function of bipolar patients.[7]

Other potential pharmacological strategies—Erythropoietin is traditionally used for treatment of anemia but has also been found to exhibit neuroprotective and neurotrophic effects in animal models of brain injury, possibly because of its effects on a nonhematopoietic receptor system in the central nervous system. Moreover, improvements in the neuropsychological performance of schizophrenic patients, measured through a composite score of a set of cognitive tests (delayed memory, language–semantic fluency, attention, and perseverative errors of the WCST), were observed in association with administration of erythropoietin.[76] An ongoing randomized clinical trial is currently evaluating the impact of erythropoietin, administered intravenously at the dose of 40,000 IU weekly for 8 weeks, on the cognitive performance of bipolar patients.[77]

Similarly, D-cycloserine, a glutamatergic N-methyl-D-aspartate receptor agonist, has been shown to enhance the cognitive performance of schizophrenic patients when associated with cognitive remediation (CR).[78] A clinical trial assessing its possible efficacy among bipolar patient is currently in progress.

Methylene blue, traditionally used for the treatment of metahemoglobinemia, seems to have neuroprotective properties, possibly secondary to its inhibitory effects on the enzymes nitric oxide synthase and guanylate cyclase.[79] Its putative role in the treatment of cognitive impairment in BP is currently under investigation.[7]

Furthermore, modafinil, an agent commonly used for the treatment of narcolepsy, has shown promising preliminary results as an augmentation strategy for patients with bipolar depression.[69] An ongoing clinical trial is currently assessing its impact on the cognitive performance of stable bipolar patients.[7]

Finally, a randomized, double-blind study is aiming at evaluating the effect of the antiviral agent valacyclovir on the cognitive performance of bipolar patients previously infected with herpes simplex virus type 1. A similar design demonstrated the benefit of the agent in question in the treatment of cognitive deficits in schizophrenia, suggesting that previous

exposure to herpes simplex virus type 1 might be involved, at least partially, in the pathophysiology of cognitive deficits in some patients.[80]

Nonpharmacological interventions

CR is a form of neuropsychological rehabilitation defined as a training-based intervention focused on improving cognitive processes by compensatory and adaptive strategies for longer lasting benefits.[81,82] CR was specifically developed to address the cognitive deficits found in patients with schizophrenia. The effects of CR among patients with affective disorders are not well established. However, a recent meta-analysis suggested that its benefits (effects) in mood disorders might be similar to the ones observed among schizophrenic patients.[83]

With respect to BD, a small, uncontrolled study evaluated the effect of 14 CR sessions on the neuropsychological and functional status of bipolar patients.[84] In this study, the improvement in executive functioning at the follow-up assessment correlated positively with improvements in the occupational status of the patients. The lack of a control group and the small sample size limit the generalization of the findings. Of notice, a larger, randomized, evaluator-blind, between-group designed study is currently addressing the efficacy of CR in BP.[85] The primary outcome focuses on declarative memory, whereas the secondary outcomes will include attention, executive function, and functional status.

Perspectives in the treatment of cognitive impairment in BD

Neuroplasticity-based computerized CR is an intervention that takes into account findings on basic neuroscience research regarding neuroplasticity-based learning in the adult brain.[85] In other words, its clinical benefits seem to result from changes in neural circuits and synaptic connectivity. Current evidence suggests that neuroplasticity-based computerized CR is a promising approach in the management of age-related cognitive declines and in the neuropsychological deficits present in patients with schizophrenia and geriatric depression. An ongoing trial is currently investigating its usefulness in the treatment of cognitive deficits among BD patients.

Similarly, a growing amount of evidence points to a possible role of noninvasive brain stimulation techniques, such as transcranial magnetic stimulation, in the management of cognitive impairment across Alzheimer disease, traumatic brain injury, and other neurological conditions.[86,87] These interventions that have been shown are able to modulate neuroplasticity processes and ultimately contribute to the restoration of damaged neuronal networks underlying neuropsychological impairment. A randomized, double-blind clinical trial is currently evaluating the possible effects of deep transcranial magnetic stimulation on bipolar depression, with a focus not only on mood but also on cognitive impairment.[78] Further research is necessary to clarify the actual impact of these strategies on the cognitive function of bipolar patients.

Finally, growing evidence points to the role of inflammatory processes in the pathophysiology of BD, and some studies point to correlations between inflammatory cytokines and cognitive impairment in BP.[88] Therefore, the possible role of

antiinflammatory agents in the treatment of cognitive impairment in BP seems to be a promising target for future studies.

Conclusions

Despite the negative impact of cognitive deficits on the functional status of BD patients, there is no Food and Drug Administration–approved pharmacological agent for the management of cognitive symptoms among bipolar patients. The variability of available findings suggests that medications might be of marginal benefit in the treatment of these deficits, and it is still unclear which deficits are more likely to respond to therapeutic interventions. However, interventions such as CR and noninvasive brain stimulation techniques have not yet been properly explored among bipolar patients. It is expected that the role of these approaches in the treatment of cognitive deficits in BD be clarified over the next years. Did you notice trends in terms of what kind of cognitive domains respond better to treatments?

Moreover, the cyclic nature of BD makes the study of cognitive deficits in this condition particularly challenging. Although a large number of studies include cognitive/neuropsychological performance as a secondary outcome in clinical trial evaluating the treatment of bipolar depression, there is a paucity of studies addressing specifically the management of cognitive impairment among bipolar patients. Finally, there is a need for additional studies evaluating the efficacy of interventions combining cognitive rehabilitation and biological treatments.

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Table 1
Studies addressing the pharmacological treatment of cognitive deficits in BP

Study	Agent	Sample	Main findings	Notes
Young et al[59]	Mifepristone (600 mg/d for 1 wk)	20 BP	Improvement in spatial working memory, spatial recognition memory, and verbal fluency	Double-blind, crossover design; improvement in mood in addition to cognitive function
Gildengers et al[60]	Donepezil (5-10 mg/d for 3 mo)	12 BP	Negative	Open label; no placebo group; only late-onset cases
Kelly[61]	Donepezil	58 BP	Subjective improvement in 67% of patients (CGI-improvement), benefit restricted to BP II and NOS	Naturalistic case series, no placebo group, no objective cognitive measure
Ghaemi et al[62]	Galantamine	30 BP	Galantamine: improved performance on the CVLT, placebo: improved performance on the D-KEFS (trail-making test and category fluency)	Small sample; high rate of drop-outs
Iosifescu et al[63]	Galantamine ER (8–24 mg/d for 4 mo)	19 BP, 10 HC	BP: significant improvement in subjective cognitive performance and on Conner continuous performance test (Conner CPT) and verbal episodic memory (CVLT); increase in N-acetyl-aspartate and decrease in Cho at the left hippocampus	Open-label, small sample, no placebo group
Burdick et al[64]	Pramipexole for 8 wk (0.25–0 1.5 mg/d)	45 BP	Mostly negative	Some cognitive improvement for patients without residual mood symptoms
Dean et al[65]	N-acetyl cysteine (2000 mg/d for 6 mo)	46 BP	Negative	Small sample size, high rate of dropouts
McIntyre et al[66]	Intranasal insulin (40 IU/d for 8 wk)	52 BP-I, 10 BP-II	Insulin: improvement in executive function (TMT Part B)	Only euthymic patients
Watson et al[67]	Mifeprestone (600 mg/d for 1 wk)	60 BP	Improvement in spatial working memory (sustained improvement for 2 wk)	Improvement in cognition was independent from mood
Chengappa et al[68]	Extract of *Withania somnifera* (50 mg/d for 8 wk)	60 BP	Improvement in digit span backward, Eriksen Flanker neutral response time, and the facial emotion rating scale of the Penn Emotional Acuity Test	Only euthymic patients