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REVIEW

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Efficacy and safety of established and off-label ADHD drug therapies for cognitive impairment or attention-deficit hyperactivity disorder symptoms in bipolar disorder: A systematic review by the ISBD Targeting Cognition Task Force

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Abstract

Background: Abnormalities in dopamine and norepinephrine signaling are implicated in cognitive impairments in bipolar disorder (BD) and attention-deficit hyperactivity disorder (ADHD). This systematic review by the ISBD Targeting Cognition Task Force therefore aimed to investigate the possible benefits on cognition and/or ADHD symptoms and safety of established and off-label ADHD therapies in BD.

Methods: We included studies of ADHD medications in BD patients, which involved cognitive and/or safety measures. We followed the procedures of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement. Searches were conducted on PubMed, Embase and PsycINFO from inception until June 2023. Two authors reviewed the studies independently using the Revised Cochrane Collaboration's Risk of Bias tool for Randomized trials.

Results: Seventeen studies were identified ($N = 2136$), investigating armodafinil ($k = 4$, $N = 1581$), methylphenidate ($k = 4$, $N = 84$), bupropion ($k = 4$, $n = 249$), clonidine ($k = 1$, $n = 70$), lisdexamphetamine ($k = 1$, $n = 25$), mixed amphetamine salts ($k = 1$, $n = 30$), or modafinil ($k = 2$, $n = 97$). Three studies investigated cognition, four ADHD symptoms, and 10 the safety. Three studies found treatment-related ADHD symptom reduction: two involved methylphenidate and one amphetamine salts. One study found a trend

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[Correction added on 06 May 2024, after first online publication: The spelling of the third and sixth author's names were corrected from Riccardo Gugliemo to Riccardo Guglielmo and Vicente Balanzá-Martínez to Vicent Balanzá-Martínez.]

towards pro-cognitive effects of modafinil on some cognitive domains. No increased risk of (hypo)mania was observed. Five studies had low risk of bias, eleven a moderate risk, and one a serious risk of bias.

Conclusions: Methylphenidate or mixed amphetamine salts may improve ADHD symptoms in BD. However, there is limited evidence regarding the effectiveness on cognition. The medications produced no increased mania risk when used alongside mood stabilizers. Further robust studies are needed to assess cognition in BD patients receiving psychostimulant treatment alongside mood stabilizers.

KEYWORDS

attention-deficit hyperactivity disorder, cognitive impairment, bipolar disorder, ISBD task force, medication, recommendations, systematic review

1 | INTRODUCTION

Bipolar disorder (BD) and attention-deficit hyperactivity disorder (ADHD) are neuropsychiatric disorders with a broad overlap in psychopathology, and possibly, pathophysiology. Comorbidity of BD and ADHD is common, with an estimated frequency of 9%–35% in adults and 38%–98% in children with juvenile BD.[1–3] There are important differences between the disorders, such as the episodic nature, the changing polarity in BD and the on average earlier onset in ADHD. However, the disorders also share important features, including impulsivity, psychomotor agitation, poor sleep, and cognitive impairments, including inattention and distractibility. The cognitive impairments represent a pressing treatment target[4,5] given their negative impact on psychosocial and vocational functioning and prognosis.[6–12] The pattern of cognitive impairments is similar in BD and ADHD, with broad deficits across several cognitive domains that vary in their relative severity.[10,11] According to meta-analyses, verbal memory, working memory, and executive function are particularly affected in BD (e.g., Ref. [3,12] although with some heterogeneity, Ref. [13,14]). In ADHD, the greatest deficits have been observed in working memory, response inhibition, and reaction time variability.[15] Taken together, the symptomatic overlap, comorbidity, and similar cognitive impairments suggest common neurobiological underpinnings in BD and ADHD that may be targeted to improve cognitive outcomes and daily functioning.[16]

Abnormal dopamine signaling likely plays a role in the cognitive difficulties across BD and ADHD. Both disorders have been linked to dysfunction of the dopamine transporter (DAT), a transmembrane protein that reduces dopamine signaling by driving its reuptake into the presynaptic neuron. Specifically, a rare functional variant of the DAT gene that confers abnormal dopamine efflux in vitro and in vivo has been found in both disorders.[17–20] DAT also serves as a key target for various stimulant and nootropic ADHD medications.[21] More broadly, cognitive impairment across neuropsychiatric disorders has also been linked to the risk variant of the catechol-O-methyltransferase (COMT) gene (the Val158Met polymorphism), which mediates the degradation of dopamine in the synaptic cleft.[22] In particular, the Val allele is associated with lower levels of synaptic dopamine in the prefrontal cortex, while the Met allele is related to greater prefrontal dopamine.[23] In general, studies have linked low cortical dopamine tonus to cognitive impairments across patients and healthy individuals,[22,24,25] with relatively consistent evidence for poorer attention, working memory, and executive function in Val homozygotes (with low PFC DA tonus) than in Met carriers. In keeping with this, we found that Val (compared with Met) homozygous BD individuals showed reduced recruitment of dorsolateral prefrontal resources during working memory, which was accompanied by impaired task performance.[26] Importantly, such task-related dorsal prefrontal hypo-frontality has been proposed as a key neurocircuitry biomarker of cognitive impairment across neuropsychiatric disorders[27] including BD[28] and ADHD.[29,30]

Medications that increase brain dopamine and/or norepinephrine are widely used for treating ADHD to improve cognitive and daily functioning. The stimulant medication methylphenidate, which is the most used ADHD medication, increases extracellular dopamine in the striatum by blocking the DAT.[31,32] Furthermore, nonstimulants like atomoxetine and antidepressants used in ADHD, such as bupropion, increase norepinephrine and dopamine levels in the prefrontal cortex.[33] Finally, alpha-2-adrenergic agonists, including clonidine and guanfacine, facilitate norepinephrine neurotransmission by stimulating the norepinephrine alpha 2A receptors on prefrontal cortical neurons.[34] A common mechanism of these medications at a systems level in the brain, is to reverse hypo-activity in the prefrontal cortex.[35–37] Pharmacologic upregulation of dopamine and/or noradrenaline may thus be a promising avenue to target the hypo-frontality to improve cognitive functions in BD. Nevertheless, there is a paucity of studies investigating how these medications influence cognition in BD. This is due to an ongoing concern that psychostimulant medications could trigger or aggravate manic symptoms in patients with BD.[38,39]

The assumption linking ADHD hyperactivity and bipolar mania lacks empirical evidence, mainly relying on animal studies. In contrast, the "vigilance regulation model of mania" suggests that unstable wakefulness due to low dopamine levels contributes to mania symptoms in both ADHD and BD.[40] Manic behavior is seen as an attempt to stabilize wakefulness through external stimulation.[40] Following this, it has been suggested that medications enhancing dopamine signaling may reduce mania symptoms by improving vigilance.[40] The efficacy

of methylphenidate in acute mania remains controversial, but it does not appear to worsen mania symptoms.[41] Corroborating this finding, a large-scale registry-based study found that methylphenidate was safe and not associated with manic switch in BD patients who received concomitant mood-stabilizing medication, although mania risk did increase in people *not* taking mood stabilizers.[42] Similarly, armodafinil was also found to be well tolerated in bipolar depression, in terms of no increase in mania risk.[43,44] An open-label study of lisdexamfetamine dimesylate likewise showed that the drug was well tolerated in BD with no increases in manic symptoms.[45]

Given the similar cognitive impairments in BD and ADHD, overlapping neurobiological underpinnings, and pressing need to identify effective pro-cognitive treatments in BD,[46] it seems timely to re-examine the potential benefits on cognition and ADHD symptoms and the safety of ADHD medications in BD. We did not conduct a quantitative meta-analysis of the available studies due to the significant heterogeneity in terms of intervention characteristics (pharmacological compounds, dose, and combination with other drugs), and population characteristics (child and adolescent versus adult populations, BD with comorbid ADHD versus BD only). Instead, this systematic review by the ISBD Targeting Cognition Task Force aimed to: (I) examine the evidence in the field for potential benefits of medications that are used to treat ADHD, either established or off-label drug therapies, on cognition and/or ADHD symptoms in patients with BD with or without ADHD comorbidity, and (II) investigate the side effects of these medications in BD, with a particular focus on its potential to trigger and/or aggravate mania symptoms.

2 | METHOD

This review was conducted in accordance with the PRISMA 2020 statement. The systematic review protocol was registered in the online PROSPERO database (registration number: CRD-42023385497).

2.1 | Review question

The PICO framework (Population, Intervention, Comparison, Outcome) was used to structure the review question. This review aimed to critically examine data from randomized and non-randomized controlled trials investigating (a) the efficacy of established or off-label ADHD drug therapies to treat cognitive impairments and/or ADHD symptoms in BD patients with or without comorbid ADHD (BD-cADHD), (b) the side effects of these interventions with a focus on the risk of inducing hypo/manic symptoms.

2.2 | Search strategy

We performed systematic computerized literature searches using the databases PubMed, Embase, and PsycINFO up until June 2023. The search term "bipolar disorder" and the database-specific variant terms were combined with search terms for several classes of psychotropic drugs used for the treatment of ADHD. These classes include medical psychostimulants (methylphenidate and amphetamine derivatives), alpha-2-adrenergic agonists (e.g., clonidine and guanfacine), norepinephrine reuptake inhibitors (e.g., atomoxetine and viloxazine), and pharmacological compounds used off-label in the treatment of ADHD (e.g., bupropion, modafinil, armodafinil). For the drugs approved for ADHD treatment, the database-specific keywords were used in the search strings. For the most common drugs, popular brand names were added (Ritalin, Concerta, Vivanse, Dexedrine). See Appendix S1 for details.

The included off-label compounds sometimes used to treat ADHD were included because we judged there is enough experimental evidence of the possible efficacy in ADHD treatment to warrant inclusion in the review. This is especially because modafinil and armodafinil are both psychostimulant compounds classified as wakefulness-promoting drugs that increase dopamine in the brain[47] like approved ADHD psychostimulant drug therapies. Modafinil had enough evidence backing it for FDA approval as a drug to manage ADHD in children and adolescents but was rejected due to concerns about dermatological side effects.[48] There is also experimental evidence that modafinil could be effective in treating ADHD in adults.[49] While there, to our knowledge, are no studies investigating armodafinil, it is a longer lasting isomer of modafinil,[47] which makes it pharmacologically similar enough to modafinil to warrant inclusion in the present review. Like atomoxetine which is approved for ADHD treatment, bupropion also increases the availability of dopamine and norepinephrine, albeit by a different mechanism of action than atomoxetine. There is experimental evidence that bupropion is effective in treating ADHD.[50] The combination of the similar neuropharmacological effects of bupropion to other approved ADHD drug therapies, and the experimental evidence of its treatment efficacy for ADHD led us to include bupropion in our review. As for *other drug classes*, such as dopamine agonists and COMT inhibitors that increase dopamine and/or norepinephrine in the brain, we are unaware of any evidence in human participants, experimental or otherwise, of efficacy in treating ADHD. Furthermore, a recent study of the dopamine agonist pramipexole suggested that the compound had no pro-cognitive efficacy in BD patients.[51] For these reasons, dopamine agonists and COMT inhibitors were not included in the present review.

The relatively broad search strategy was chosen for two reasons. First, because of the suspected paucity of studies investigating possible pro-cognitive effects of medications that increase dopamine and/or norepinephrine in BD. Second, reviewing possible side effects of these compounds in addition to their cognitive benefits was considered important because of a frequent concern that the compounds could induce manic/hypomanic symptoms.

Two authors (RG and ZO) independently conducted a primary title and abstract screening to identify potentially eligible articles, and a subsequent full-text screening. The systematic literature searches were supplemented using Google Scholar's 'Related Articles'

function, as well as manual citation searches using the included articles. Conflicts were resolved through discussion, and if needed, through further discussion with two other authors (KWM, GH).

Screening, selection, data extraction, and risk-of-bias assessments were conducted using the Covidence platform.[52] Throughout the screening phases, the eligibility of the articles was evaluated based on their accordance with our inclusion/exclusion criteria.

2.3 | Selection criteria

Studies were included if they (a) examined changes in neurocognitive function or ADHD symptoms as a primary, secondary, or tertiary outcome and/or (b) investigated side effects of the interventions in BD. Cognitive change was operationalized as changes in objective neurocognitive test performance, while ADHD symptom change was measured with ADHD symptom rating scales (see Appendix S1, for details on the represented ADHD symptom measures).

The following inclusion criteria for the studies were applied: (a) participants had BD with or without ADHD comorbidity in any phase of their illness (depressive, manic, remitted, or mixed); (b) the study design involved a control group of participants who received mood stabilizing drugs, placebo, or another psychopharmacological intervention; (c) the study findings were reported in peer-reviewed articles, as defined either at the journal website or noted in the article with information on when it was received, revised, and accepted. In addition, relevant studies by ISBD Targeting Cognition Task Force members that were under review at the time of writing were also included; (d) the articles were written in English. Studies were excluded if they examined mixed samples with several diagnoses, unless data for BD with or without comorbid ADHD were reported separately, and if they were case reports or series.

2.4 | Data extraction

RG and ZO extracted the following predefined data items of interest: author, title, year of publication, participant details (including sample size, diagnosis, psychiatric comorbidities, and medication status), intervention details (e.g., dose, duration, frequency), cognitive measures (scores in various cognitive tasks or ADHD symptoms), as well as functional and mood scale measures, and side effects.

2.5 | Quality assessment

Included studies were assessed for risk-of-bias using either the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB2),[53] the RoB2 crossover version[53] or the Risk-of-Bias in Non-Randomized Studies—of Interventions (ROBIN-S) assessment tool.[54] RG and ZO independently evaluated included studies using the appropriate, above-described tools and subsequently reached consensus following the Covidence protocol. Only outcomes which correspond to this review's primary or secondary outcome were assessed for bias, regardless of the respective study's priority of outcomes. To aid RoB assessments, trial protocols, statistical analysis plans, and non-commercial trial registry records were obtained whenever available. All RoB assessments were of the *intent-to-treat* (ITT) analyses of the effects.

3 | RESULTS

After the removal of duplicate hits, the literature searches yielded 1957 articles. These articles were subjected to a primary title and abstract screening (primary screening), which excluded 1927 articles, leaving 30 studies for full-text review (secondary screening) (see PRISMA flowchart in Figure 1). One study was included via other methods, namely a study by a task force member that was under review at the time of writing. Seventeen studies met our inclusion criteria and were included in the review (see Tables 1 and 2).

3.1 | Study characteristics

Among the 17 identified intervention studies, three included neuropsychological cognitive change measures,[41,55,56] while four studies investigated treatment-related ADHD symptom change.[57–60] Of the latter, three were conducted in juvenile samples ranging from 5 to 17 years of age.[57,58,60] Another 10 studies investigated side effects of these medications in BD.[43,61–69]

Of the 17 studies, 12 examined psychostimulant interventions,[41,43,56–63,65,66] while five examined nonstimulant ADHD drug medications.[55,64,67–69] 16 studies were RCTs,[41,43,55–57,59–69] while one study had a non-randomized, controlled extension trial design.[58] The study characteristics are displayed in Tables 1 and 2.

A variety of approved and experimental ADHD medications were investigated. Armodafinil was the most represented of the eligible interventions, being examined in four studies with a total of 1581 participants.[43,61,63,65] Methylphenidate (immediate release) was also examined in four studies, although with smaller samples ($n = 84$).[41,57,58,60] Bupropion was examined in four studies ($n = 249$).[54,67–69] Two studies examined modafinil ($n = 97$).[56,62] Finally, single studies examined clonidine ($n = 70$),[55] lisdexamphetamine ($n = 25$),[66] and mixed amphetamine salts ($n = 30$),[59] respectively. Medication dosages of each compound were similar across the studies (see Tables 1 and 2).

3.2 | Cognitive and ADHD symptom change

3.2.1 | Methylphenidate

In the methylphenidate studies, a total of 66 participants received the active immediate release compound, while 54 received placebo.

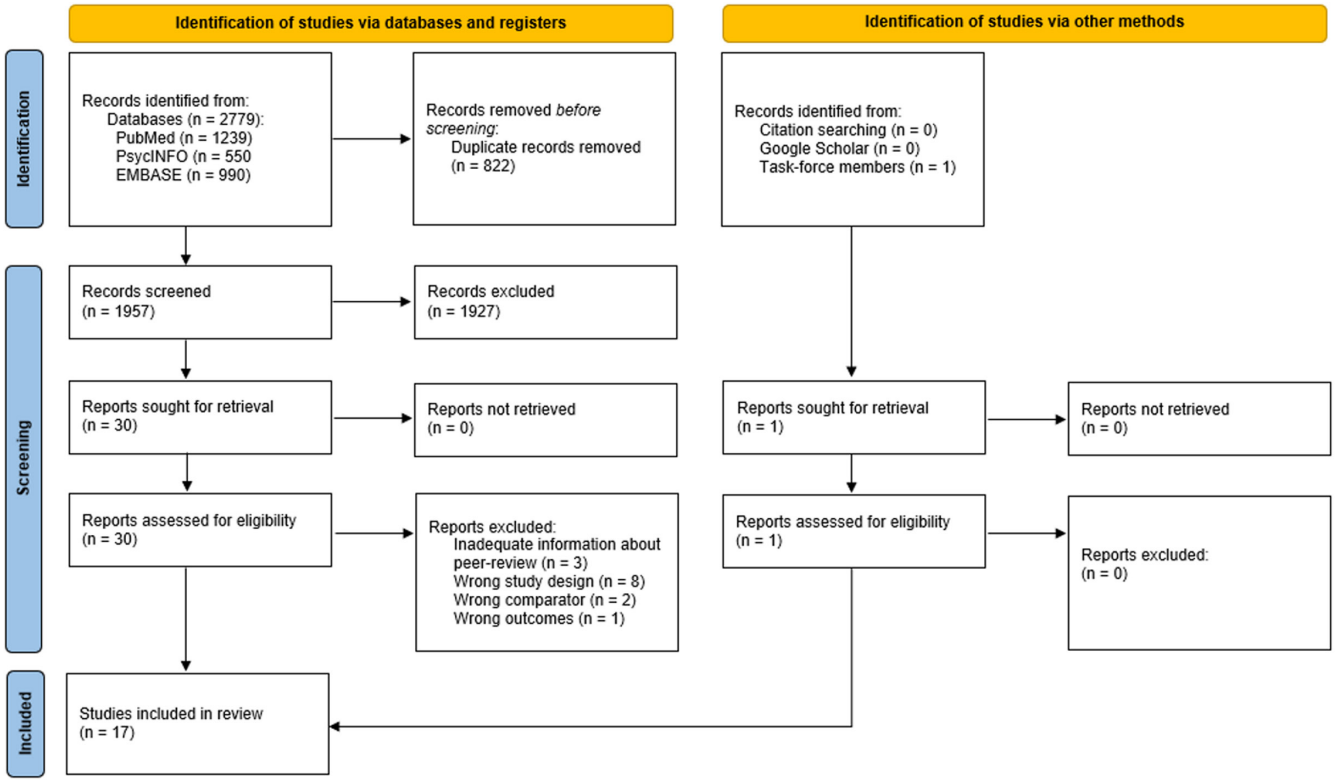

FIGURE 1 PRISMA flowchart. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

This includes two crossover studies in children/adolescents,[57,60] where 38 participants went through both active treatment and placebo conditions. Dosages of methylphenidate ranged from five to 40 mg/day. In all studies, methylphenidate was given twice a day, generally in the morning and at midday. None of the methylphenidate studies were sponsored by the pharmaceutical industry. In two cases,[41,57] the study medication was donated by pharmaceutical companies (Abbott Laboratories, Chicago, IL, USA; Medice, Iserlohn, Germany).

One study examined the effects of three weeks of methylphenidate administration in combination with mood stabilizing medications, mostly a combination of lithium and divalproex sodium, given for at least five days prior to study start.[57] The study was conducted in a sample of 16 euthymic children and adolescents with BD and ADHD. Change in ADHD symptoms was defined as the primary outcome with change in affective symptoms being the secondary outcome. Participants were allowed clonidine as a soporific agent at the discretion of research clinicians but not tricyclic antidepressants or antipsychotic medication. Participants received five mg twice daily, then 10 mg twice daily, and then 15 mg twice, each for 1 week, over a course of three weeks. The study was crossover- and placebo-controlled and double-blinded. Methylphenidate was significantly more efficacious than placebo in reducing ADHD symptoms, with a large effect size ($d=0.9$), measured with the ADHD Rating Scale (ARS-IV) (primary outcome). Paired sample t test also revealed significant reductions compared to placebo on the Conners Parent Rating Scale 48 (CPRS-48) Conduct Problems subscale ($p=0.05$), Impulsivity–Hyperactivity subscale ($p=0.02$), and Hyperactivity Index subscale ($p=0.02$) (secondary outcomes). There were no significant differences between methylphenidate and placebo on mood symptoms measured with the Young Mania Rating Scale (YMRS) or the Children's Depression Rating Scale Revised (CDRS-R).

A second study examined methylphenidate compared with placebo in a double-blind design for treating 42 adult patients with acute mania.[41] Severity of manic symptoms was defined as the primary outcome, while cognitive change was a secondary outcome. Patients received 15 mg of methylphenidate at 10 a.m. and 3 p.m. on Day 1, 20 mg at 9 a.m. and 3 p.m. on Day 2, and 20 mg at 9 a.m. on Day 3. The timing of the cognitive assessments was not specified. 91% of participants received concomitant lithium, valproate, carbamazepine, antipsychotics, or benzodiazepines. Participants were excluded if they had taken MAO-inhibitors within 14 days prior to study start, fluoxetine within six weeks, or other classes of primarily psychotropic drugs within the prior week.[41] Cognitive change was measured with the Screen for Cognitive Impairment in Psychiatry (SCIP) from the baseline assessment to on the final of treatment after the initiation of methylphenidate/placebo treatment. No differences between methylphenidate and placebo groups were found in cognitive change or in mania symptoms, and no significant side effects were detected.

In a third study of combination pharmacotherapy, 35 child and adolescent participants with BD and comorbid ADHD underwent

TABLE 1 Studies with stimulants or stimulant-like substances.

Reference	Population	Intervention	Comparator	Outcome	Design	Main findings
Calabrese et al 2010	Adult patients with Bipolar I and a current depressive episode unresponsive to mood stabilizers. *N* = 257	Adjunctive armodafinil 150 mg/day	Placebo pills	Change in depressive symptoms measured with the IDS-C30 (primary outcome), MADRS, HARS, CGI-BP, QIDS-SR16, Q-LES-Q-SF (secondary outcomes) tolerability, and adverse events (tertiary outcome)	Phase 2, 8-week, double-blinded, randomized, placebo-controlled, parallel-group, fixed dose, multicenter, proof-of-concept study	Adjunctive armodafinil improved some (the primary efficacy measure), but not secondary measures of depressive symptoms in patients with bipolar I disorder. The compound was generally well tolerated
Calabrese et al 2014	Adult patients with Bipolar I experiencing a current depressive episode despite mood stabilizing treatment. *N* = 433	Adjunctive armodafinil 150 or 200 mg/day	Placebo pills	Change in depressive symptoms measured with IDS-C30 (primary outcome), CGI-S, GAF (secondary outcomes), and adverse events/side effects (tertiary outcomes)	Phase 3, 8-week, double-blind, randomized, placebo-controlled, parallel-group, fixed dose, multicenter study	Adjunctive armodafinil decreased depression severity. The intervention was generally well tolerated.
Findling et al 2007	Children and adolescents with bipolar disorder and ADHD, euthymic. *N* = 16	Adjunctive methylphenidate immediate release 5, 10, and 15 mg/day	Placebo pills	Total score on ARS-IV (primary outcome), CPRS-48, CDRS-R, YMRS, CGI-S, and SEBMS (secondary outcomes)	4-week double-blinded, randomized, placebo-controlled crossover design trial	Adjunctive methylphenidate decreased ADHD symptoms in euthymic children and adolescents with bipolar disorder with a large effect size. The intervention was generally well tolerated
Frye et al 2007	Adult patients with bipolar depression (I and 2) that were not adequately responsive to mood stabilizers with or without concomitant antidepressant therapy. *N* = 85	Adjunctive modafinil 100–200 mg/day	Placebo pills	Change in depressive symptoms from baseline to endpoint measured with IDS-C30 (primary outcome), clinical response (defined as a 50% reduction in IDS-C30 scores), remission (defined as IDS-C30 score <12), CGI-BP, YMRS and side effects (secondary outcomes)	6-week, double-blinded, randomized, placebo-controlled trial	Adjunctive modafinil improved symptoms of depression over placebo. The treatment was safe and well tolerated, with only minor side effects
Frye et al 2015	Adult patients with Bipolar I and a current depressive episode unresponsive to mood stabilizers. *N* = 399	Adjunctive armodafinil 150 mg/day	Placebo pills	Change in depressive symptoms measured with IDS-C30 (primary outcome), CGI-S, GAF, YMRS, C-SSRS-SLV, HAM-A, ISI, and side effects (secondary outcomes)	Phase 3, 8-week, double-blinded, randomized, placebo-controlled, parallel-group, fixed dose, multicenter study	Adjunctive armodafinil had no effect on depressive symptoms in patients with bipolar I disorder, when compared to placebo. However, secondary measures of illness severity and functioning did improve more in patients receiving armodafinil. The intervention was well tolerated
Hegerl et al 2018	Adult patients with bipolar disorder and an acute manic episode. *N* = 42	Methylphenidate, immediate release 20–40 mg/day	Placebo pills	Severity of manic symptoms measured with YMRS (primary outcome), severity of agitation measured with the PANSS-EC, CGI-BP change from baseline to endpoint, cognitive change measured with SCIP, EEG-vigilance, and total movements during the study (secondary outcomes)	2.5-day, double-blinded, randomized, placebo-controlled, multicenter study	Methylphenidate was well tolerated and safe in patients with acute mania. However, it did not reduce manic symptoms or alter cognitive function

TABLE 1 (Continued)

Reference	Population	Intervention	Comparator	Outcome	Design	Main findings
Ketter et al 2015	Adult patients with Bipolar I and a current depressive episode unresponsive to mood stabilizers. *N* = 492	Adjunctive armodafinil 150 or 200 mg/day	Placebo pills	Change in depressive symptoms measured with IDS-C30 (primary outcome), CGI-S, GAF, YMRS, C-SSRS-SLV, HAM-A, ISI, and side effects (secondary outcomes)	Phase 3, 8-week, double-blinded, randomized, placebo-controlled, parallel-group, fixed dose, multicenter study	Adjunctive armodafinil reduced symptoms of depression, but the effect did not reach statistical significance. Both adjunctive armodafinil at doses of 150 mg and 200 mg per day were well tolerated
Kowatch et al 2003	Children and adolescents with bipolar disorder (I and II), in any phase of their illness, who had previously participated in a study treating acute mania with a single mood stabilizer. *N* = 35	Adjunctive mood stabilizer for non-responders with predominant bipolar symptoms. Adjunctive methylphenidate immediate release 5–10 mg/day for patients with predominant ADHD symptoms. Adjunctive Bupropion or SSRI for non-responders with predominant depressive symptoms. Adjunctive atypical antipsychotic agent for non-responders with psychotic symptoms	Continued monotherapy with a mood stabilizer despite non-response	Change in manic symptoms measured with YMRS with response defined as >50% improvement from baseline to endpoint (primary outcome), baseline to endpoint change in K-SADS mania and depression items, CGI-BP, and ADHD symptoms measured with changes in CGAS scores (secondary outcomes) and side effects (tertiary outcome)	2-week evaluation phase during acute mania followed by 6–8 weeks of stabilization with a mood stabilizer. subjects entered extension phase for another 16 weeks. Open-label, non-randomized trial	58% of participants were treated with an adjunctive mood stabilizer, methylphenidate, an atypical antipsychotic, or an antidepressant agent. Response to combination therapy was good with 80% responding to an adjunctive mood stabilizer, an anti-depressive response in participants receiving an antidepressant, and a clinical benefit from adding methylphenidate to treatment in patients with ADHD. Adjunctive methylphenidate was safe and well tolerated
Lipschitz et al 2023	Euthymic, adult patients with bipolar disorder I/II and subjective sleep problems and/or clinically significant cognitive impairment	Modafinil, flexible dose (100–200 mg/day) adjunctive to treatment with a mood stabilizer	Placebo pills	Safety (primary outcomes): Clinician administered side effect checklist, BSS, C-SSRS, HDRS, CARS-M. Cognitive change (secondary outcomes): MCCB composite score change from baseline to endpoint (primary cognitive outcome), MCCB domain score change from baseline to endpoint (secondary cognitive outcomes) Sleep quality and daytime wakefulness (secondary outcomes): PSQI change from baseline to endpoint, ESS change from baseline to endpoint	8-week, randomized, double-blinded, controlled trial.	Modafinil was found to be relatively safe for euthymic BD patients when given adjunctively to mood stabilizing medication. The study found "near significant" pro-cognitive effects on some domain scores of the MCCB, specifically processing speed and verbal learning, suggesting a trend towards cognitive improvements from modafinil. The study also found that those participants who received modafinil reported less daytime sleepiness, but worse sleep quality compared with the placebo group

TABLE 1 (Continued)

Reference	Population	Intervention	Comparator	Outcome	Design	Main findings
McElroy et al 2015	Adult patients with bipolar disorder I/II who were experiencing a major depressive episode unresponsive to mood stabilizers and/or antipsychotics. *N* = 25	Adjunctive lisdexamfetamine dimesylate 20–30 mg/day	Placebo pills	Change in depressive symptoms measured with MADRS (primary outcome), and self-rated depression, overall severity measured with CGI-BP, YMRS, ESS, FSS, FCI, BES, MADRS response (i.e., ≥50% reduction from baseline) and remission (i.e., <12 MADRS score at endpoint), metabolic variables (i.e., BMI, hemoglobin A1C, etc.), safety/tolerability (i.e., physical medical examination, blood- and urine panels, etc.) (secondary outcomes. No priority ratings among these explicated in the trial article)	8-week, double-blinded, randomized, placebo-controlled, parallel-group, flexible dose trial	Adjunctive lisdexamfetamine did not reduce the primary measure depressive symptoms but did reduce self-rated depressive symptoms and daytime sleepiness. Lisdexamfetamine was was generally well tolerated, albeit with one case of suspected misuse
Scheffer et al 2005	Pediatric patients with bipolar disorder (I and II) who were manic, hypomanic, or mixed. *N* = 30	Mixed amphetamine salts 2×5 mg/day after stabilization with Divalproex Sodium	Placebo pills	Change in manic symptoms measured with YMRS and change in ADHD symptoms measured with CGI-I (primary outcomes), and side effects (secondary outcome)	2-week evaluation phase followed by an 8-week open-label trial of monotherapy with Divalproex Sodium. Crossover into 4-week double-blind, randomized, placebo-controlled trial followed by a 12-week open-label follow-up phase	Divalproex sodium alone is not effective in reducing ADHD symptoms in bipolar disorder. Adding mixed amphetamine salts after stabilization with divalproex sodium significantly improved ADHD symptoms and was safe and well tolerated
Zeni et al 2009	Children and adolescents with juvenile bipolar disorder and ADHD whose manic symptoms responded to treatment with aripiprazole but still presented with significant ADHD symptoms. *N* = 14	Methylphenidate, immediate release, combined with aripiprazole	Placebo pills	Between-group differences in symptoms of mania measured with YMRS and symptoms of ADHD measured with SNAP-IV, depressive symptoms measured with CDRS-R (primary outcomes), and between-group differences in CMRS-P, CGI-S, KADS (secondary outcomes), adverse events measured with SAERS, and weight changes (tertiary outcomes)	4-week, double-blinded, randomized, placebo-controlled, crossover trial	Methylphenidate after stabilization with aripiprazole did not impact manic symptoms, however significant improvements in self-reported depressive symptoms were observed. The intervention was not significantly more effective than placebo in reducing ADHD symptoms. Methylphenidate and aripiprazole were generally well tolerated despite the onset of a mixed episode in one patient

TABLE 2 Studies of nonstimulant ADHD drug therapies.

Reference	Population	Intervention	Comparator	Outcome	Design	Main findings
Ahmadpanah et al 2022	Adult patients with Bipolar I, manic phase. *N* = 70	Adjunctive clonidine 0.2–0.6 mg/day	Placebo pills	Change in manic symptoms measured with Young Mania Rating Scale, sleep disturbances measured with the PSQI, and cognitive change from baseline to follow-up measured with MMSE (all prioritized as primary outcomes)	24-day, double-blinded, randomized, placebo-controlled trial	Adjunctive clonidine to lithium treatment significantly reduced symptoms of mania measured on the Young Mania Rating Scale, and subjective sleep quality. However, clonidine did not significantly impact cognitive performance as measured by the Mini-Mental State Examination when compared to placebo
Grossman et al 1999	Bipolar I patients in a depressive phase. *N* = 14	Idazoxan titrated to 240 mg/day and placebo bupropion	Bupropion titrated to 450 mg/day and placebo idazoxan	Change in depressive symptoms measured with HDRS and presence of psychotic symptoms measures with BPRS (primary outcomes), change in manic symptoms measured with BPRS, and side effects (secondary outcomes)	6-week, double-blinded, randomized controlled trial	Both idozoxan and bupropion reduced depressive symptoms, with idozoxan being significantly more efficacious. Both treatments were generally well tolerated with no significant differences in adverse events and side effects
McIntyre et al 2002	Adult patients with bipolar I/II in a depressive phase receiving mood stabilizers. *N* = 36	Adjunctive topiramate 50–300 mg/day	Adjunctive bupropion sustained release 100–400 mg/day	Percentage anti-depressive response rated defined as ≥50% decrease from baseline measured with HDRS-17 (primary outcome), MADRS, CGI-S, CGI-I change in manic symptoms measured with YMRS, and adverse events/side effects (secondary outcomes. No priority ratings among these explicated in the trial article)	8-week, single blinded (rater), randomized controlled trial	Both topiramate and bupropion improved symptoms of depression, with no differences between in their relative efficacy. Both treatments were generally well tolerated
Post et al 2006	Patients with bipolar depression I/II receiving mood stabilizers. *N* = 184	Adjunctive bupropion 75–450 mg/day, sertraline 50–200 mg/day, or venlafaxine 37.5–375 mg/day	Adjunctive placebo bupropion, placebo sertraline, or placebo venlafaxine	Antidepressant response (defined as ≥50% reduction in scores on IDS-C30 or a CGI-BP decrease of ≥2 points, both from baseline to endpoint), antidepressant remission (<12 on IDS-C30 and/or CGI-BP severity score of 1 at endpoint), antidepressant switch rates (i.e., ≥2 increase on CGI-BP, or CGI-BP manic severity of ≥3, or a YMRS score above 13, at any point (primary outcomes. No priority ratings among these explicated in the trial article)	10-week, randomized, placebo-controlled, flexible dose trial	All three antidepressants had similar rates of acute efficacy (49%–53%) and remission rates (34%–41%). There were significantly more patients who switched into mania/hypomania in the venlafaxine group (15%) compared with bupropion and sertraline, where the switch rates were low (4% and 7%, respectively)

TABLE 2 (Continued)

Reference	Population	Intervention	Comparator	Outcome	Design	Main findings
Sachs et al 1994	Adult patients with bipolar disorder I/II, and a current episode of major depression. $N=15$.	Bupropion and matching placebo added to lithium or anti-convulsant treatment (valproate or carbamazepine). Mean dosage 358 ± 62 mg/day	Desipramine and matching placebo added to lithium or anti-convulsant treatment (valproate or carbamazepine). Mean dosage 140 ± 46 mg/day	Antidepressant efficacy (primary outcome) measured as the number of participants meeting criteria for antidepressant response defined as (a) two or more weeks with ≥50% improvement in HAM-D-31 score from baseline, and patient answering "no" to SCID screening questions about current depressed mood and lack of interest at acute treatment phase follow-up. Rate of treatment emergent mood-elevation (secondary outcome) measured with the YMRS (threshold for (hypo)mania not defined explicitly in the paper).	8-week acute phase, 1-year continuation phase, double dummy, randomized controlled trial (with possible crossover to a second acute blinded treatment phase with the alternate agent given a lack of antidepressant response)	63% of those who received bupropion achieved antidepressant response. 71% of those receiving desipramine achieved antidepressant response. None of the crossover patients achieved antidepressant response. Including the crossover patients, the overall efficacy was 50% and 55% for desipramine and bupropion, respectively. In the acute phase 30% of subjects receiving desipramine switched into (hypo)mania, while 11% of subjects receiving buproprion did so. Over the entire study period the switch rates for desipramine were 50% ($N=5$), and 11% for bupropion ($N=1$). In sum the antidepressant efficacy of bupropion and desipramine did not differ significantly. However, the findings suggest that bupropion is less likely to induce (hypo)mania than desipramine.

Abbreviations: ARS-IV, ADHD Rating Scale, IV; BES, Binge Eating Scale; BMI, Body Mass Index; BPRS, Brief Psychiatric Rating Scale; BSS, Beck Scale for Suicidal Ideation; CARS-M, Clinician Administered Rating Scale for Mania; CGAS, Children's Global Assessment Scale; CGI-BP, Clinical Global Impressions, Bipolar Scale; CGI-I, Clinical Global Impressions, Improvement scale; CGI-S, Clinical Global Impressions, Severity scale; CMRS-P, Child Mania Rating Scale, Parent version; CPRS-48, Conners Parent Rating Scale-48; C-SSRS-SLV, Columbia-Suicide Severity Rating Scale Since Last Visit; ESS, Epworth Sleepiness Scale; FCI, Food Craving Inventory; FSP, Fatigue Severity Scale; GAF, Global Assessment of Functioning; HAM-A, Hamilton Anxiety Rating Scale; HAM-D-31, 31-item Hamilton Rating Scale for Depression; HDRS, Hamilton Depression Rating Scale; IDS-C30, 30-Item Inventory of Depressive Symptomatology, Clinician rated; IDS-SR, Inventory of Depressive Symptomatology, Self-Report; ISI, Insomnia Severity Scale; KADS, Kutcher Adolescent Depression Scale; K-SADS, Schedule for Affective Disorders Schizophrenia for School-Age Children, Present and Lifetime Version; MADRS, Montgomery-Asberg Depression Rating Scale; MCCB, MATRICS Consensus Cognitive Battery; MMSE, Mini-Mental State Examination; PANSS-EC, Positive and Negative Syndrome Scale, Excited Component; PSQI, Pittsburgh Sleep Quality Index; QIDS-C16, 16 item Quick Inventory of Depressive Symptomatology, Clinician rated; QIDS-SR16, 16 item Quick Inventory of Depressive Symptomatology, Self-Report; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire, Short Form; SAERS, Barkley Stimulant Adverse Events Rating Scale; SCIP, Screen for Cognitive Impairment in Psychiatry; SEBMS, Side effects Behavior Monitoring Scale; SNAP-IV, Swanson, Nolan, and Pelham Questionnaire, IV; YMRS, Young Mania Rating Scale.

eight weeks of open-label treatment (with no placebo control) with either lithium, carbamazepine, or divalproex sodium after which those presenting with predominating ADHD symptoms were given adjunctive methylphenidate and, in some cases, a second mood stabilizer in a 16-week open-label continuation phase.[58] These participants were given 5–10 mg of methylphenidate twice daily (titration procedure not specified). The treatment was found to be efficacious in reducing ADHD symptoms measured using the Clinical Global Impressions-Improvement scale, with an overall reported response rate of 92% ($n = 12/13$ of participants receiving adjunctive methylphenidate) defined as a score of 1 or 2 (no further statistics were specified regarding ADHD symptoms).

The fourth study examined low-dose methylphenidate adjunctive to aripiprazole for euthymic child- and adolescent participants with BD and comorbid ADHD over a 4-week period.[60] The study included 14 participants and utilized a placebo- and crossover-controlled, double-blind design. Primary outcomes were the change in ADHD symptoms and change in manic symptoms. Participants were excluded if they had received any other psychotropics within 10 weeks prior to the study. Patients treated with aripiprazole and low-dose methylphenidate (0.3–0.7 mg/kg/day) showed no significant reduction ADHD symptoms, measured using the Swanson, Nolan and Pelham Questionnaire (SNAP IV), compared to aripiprazole and placebo. No significant changes in manic symptoms were detected.

In summary, two studies showed that methylphenidate treatment adjunctive to mood stabilizers improved ADHD symptoms in pediatric BD populations. In contrast, one study found no effect on ADHD symptoms of methylphenidate adjunctive to aripiprazole in a pediatric population. Finally, one study examined the antimanic and cognitive effects of short-term methylphenidate for adults with acute mania but found no treatment effects on cognition of mania symptoms. For details on these studies, see Table 1.

3.2.2 | Other psychostimulants

One study to date investigated the effects of other psychostimulants on ADHD symptom change in BD. This placebo-controlled, crossover study investigated the effects of four weeks of mixed amphetamine salts (5 mg/daily) adjunctive to divalproex sodium on ADHD symptoms and manic symptoms in 30 pediatric patients with BD and comorbid ADHD.[59] Patients were eligible for inclusion if they were in a (hypo)manic or mixed affective state at the start of the first study phase where divalproex sodium was given as monotherapy. Participants who were responsive to treatment, defined as 50% or greater reduction in symptoms measured with the YMRS, were subsequently crossover into the phase where they received mixed amphetamine salts in addition to divalproex sodium. Patients were required to not have taken any other psychotropic drugs for two weeks or fluoxetine for four weeks prior to study start. The study found that mixed amphetamine salts were significantly more effective in reducing ADHD symptoms than placebo as measured with the Clinical Global Impressions-Improvement scale (CGI-I). The authors reported that the improvement from divalproex sodium plus mixed amphetamine salts was 1.9 points greater on the CGI-I than when patients were taking divalproex sodium plus placebo. The difference was significant ($p = < 0.0001$). The reported mean CGI-I score while patients were taking mixed amphetamine salts was 1.8 (SD = 0.6) while the mean score when taking placebo was 3.7 (SD = 1.0). There were no significant changes in manic symptoms associated with mixed amphetamine salts compared to placebo.

Another study of the effect of other psychostimulants examined the safety of 100–200 mg/day of modafinil adjunctive to mood stabilizing medication, with cognitive change and sleep measures as secondary outcomes.[56] This 8-week, randomized, double-blind, placebo-controlled trial was conducted with an adult sample of 12 euthymic patients with BD who also presented with subjective sleep problems and/or clinically significant cognitive impairments. Patients were not allowed to take more than three psychotropic medications, or any drug known to interact with modafinil. Patients were also not allowed to take any medications with known adverse cognitive effects (topiramate, tricyclic antidepressants, and anticholinergics), compounds that may enhance cognition (amphetamine and dopamine agonists), or benzodiazepines. Cognitive change was measured with the MATRICS Consensus Cognitive Battery (MCCB), with the primary cognitive outcome being the MCCB composite score from baseline through Week 4, and follow-up at Week 8. The secondary cognitive outcomes were the MCCB domain scores, including processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning, and problem solving, and social cognition. The study found that adjunctive modafinil was generally safe in terms of (hypo)mania risk, and side effects. However, the authors noted that some people may not tolerate modafinil well, as two people discontinued the drug during the trial. Additionally, the study found near significant positive effects on some domains of cognitive function, specifically processing speed and verbal learning, as well as increased daytime wakefulness. However, a negative effect of modafinil was found on sleep quality.

3.2.3 | Nonstimulant ADHD drug therapies

One double-blinded, placebo-controlled study investigated the use of clonidine (0. 2–0.6 mg/day divided in two daily doses) or placebo in combination with mood stabilizing medication (lithium or valproate sodium) for cognitive change as measured with the dementia screening tool, the Mini-Mental State Examination (MMSE) for 70 individuals with acute mania.[55] In addition to cognitive change, the study examined the interventions effects on manic symptoms and sleep disturbances, with none of the outcomes prioritized over others. In total, 36 manic participants received clonidine, while 34 received a placebo. Participants were allowed to also receive concomitant antipsychotics, but not anticholinergic drugs or tricyclic antidepressants. No differences in cognitive change were found between the clonidine and the placebo-treated patients. However, significant

reductions in the severity of manic symptoms and sleep disturbances were observed, both with medium effect sizes. No eligible studies were found that examined the effectiveness of nonstimulant medications used for ADHD treatment in participants with BD.

3.3 | Interim summary of cognitive or ADHD symptom change

Three out of four studies examining change in ADHD symptoms showed positive effects of ADHD drug therapies. These three positive studies were all conducted in children or adolescents; two studies were of methylphenidate, while one was of mixed amphetamine salts. Of the three studies investigating objective neurocognitive change, one found no effect of short-term (2.5 days) methylphenidate in acute mania on the SCIP, another found no effects of clonidine on the MMSE, while a third found marginally significant pro-cognitive effects on the MCCB processing speed and verbal learning domains. These findings indicate that psychostimulant treatment with methylphenidate or mixed amphetamine salts adjunctive to mood stabilizers may lead to ADHD symptom improvements, whereas there is insufficient evidence to make any conclusions regarding efficacy on cognition. However, caution should be taken in interpreting the results as it is a very small number of studies.

4 | SIDE EFFECTS

4.1 | Psychostimulants

Twelve studies examined the side effects of psychostimulants given either as an add-on to mood stabilizing medication to a total of 1775 participants[43,56–63,65,66] or as monotherapy for 42 participants in one study.[41] In 11 of 12 studies, the control condition was placebo under double-blind conditions, while baseline measures and alternative non-ADHD pharmacotherapy served as the control in a final study.[58]

In all 12 studies, psychostimulant treatments were found to be well tolerated, with no study reporting a statistically significantly increased risk of (hypo)manic symptoms compared to the control condition (see Table 3 for details). Side effects of special interest for the review purposes were presence of/worsening of hypomania or mania. In total, 11 patients (1.3%) in the treatment groups versus eight (0.9%) experienced hypomania across the studies. Eleven (1.3%) in the intervention groups versus nine (1%) in placebo groups became manic.

Overall, side effects of psychostimulants were similar across studies (see Table 3). 11 of 12 studies reported side effect data, while one study merely stated that the active treatment (methylphenidate) was well tolerated.[58] Another study of adjunctive methylphenidate did not report side effects in such a way where it is possible to determine how many participants and what percentage experienced the measured side effects.[60] Yet, another study reported side effects in a way where it was not possible to determine which condition (active/control) the side effect occurred in.[59] These three studies are thus not represented in the numbers in Table 3, but all showed that there were no significant differences in side effects between the active and control conditions.

Transient headache was the most frequently reported side effect experienced by 110 (14.6%) participants out of the total number of 751 participants receiving the active psychostimulant treatments across the nine studies detailed in Table 3. Of the 850 participants receiving placebo, 80 (9.4%) also reported experiencing transient headache. Nausea, insomnia, and diarrhea were the next most reported side effects in decreasing order of frequency, with some studies finding that one or more of these were more common in the active conditions versus placebo (see Table 3 for details). However, only two studies employed a psychometrically validated measure of side effects.[57,60]

4.2 | Nonstimulant ADHD drug therapies

Side effects of nonstimulant ADHD drug therapies are summarized in Table 4. The five studies of side effects of nonstimulant ADHD drug therapies, all suggest that these treatments are well tolerated. Specifically, adjunctive clonidine, and adjunctive bupropion, as well as bupropion monotherapy did not increase the risk (hypo)mania in the BD cohorts when compared to the studies' respective control conditions.

In the single study of adjunctive clonidine in 70 acutely manic patients, the authors did not report side effects explicitly.[55] Thus, the study is only relevant to the side effects of special interest insofar as it showed that clonidine was associated with a greater decrease in manic symptoms when compared to placebo, with a medium effect size.

Among the four studies involving bupropion, none compared the drug to placebo, but rather other antidepressants, which do not serve as off-label ADHD treatments.[64,67–69]

One study with 14 participants did not report explicitly on side effects other than stating that, overall, both bupropion and idazoxan were well tolerated and that there were no distinguishable differences between them in terms of side effects.[64] However, the authors state that a psychometrically validated side effect measure was used.

Another study with 36 participants reported specific side effects (see Table 4).[67] In this study, comparing bupropion to topiramate, no patients experienced a manic switch, and difficulty sleeping was the only side effect that was more frequent in the bupropion group.[67] A psychometric measure of side effects was also used in this study.

A third study with 184 participants reported on the risk of affective switch into (hypo)mania using two different measures with different thresholds for determining when a switch had occurred.[68] Using the YMRS, a manic switch was defined as a score of ≥13, while it required a score of ≥3 using the CGI-BP. Using the YMRS criterion, 4% of participants receiving bupropion switched into mania or hypomania, compared to 7% and 15% for sertraline and venlafaxine,

TABLE 3 Psychostimulant side effects.

	Calabrese et al[61]		Calabrese et al[43]		Findling et al[57]		Frye et al[62]		Frye et al[63]		Hegerl et al[41]	
	Armo vs Pla		Armo vs Pla		Mph vs Pla		Mod vs Pla		Armo vs Pla		Mph vs Pla	
Study	TR	PL	TR	PL	TR[a]	PL	TR	PL	TR	PL	TR	PL
N	126	125	198	199	16	16	41	44	200	199	22	20
Headache	14 (11%)	12 (10%)	19 (10%)	20 (10%)	0 (0%)	0 (0%)	4 (10%)	1 (2%)	29 (14%)	15 (7%)	2 (9%)	0 (0%)
Measurement tool	Not reported		Not reported		Yes		Not reported		Not reported		Yes	
Irritability	–		1 (<1%)	0 (0%)	0 (0%)	6 (37.5%)	–		–		–	
Measurement tool	–		Not reported		Yes		–		–		–	
Insomnia	13 (10%)	10 (8%)	8 (4%)	8 (4%)	0 (0%)	2 (12.5%)	2 (5%)	0 (0%)	6 (3%)	4 (2%)	–	
Measurement tool	Yes		Yes		Yes		Yes		Yes		–	
Nausea	9 (7%)	6 (5%)	11 (6%)	9 (5%)	–		1 (2%)	1 (2%)	12 (6%)	7 (3%)	–	
Measurement tool	Not reported		Not reported		–		Not reported		Not reported		–	
Dry mouth	8 (6%)	5 (4%)	9 (5%)	4 (2%)	–		–		–		–	
Measurement tool	Not reported		Not reported		–		–		–		–	
Restlessness/feeling jittery	7 (6%)	1 (<1%)	1 (<1%)	1 (<1%)	–		–		–		–	
Measurement tool	Not reported		Not reported		–		–		–		–	
Migraine	–		0 (0%)	1 (<1%)	–		–		–		–	
Measurement tool	–		Not reported		–		–		–		–	
Decreased appetite	–		–		4 (25%)	1 (6.3%)	–		–		–	
Measurement tool	–		–		Yes		–		–		–	
Palpitations	–		–		–		–		–		–	
Measurement tool	–		–		–		–		–		–	
Hypomania	2 (2%)	1 (<1%)	0 (0%)	1 (<1%)	–		6 (14.6%)	5 (11.4%)	0 (0%)	1 (0.5%)	–	
Measurement tool	Yes		Yes		Yes		Yes		Yes		Yes	
Worsening/presence of mania	1 (<1%)	5 (4%)	3 (1%)	2 (1%)	–		1 (2%)	1 (2%)	–		2 (9%)	1 (5%)
Measurement tool	Yes		Yes		Yes		Yes		Yes		Yes	
Anxiety	5 (4%)	2 (2%)	7 (4%)	0 (0%)	1 (6.3%)	3 (18.8%)	–		8 (4%)	5 (2.5%)	–	
Measurement tool	Yes		Yes		Yes		–		Yes		–	
Worsening/presence of depression	3 (2%)	3 (2%)	1 (<1%)	3 (2%)	–		0 (0%)	1 (2%)	–		–	
Measurement tool	Yes		Yes		Yes		Yes		Yes		Yes	
Diarrhea	12 (10%)	8 (6%)	17 (9%)	13 (7%)	–		–		–		0 (0%)	1 (5%)
Measurement tool	Not reported		Not reported		–		–		–		Yes	

TABLE 3 (Continued)

	Calabrese et al[61]		Calabrese et al[43]		Findling et al[57]		Frye et al[62]		Frye et al[63]		Hegerl et al[41]	
	Armo vs Pla		Armo vs Pla		Mph vs Pla		Mod vs Pla		Armo vs Pla		Mph vs Pla	
Study	TR	PL	TR	PL	TR[a]	PL	TR	PL	TR	PL	TR	PL
Dizziness	–		–		0 (0%)	0 (0%)	–		–		–	
Measurement tool	–		–		Yes		–		–		–	
Sedation somnolence	6 (5%)	2 (2%)	–		–		–		2 (1%)	2 (1%)	–	
Measurement tool	Yes		–		–		–		Yes		–	
Rash	–		1 (<1)	1 (<1%)	–		–		–		1 (4.5%)	0 (0%)
Measurement tool	–		Yes		–		–		–		Yes	
Emergence/worsening of suicidal ideation	–		4 (2%)	2 (1%)	–		–		1 (0.5%)	0 (0%)	–	
Measurement tool	–		Yes		–		–		Yes		–	
Decreased body weight	–		–		–		–		–		–	
Measurement tool	–		–		–		–		–		–	
Increased body weight	–		–		–		–		4 (2%)	9 (4.5%)	–	
Measurement tool	–		–		–		–		Yes		–	
Psychosis	–		2 (1%)	0 (0%)	–		–		1 (0.5%)	0 (0%)	–	
Measurement tool	–		Yes		–				Yes		–	
Infection	6 (5%)	9 (7%)	–		–		0 (0%)	1 (2%)	–		–	
Measurement tool	Yes		–		–		Yes		–		–	
Physical pain	–		–		–		–		–		1 (4.5%)	0 (0%)
Measurement tool	–		–		–		–		–		Yes	
Tremor	–		–		–		–		–		–	
Measurement tool	–		–		–		–		–		–	
Fatigue	–		–		–		–		–		–	
Measurement tool	–		–		–		–		–		–	

TABLE 3 (Continued)

	Ketter et al[65]		Lipschitz et al[56]		McElroy et al[66]	
	Armo vs Pla		Mod vs Pla		Ldx vs Pla	
Study	TR	PL	TR	PL	TR	PL
N	231	229	6	4	11	14
Headache	36 (16%)	30 (13%)	0 (0%)	0 (0%)	5 (45%	2 (14%)
Measurement tool	Not reported		Yes		Not reported	
Irritability	–		–		2 (18%)	0 (0%)
Measurement tool	–		–		Not reported	
Insomnia	11 (5%)	7 (3%)	0 (0%)	1 (25%)	4 (36%)	1 (7%)
Measurement tool	Yes		Yes		Yes	
Nausea	16 (7%)	4 (2%)	0 (0%)	0 (0%)	2 (18%)	1 (7%)
Measurement tool	Not reported		Yes		Not reported	
Dry mouth	–		0 (0%)	0 (0%)	4 (36%)	0 (0%)
Measurement tool	–		Yes		Not reported	
Restlessness/feeling jittery	–		0 (0%)	0 (0%)	4 (36%)	0 (0%)
Measurement tool	–		Yes		Not reported	
Migraine	–		–		0 (0%)	1 (7%)
Measurement tool	–		–		Not reported	
Decreased appetite	–		–		2 (18%)	2 (14%)
Measurement tool	–		–		Not reported	
Palpitations	–		1 (25%)	0 (0%)	1 (9%)	1 (7%)
Measurement tool	–		Yes		Not reported	
Hypomania	2 (1%)	0 (0%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)
Measurement tool	Yes		Yes		Yes	
Worsening/presence of mania	4 (2%)	0 (0%)	–		0 (0%)	0 (0%)
Measurement tool	Yes		–		Yes	
Anxiety	–		0 (0%)	0 (0%)	2 (18%)	0 (0%)
Measurement tool	–		Yes		Yes	
Worsening/presence of depression	3 (7%)	2 (5%)	–		–	
Measurement tool	Yes		–		Yes	
Diarrhea	11 (5%)	13 (6%)	0 (0%)	0 (0%)	1 (9%)	1 (7%)
Measurement tool	Not reported	Yes		Not reported		
Dizziness	–	0 (0%)	0 (0%)	–		

TABLE 3 (Continued)

	Ketter et al[65]		Lipschitz et al[56]		McElroy et al[66]	
	Armo vs Pla		Mod vs Pla		Ldx vs Pla	
Study	TR	PL	TR	PL	TR	PL
Measurement tool	–	Yes		–		
Sedation somnolence	1 (0.4%)	3 (1%)	–	–		
Measurement tool	Yes	–		–		
Rash	–	0 (0%)	0 (0%)	–		
Measurement tool	–	Yes		–		
Emergence/worsening of suicidal ideation	–	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Measurement tool	–	Yes		Yes		
Decreased body weight	–	–		–		
Measurement tool	–	–		–		
Increased body weight	–	–		–		
Measurement tool	–	–		–		
Psychosis	–	–		–		
Measurement tool	–	–		–		
Infection	–	–		1 (9%)	1 (7%)	
Measurement tool	–	–		Yes		
Physical pain	–	–		–		
Measurement tool	–	–		–		
Tremor	–	0 (0%)	0 (0%)	3 (27%)	0 (0%)	
Measurement tool	–	Yes		–		
Fatigue	–	1 (25%)	0 (0%)	1 (9%)	2 (14%)	
Measurement tool	–	Yes		Yes		

Abbreviations: Armo, armodafinil; Ldx, lisdexamfetamine; Mod, modafinil; Mph, methylphenidate; Pla, placebo.

(Continues)

TABLE 4 Nonstimulant ADHD drug therapies side effects.

	Grossman et al[64]		McIntyre et al[67]		Post et al[68]		
	Bupropion versus Idazoxane		Bupropion versus topiramate		Bupropion versus sertraline versus venlafaxine		
Study	T (Bup)	P	T	P	T	S	V
N	7	7	13	14	51	58	65
Headache	–		2.89 (22.3%)	2.7 (19.7%)	–		
Measurement tool	–		Yes		–		
Irritability	–		–		–		
Measurement tool	–		–				
Insomnia	–		3.6 (27.8%)	2.2 (16%)	–		
Measurement tool	–		Yes		–		
Nausea	–		2.3 (17.8%)	2.9 (21.1%)	–		
Measure–ment tool	–		Yes		–		
Dry mouth	–		2.2 (17.2%)	3 (21.5%)	–		
Measurement tool	–		Yes		–		
Restlessness/feeling jittery	–		3.6 (27.8%)	2.2 (16%)	–		
Measurement tool	–		Yes		–		
Migraine	–		–		–		
Measurement tool	–		–		–		
Decreased appetite	–		1.9 (15.3%)	2.3 (16.8%)	–		
Measurement tool	–		Yes		–		
Seizures	1 (14%)	0 (0%)	–		–		
Measurement tool	–		–		–		
Palpitations	–		–		–		
Measurement tool	–		–		–		
Hypomania	–		–		2 (4%)	1 (0.58%)	6 (9.2%)
Measurement tool	–		–		Yes		
Worsening/presence of mania	–		–		2 (4%)	1 (0.58%)	1 (1.5%)
Measurement tool	–		–		Yes		
Anxiety	–		2 (16.8%)	2 (15.1%)	–		
Measurement tool	–		Yes		–		
Worsening/presence of depression	–		–		8 (15%)	9 (15.5%)	10 (15.3%)
Measurement tool	–		–		Yes		
Diarrhea	–		–		–		
Measurement tool	–		–		–		
Dizziness	–		–		–		
Measurement tool	–		–		–		
Sedation/somnolence	–		–		–		
Measurement tool	–		–		–		
Rash	–		–		–		
Measurement tool	–		–		–		
Emergence/worsening of suicidal ideation	–		–		0 (0%)	0 (0%)	1 (1.5%)
Measurement tool	–		–		Yes		
Increased body weight	–		–		–		
Measurement tool	–		–		Yes		
Decreased body weight	–		–		–		
Measurement tool	–		–		Yes		
Psychosis	–		–		0 (0%)	1 (0.58%)	1 (1.5%)

TABLE 4 (Continued)

	Grossman et al[64]		McIntyre et al[67]		Post et al[68]		
	Bupropion versus Idazoxane		Bupropion versus topiramate		Bupropion versus sertraline versus venlafaxine		
Study	T (Bup)	P	T	P	T	S	V
Measurement tool	–		–		Yes		
Infection	–		–		–		
Measurement tool	–		–		–		
Physical pain	–		–		–		
Measurement tool	–		–		–		
Tremor	–		3.2 (25.1%)	2.5 (18.1%)	–		
Measurement tool	–		Yes		–		
Fatigue	–		–		–		
Measurement tool	–		–		–		

respectively.[68] Using either the YMRS or the CGI-BP criterion, the percentage of participants who met one of the thresholds for a manic switch were 14%, 16%, and 20%, respectively. Post hoc analyses demonstrated a lesser risk of hypo/mania with bupropion than venlafaxine, with no differences between sertraline and venlafaxine or bupropion and sertraline.[68]

A fourth study with 15 participants reported on the risk of affective switch into (hypo)mania using the YMRS, but without specifying the threshold scores they used to determine (hypo)mania.[69] The study was designed such that patients underwent an 8-week acute treatment phase followed by a continuation phase that lasted up to 1 year, or until patients met DSM-III-R criteria for hypomania, mania, or depression. The study found that 30% ($N=3$) of those receiving desipramine and only 11% ($N=1$) of those receiving bupropion developed mania during the 8-week acute treatment phase. During the continuation phase, two desipramine-treated and no bupropion-treated patients experienced hypomania or mania, making the incidence of affective switch over the entire study 50% ($N=5$) and 11% ($N=1$) for the desipramine and bupropion patients, respectively.

4.3 | Summary of side effects

Overall, the studies suggest that psychostimulant treatments and alternative ADHD drug therapies such as clonidine and bupropion are well tolerated, especially when given as adjunctive interventions to mood stabilizing medications, and that they do not impose any increased risk of inducing (hypo)mania in BD patients when compared to placebo or other control conditions. Notably, this evidence comes from a vast majority of studies in which these medications were given in combination with mood stabilizing medications ($n=895$ participants) but also from a small sample of patients who received them as monotherapy ($n=56$). Hence, it can be concluded with greatest confidence that the compounds are safe regarding induction of mania when used *in combination with* mood stabilizers. Regarding non-psychiatric side effects such as transient headache and diarrhea, it is uncertain how most of the studies monitored these side effects, which makes the validity of the reported differences between treatment and placebo conditions less certain.

4.4 | Risk-of-bias assessments

The risk-of-bias (RoB) assessment was conducted with three different tools: the RoB2, RoB2 crossover version, and the ROBINS-I for the RCTs, the crossover RCTs, and the non-randomized studies, respectively. The results of these assessments are displayed in Figure 2A–C, respectively. Five of the 17 studies (29%) were rated as being at low risk of bias,[55,57,60,66,68] while 11 studies (65%) were rated as having "some concerns" or a "moderate" risk of bias.[41,43,56,59,61–65,67,69] The one study that was rated as being at serious risk of bias was the non-randomized study of methylphenidate[58] (note that "serious" is the second worst rating in ROBINS-I with "critical" being the worst).

The most common source of bias among the RCT was inadequate information about the allocation sequence and/or concealment, which made it difficult to determine whether participant allocation was truly random.[43,59,61–65,67,69] However, we identified no baseline imbalances between intervention and control groups in these studies that could have suggested problems with the randomization process. The only other bias domain among the RCTs that was rated "some concerns" was the measurement domain in a study of methylphenidate in patients with acute mania[41] because it was considered that two days was too short a time for measurable cognitive change to occur. In the non-randomized study of methylphenidate,[58] the greatest source of bias was confounding bias, which limited the ability to determine whether the observed effects were due to the intervention or other factors that were not controlled.

5 | DISCUSSION

This systematic review by the ISBD Targeting Cognition Task Force investigated the possible benefits on cognition or ADHD symptoms and

(A) Risk of bias: ROBINS-I

Unique ID	D1	D2	D3	D4	D5	D6	D7	Overall
Ketter et al. (2016)								
Kowatch et al. (2003)								

D1 = Bias due to confounding
D2 = Bias in selection of participants
D3 = Bias in classification of interventions
D4 = Bias due to deviations from intended interventions
D5 = Bias due to missing data
D6 = Bias in measurement of outcomes
D7 = Bias in selection of the reported result

Low =
Moderate =
Serious =
Critical =

(B) Risk of bias: RoB2

Unique ID	D1	D2	D3	D4	D5	Overall
Ahmadpanah et al (2022)						
Calabrese et al. (2010)						
Calabrese et al. (2014)						
Frye et al. (2007)						
Frye et al (2015)						
Grossman et al. (1999)						
Hegerl et al. (2018)						
Ketter et al. (2015)						
Lipschitz et al. (2023)						
McElroy et al. (2015)						
McIntyre et al. (2002)						
Post et al. (2006)						
Sachs et al. (1994)						

D1 = Bias arising from the randomization process
D2 = Bias due to deviations from the intended interventions
D3 = Bias due to missing outcome data
D4 = Bias in measurement of outcomes
D5 = Bias in selection of the reported results

Low =
Some concerns =
High =

(C) Risk of bias: RoB2 Crossover version

Unique ID	D1	DS	D2	D3	D4	D5	Overall
Findling et al. (2007)							
Scheffer et al. (2005)							
Zeni et al. (2009)							

D1 = Bias arising from the randomization process
DS = Bias arising from period and carryover effects
D2 = Bias due to deviations from the intended interventions
D3 = Bias due to missing outcome data
D4 = Bias in measurement of outcomes
D5 = Bias in selection of the reported results

Low =
Some concerns =
High =

FIGURE 2 Risk-of-bias evaluations. [Correction added on 06 May 2024, after first online publication: Figure 2 has been updated in color.]

safety of ADHD medications in patients with BD. In total, 17 studies were identified ($N=2136$) that investigated armodafinil ($k=4$), methylphenidate ($k=4$), bupropion ($k=4$), clonidine ($k=1$), lisdexamphetamine ($k=1$), mixed amphetamine salts ($k=1$), or modafinil ($k=2$). Of these, four studies investigated the effects on ADHD symptoms and three studies the effects on cognition. The remaining 11 studies investigated the safety of the medications regarding possible mania induction. Three of the four studies on ADHD symptoms were conducted in pediatric and adolescent populations and one in an adult population. The three studies of cognitive change effects were conducted in adult populations. Studies of safety only were conducted in adult populations.

Regarding aim (I), we identified preliminary evidence for efficacy on ADHD symptoms, with beneficial effects on three of the four studies: Two studies of methylphenidate and one of amphetamine salts, all conducted in pediatric or adolescent populations. Only two

studies, of which two were negative and one identified marginally significant pro-cognitive effects, investigated cognition. Regarding Aim (II), the use of ADHD medications was safe in BD regarding mania symptoms, with none of the studies indicating any risk of mania switch in these patients who mostly received concomitant mood stabilizing treatment. The studies were generally characterized by low or moderate risk of bias, of which the latter was mainly due to a lack of details on the randomization procedure.

A common concern in the clinic is that stimulant medications carry a risk of manic switch or worsening of mania symptoms in patients with BD. Therefore, BD patients who previously received ADHD medications often have this medication removed when they get their BD diagnosis. This clinical practice contrasts with the observed *lack* of evidence for mania-inducing effects of ADHD medications in the present and previous systematic reviews.[42,43] Importantly, most of the studies included in the present review involved patients who received concomitant mood stabilizing medications. Therefore, based on the lack of evidence for mania risk in these 12 studies, we can only conclude that ADHD medication does not seem to be counter indicated in BD patients *when they receive concomitant mood stabilizing mediations*, since no increased mania risk was identified in these cases. However, it must be remembered that the data with regards to manic switch risk with commonly used ADHD medications, such as methylphenidate and amphetamine salts, is limited. Of other side effects reported in the reviewed studies of ADHD medications, transient headache was most common and mainly related to armodafinil treatment. Other common side effects were nausea, insomnia, and diarrhea. Sleep problems may be important because sleep and circadian rhythms are a common symptom in BD.[70] When considering ADHD medications for BD patients, careful consideration should also be given to irritability, a mixed/unspecific symptom in BD that may be enhanced by stimulants. Furthermore, anxiety symptoms, which are common in BD patients, could also be worsened by stimulants.[71] Future studies of ADHD medications in BD should therefore include acceptability/tolerability aspects such as worsening of headaches, insomnia, irritability, and anxiety. Notwithstanding these considerations, adjunctive ADHD medications to mood stabilizers seems to be safe in BD patients with ADHD comorbidity based on the reviewed studies.

While administration of ADHD medications is a viable option from a safety perspective, there is a paucity of studies into its benefits for treating concomitant ADHD symptoms and cognitive impairments in BD. Notably, three of the four studies of ADHD symptoms found remarkable benefits with either a large effect size or a large response rate (92%) of methylphenidate or amphetamine salt treatment in pediatric or adolescent populations with BD.[57,58,60] We therefore consider add-on of these ADHD medications to mood stabilizers as a viable option for BD patients with comorbid ADHD symptoms based on their beneficial effects on ADHD symptoms, good safety profile (i.e., no increase in mania risk) when taken together with mood stabilizing medication, and low risk of bias in these studies (low: k = 2, moderate: k = 1). However, we recommend that more research is conducted in adult BD patients with ADHD comorbidity given that the extant studies were mostly conducted with pediatric or adolescent populations.

In contrast, there is insufficient evidence at this stage for recommending ADHD medications to treat cognitive impairments in BD. Indeed, two of the three studies investigating cognitive change with objective neuropsychological measures showed no benefits of methylphenidate on the SCIP[41] or of clonidine on the MMSE performance,[55] whereas a study of modafinil showed only marginally significant pro-cognitive effects on MCCB processing speed and verbal learning domains.[56] Nevertheless, major methodological limitations may have obscured possible cognitive benefits. The initial methylphenidate study, focusing on cognitive change in SCIP among manic patients over a 2.5-day period,[41] presents potential confounding factors arising from acute mania symptoms.[46,72] Moreover, this timeframe is likely insufficient for observing treatment-related cognitive improvements, as suggested by the ISBD Targeting Cognition Task Force recommendations.[72] The absence of specified timing for SCIP assessments also raises concerns about potential diurnal cognitive effects. Additionally, the limited sensitivity of SCIP to executive dysfunction, that is common in BD and ADHD, further complicates interpretation. In the second study involving clonidine,[55] the use of the MMSE dementia screening tool is a limitation. While suitable for older populations when dementia is suspected, such tools prove suboptimal in younger, higher-functioning patients due to ceiling effects.[73] Moreover, the focus on the memory domain neglects executive dysfunction in BD and ADHD. The third study that demonstrated borderline significant pro-cognitive effects of modafinil, involved a very small sample ($N = 12$), making the findings hypothesis-generating in nature.[56]

Given these limitations, we encourage further studies of the possible cognitive benefits of ADHD medications in BD, which employ more comprehensive cognitive assessments and larger samples. We also suggest caution when interpreting the findings regarding possible pro-cognitive effects of the medications given the highly preliminary state of the evidence. Based on the extant evidence, our suggested algorithm in the clinical treatment of BD patients is therefore as follows: When mood stabilization for a patient has been obtained with mood stabilizers, add-on treatment with an ADHD medication in those with comorbid ADHD symptoms may be considered to target these symptoms. In contrast, for BD patients *without* comorbid ADHD symptoms, more research into the possible cognitive benefits is needed before such medications can be recommended.

There is a clear impetus for more research into the cognitive benefits of ADHD medications as add-on to mood stabilizing treatment in symptomatically stable patients with BD who experience cognitive impairments. Indeed, there is a clear knowledge gap with only two extant studies on the topic, and—in contrast with the common concern of mania risk—these medications were found to have a good safety profile when given as add-on to mood stabilizing medication. We therefore encourage studies of the pro-cognitive potential of these medications in BD given the pressing need for pro-cognitive treatments in the 40%–70% of BD patients with persistent cognitive impairments despite symptomatic remission. For the design of such studies, researchers are recommended to follow the recently

updated methodological recommendations for cognition trials that include suggestions for sample size estimations, pre-screening of cognitive impairment, selection of outcome measures, and strategies to aid transfer to daily functioning.[46] Among the key recommendations are (i) to pre-screen participants for objective cognitive impairments with a brief cognition screening battery, (ii) to generally include partially or fully remitted patients in trials to minimize "pseudospecificity" issues, (iii) to preselect one (broad) cognition measure as the primary outcome, such as a composite measure of working memory, sustained attention and executive function in trials investigating ADHD medications, (iv) in general to administer medications for several weeks, and (v) to use an add-on design if the candidate medication does not have a mood stabilizing effect for ethical reasons and to ensure generalizability.[46]

In conclusion, we identified preliminary evidence for efficacy of adjunctive ADHD medications in BD patients with comorbid ADHD symptoms, with robust beneficial effects of methylphenidate and one of amphetamine salts in three of the four studies. Importantly, none of the identified studies reported any heightened risk of mania switch in these BD patients who mostly received concomitant mood stabilizing treatment, although the study samples sizes were small. This indicates that adjunctive ADHD medications may be a viable option for some patients with BD with comorbid ADHD. Given this good safety profile of the medications and paucity of research into their possible cognitive benefits, we encourage further research into the pro-cognitive potential of these medications in BD.

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CONFLICT OF INTEREST STATEMENT

Vicent Balanzá-Martínez: reports having received honoraria from Angelini over the past three years. Christopher R. Bowie has been a consultant for Boehringer Ingelheim. He receives book royalties from Oxford University Press. He has received in-kind research user accounts from Scientific Brain Training Pro. Katherine E. Burdick received honorarium and grant funding for her leadership role in the breakthrough discoveries for thriving with bipolar disorder (BD^2). Katie Douglas reports using software provided free of charge by Scientific Brain Training Pro for Cognitive Remediation trials. Gregor Hasler reports speaker/consultant fees from Janssen, Lundbeck, OM Pharma, Otsuka, Sanofi, Schwabe, Servier, Sunovion and Takeda. Anabel Martinez-Aran receives support by d'Economia i Coneixement (2021 SGR 01128), the Centro de Investigación Biomédica en Red de Salud Mental-CIBERSAM and the Centres de Recerca de Catalunya-CERCA Programmme. Roger S. McIntyre has received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC) and

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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