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Adjunctive treatment with psychostimulants and stimulant-like drugs for resistant bipolar depression: a systematic review and meta-analysis

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Abstract

Background. Depression is considered to be the most difficult to treat phase of bipolar disorder as patients experience residual symptoms causing long-term disability. This work aims to explore the role of add-on stimulant and stimulant-like medication in resistant bipolar depression patients.

Methods. Systematic review of add-on stimulants and stimulant-like drugs in resistant bipolar depression by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Analysis was performed using the random-effects models. Heterogeneity was evaluated with Cochran's Q and I^2 statistics.

Results. Six randomized controlled trials of add-on modafinil, armodafinil, and lisdexamphetamine (LDX) (n = 813) vs placebo (n = 815) in the treatment of resistant bipolar depression were included. These drugs were more likely to induce remission from an episode of resistant bipolar depression (relative risk [RR] = 1.37; 95% confidence interval [CI]: 1.06-1.77; number needed to treat for an additional beneficial outcome = 16). Moreover, they did not induce more dropouts than placebo (RR = 1.04; 95% CI: 0.91-1.18), nor did they increase the risk of adverse effects (53/772 vs 41/771) at the end of treatment (RR = 1.30; 95% CI: 0.81-2.10; number needed to treat for an additional harmful outcome = 62). Suicidality and manic switch were not affected by active treatment. Heterogeneity was low (Cochran's Q: $P > .05$), but sometimes with a large CI.

Conclusions. LDX, modafinil, and armodafinil seem to offer a reasonably well-tolerated and safe treatment in resistant bipolar depression. Treatment guidelines should, therefore, be revised to include these medications earlier in the therapeutic algorithm for resistant acute bipolar depression. Further research is, however, necessary for the elucidation of the clinical usefulness of these and other similar compounds.

Introduction

Bipolar disorder types I and II affect about 2% to 4% of the world's population. Even with treatment, about a third of patients relapse within 1 year, and two-thirds within 2 years.[1] According to the Systematic Treatment Enhancement Program for Bipolar Disorder study, relapses of depressive polarity were twice as common as these of the manic polarity.[2] Moreover, after disease onset, patients experience residual depressive symptoms for about a third of the weeks of their lives.[3] Thus, depression, and not mania, is considered to be the most problematic phase of bipolar disorder (BD) and it is the most likely cause of long-term disability.[4] Furthermore, bipolar depression appears to be a refractory mental state during which patients may also experience psychotic symptoms, impaired functioning, compromised quality of life, and stigma.[5] Most importantly, it bears a high risk for suicide[6,7] and profound and lasting functional impairment.[8] Interestingly, antidepressants are generally proven ineffective against bipolar depression,[9] and currently available treatments are little efficacious in improving disability and the overall outcome[7,10–12] as residual symptoms may interfere with the ability of the patients to access and benefit not only from healthcare, but also from the general state welfare.[13–15] Bipolar depression treatment has proved notoriously difficult for the clinician. All guidelines propose specific or less specific treatment options for acute bipolar depression.[16–20]

Depressive episodes in the course of BD have typically a low rate of response to standard treatment,[1] and frequently bipolar depression becomes refractory. Treatment-resistant bipolar depression is common, with approximately one-third of depressed patients failing to achieve symptomatic remission.[21] There are several issues to be addressed before a patient is labeled as

refractory, however, including the possibility of misdiagnosis, the presence of somatic or mental comorbidity, nontolerability of medication, or poor compliance with treatment.

Among drugs that are anecdotally used as an add-on for the treatment of bipolar depression, psychostimulants have gained popularity in recent years despite none of them being licensed for this indication. Currently prescribed psychostimulants include methylphenidate (MPH), and the amphetamines, including the prodrug lisdexamphetamine (LDX), metabolized to the active dextroamphetamine *in vivo*. Modafinil and armodafinil are wakefulness-promoting agents, that is, stimulant-like drugs officially licensed for the treatment of sleepiness due to narcolepsy, shift work sleep disorder, or obstructive sleep apnea. They are most commonly used off-label or unlicensed in the treatment of attention-deficit/hyperactivity disorder (ADHD) and BD.[22,23]

Modafinil and armodafinil appear in the second and fourth steps respectively, of the algorithm suggested by International College of Neuro-Psychopharmacology for the treatment of acute depression in combination with a mood stabilizer,[16] and as a third-line treatment in bipolar I depression according to the 2018 Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) guidelines,[18] as their efficacy and safety in bipolar depression remains poorly understood. A meta-analysis found that modafinil, armodafinil, pramipexole, MPH, and amphetamines may present a useful alternative in the treatment of bipolar depression, with no evidence of a related increase in mood switches,[24] but on the contrary, a second meta-analysis suggested that psychostimulants, namely armodafinil, amphetamine, dextroamphetamine, LDX, MPH, or modafinil, were insufficiently studied for a firm conclusion regarding their use in bipolar depression to be drawn.[25]

Aims

The aim of the current study was to systematically review the literature on the usefulness of add-on LDX, modafinil, and armodafinil in the treatment of resistant acute bipolar depression and subsequently to meta-analyze the available data in terms of efficacy and tolerability/safety.

Experimental Procedures

Literature search

The PRISMA guidelines were followed in the design, organization, and execution of this systematic review and meta-analysis.[26] Literature search was carried out in PubMed/Medline and in the Cochrane Library to February 3, 2020 by using the following key terms: ("bipolar disorder"[MeSH Terms] OR "bipolar disorder" [All Fields] OR "mood disorder"[All Fields] OR "depressive disorder" [All Fields] OR "mania" [All Fields] OR "manic depressive disorder" [All Fields] OR "depression" [All Fields]) AND ("stimulant" [All Fields] OR "stimulants" [All Fields] OR "lisdexamfetamine"[All Fields] OR "modafinil" [All Fields] OR "armodafinil" [All Fields] OR "atomoxetine" [All Fields] OR "dexamphetamine" [All Fields] OR "methylphenidate" [All Fields] OR "dextroamphetamine" [All Fields] OR "amphetamine" [All Fields] OR "psychostimulant*" [All Fields]) AND ("randomized" [All Fields] OR "RCT" [All Fields] OR "trial"[All Fields] OR "randomized-controlled"[All Fields]). A Clinical Trials Search was also performed under the following conditions: Other Terms: efficacy OR safety OR biological effects; Study Type: Interventional; Condition/Disease: Bipolar Disorder OR Mood Disorder OR Depressive Disorder OR Mania OR Manic Depressive Disorder OR Depression; Intervention/Treatment: Stimulant OR Stimulants OR lisdexamfetamine OR atomoxetine OR dexamphetamine OR methylphenidate OR dextroamphetamine OR amphetamine OR psychostimulant OR psychostimulants; Search Results URL: http://tinyurl.com/ya3vkked.

Two authors (E.M.T. and M.M.) examined the extracted articles and decided on study inclusion. The criteria for the inclusion of studies were as follows:

- English language.
- Double blind randomized trials with placebo arm.
- Sample with bipolar depression (no contamination with other diagnoses).
- Adult participants (aged 18 years old or older).
- Using a psychostimulant or stimulant-like agent in the treatment of acute bipolar depression as therapeutic add-on agent.
- Primary outcome is efficacy of treatment.

Collected articles were then thoroughly examined for content to confirm that they were congruent with the inclusion criteria (see flowchart, Figure 1).

The references section of past reviews on the topic[16,23–25,27] and of the retrieved articles was scanned to identify potentially missed studies.

The following data were extracted from the article: location of the study (single or multiple site trial); criteria for diagnosis; criteria for outcome; sample size; mean age in the sample; gender ratio in the sample; duration of the trial; drug used in the trial; information on dropout; and information on anticipated termination of the trial because of adverse events.

Discrepancies in inclusion of articles and in extraction of data were solved by discussion.

Study quality of the Randomized Controlled Trials (RCTs) was evaluated with reference to the Cochrane risk-of-bias tool.[28]

Data analysis

Included RCTs were based on a pretest–posttest-control design, in which participants were randomly assigned to the treatment or control condition, and each participant was measured both before and after the treatment had been administered.

Relative risk (RR) with 95% confidence interval (CI) was used as effect size, and was calculated on the basis of intent-to-treat.

Two trials included in our meta-analysis[11,29] had two treatment arms. In both trials, each treatment arm corresponded to different dosages of the same treatment (armodafinil 150 mg and armodafinil 200 mg). When the trial had two treatment arms with different dosages, the analysis focused on the arm with the largest sample, since the alternative arm included too few cases to be meaningful. The Calabrese et al's[11] study included 33 subjects in the 200 mg armodafinil treatment group, with 24 of them completing the study, and the Ketter et al's[29] study included 30 patients in the 200 mg armodafinil treatment group, with 17 participants completing the study. In the Calabrese et al's[11] study, the response rate was 10 out of 33 (30%) against 61 out of 199 (31%) in the placebo, while remission rate was 4/33 (12%) against 34/199 (17%) in the placebo. The Ketter et al's[29] study did not report detailed information on response and remission rate in the 200 mg armodafinil arm.

The included studies varied as far as interventions, populations, and outcome measures, thus at preference, the results of the random-effects model were reported for the pairwise meta-analyses as they aim to provide inference about the average effect in the population.

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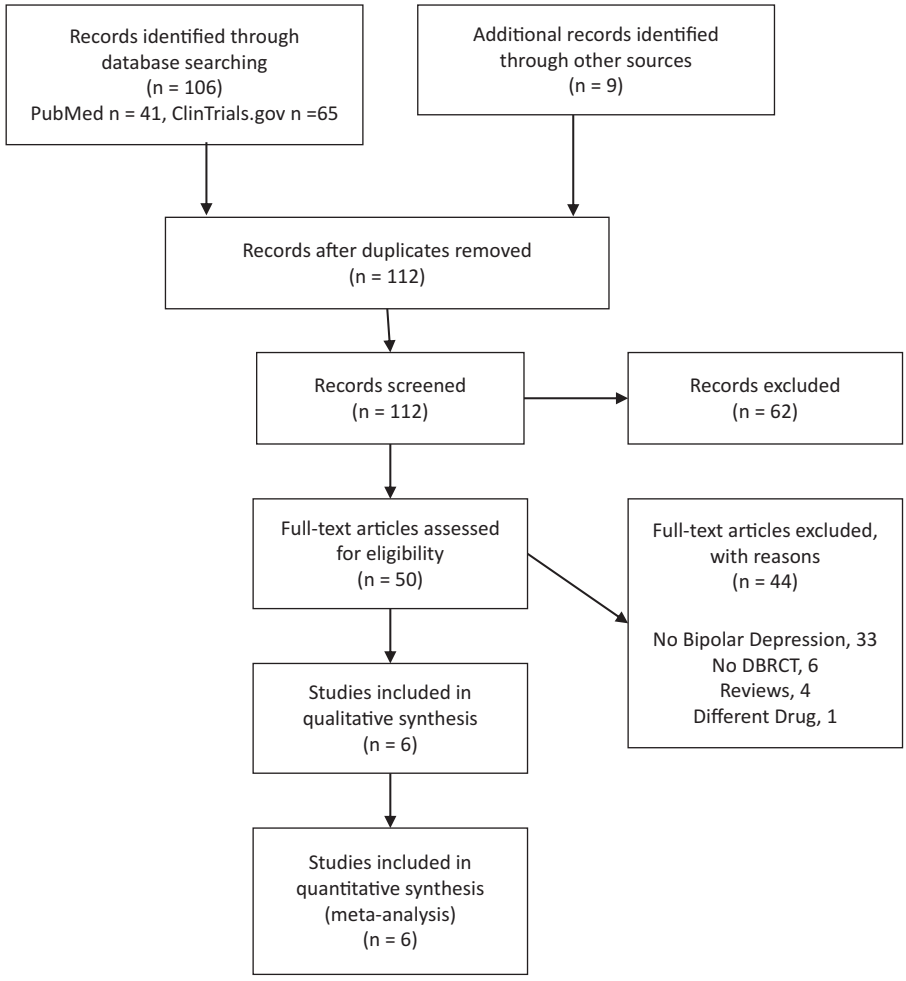

Figure 1. PRISMA flow chart.

Between-studies variance and variance of the effect size parameters across the population were estimated with the tau-squared statistics. The DerSimonian and Laird method[30] was used to fit the random effect model. The heterogeneity variance among studies in the random-effects model was estimated with the empirical Bayes estimator,[31] also known as the Paule–Mandel estimator,[32] and its 95% CI, that was calculated by using the Q-Profile method.[33] This approach is currently considered the best way to estimate the between-study variance.[34] The Hartung and Knapp[35] method was used to adjust test statistics and confidence intervals in the estimation of the random-effects model. Approximate prediction interval from the random-effects model for a new study was calculated according to Higgins et al[36] Prediction interval is helpful to establish whether the results of the meta-analysis will hold or not in future studies.

For the main measure of effectiveness (remission) and the main measure of adverse effects (anticipated termination of the trial because of adverse events), the "number needed to treat for an additional beneficial outcome" (NNT) and the "number needed to treat for an additional harmful outcome" (NNTH) were calculated. The NNT and the NNTH were calculated as the inverse of the absolute risk reduction, which is the difference between the event rate in the control and the event rate in the experimental group, and rounded to the nearest whole number.

To control for adequacy of the models, both the radial plot[37,38] and the standardized residuals plot[39] were considered. For a random-effects model, the radial plot shows the sampling variance of the observed effect size or outcome against the tau-square, that is, the amount of heterogeneity as estimated based on the model. As far as the standardized residuals plot is concerned, if a study fits the model, its standardized residual follows (asymptotically) a standard normal distribution. Therefore, for a study, a large standardized residual (above 2, as a rule of thumb) may suggest that the study does not fit the assumed model (ie, it may be an outlier).

The extent of heterogeneity was assessed using Cochran's Q and I^2 statistics.[40] Results of the heterogeneity assessment are detailed in all reported forest plots (see Figures 2 to 5). Significant Q statistic values (ie, $P < .05$) were interpreted as suggestive of relevant heterogeneity. For I^2, values between 0% and 40% might not be important; 30% and 60% may represent moderate heterogeneity; 50% and 90%: may represent substantial heterogeneity; and 75% and 100% represent considerable heterogeneity.[41] Since we retrieved less than 10 independent studies, the funnel plot, and the related statistics,[42] was not used.

Risk of bias in the studies was ascertained with the Cochrane risk-of-bias tool for randomized trials.[28] We also applied suggestions from the Agency for Healthcare Research and Quality (AHRQ) to evaluate the quality of the studies within a patient safety framework.[43]

The impact of potential moderators (sample's composition, duration of the trials, quality rate, etc.) was assessed with meta-regression. All analyses were carried with the "metaphor" package[44] or the "meta" package[45] running in R version 3.5.1.[46]

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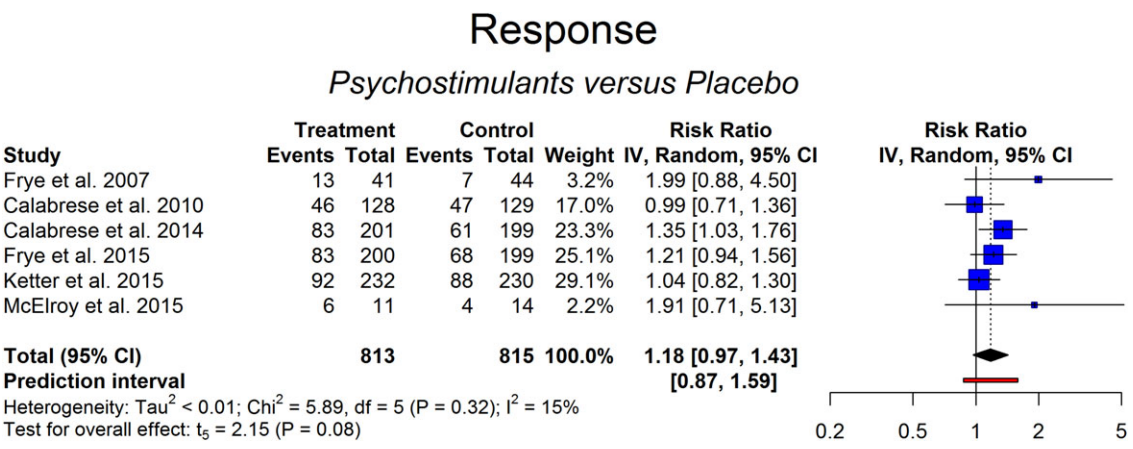

Figure 2. Response of psychostimulants vs placebo.

Results

The PRISMA flowchart is shown in Figure 1. Overall, we found six RCTs of psychostimulants or stimulant-like drugs add-on vs placebo in the treatment of resistant bipolar depression. Our search for trials comparing MPH or amphetamines as add-on treatments in bipolar depression with placebo did not yield any studies which could be included in this meta-analysis.

All, but one study, were multicenter trials. The main characteristics of these studies are summarized in Table 1. In one study, the trial duration was 6 weeks,[47] while in the remaining five trials, the duration was 8 weeks. The study samples included middle-aged patients with the mean age ranging from 42.4 to 44.5 years. The percentage of males ranged from 32% to 84%.

The diagnosis of the condition of interest (bipolar depression) was always made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria in use during the time the study was conducted and on the basis of a standardized interview.

Study quality

Random sequence generation and allocation concealment raised an "unclear risk of bias" in five studies out of six. For all other categories of bias, the studies were judged to have a low risk of bias (Table 2).

Overall, according to the AHRQ guidelines, one study[50] was judged to be of good quality, the other five studies were judged of fair quality. The study with the highest quality according to the AHRQ guidelines had the highest response and remission rates but the lowest sample size.

Efficacy (response and remission rate)

Six studies were included in the evaluation of response and remission rate in 813 patients treated with psychostimulants or stimulant-like drugs and 815 controls under placebo. The criterion used in the studies to assess response to treatment was a 50% drop in the scores of the main outcome, whatever the reached score. According to this criterion, the response rate ranged from 16% to 38% in the placebo arm and from 30% to 55% in the active treatment arm. The results of the random-effects model (RR = 1.18 [0.97-1.43], $P = .08$; prediction interval: 95%CI of RR: 0.87-1.59) suggested that response rate was not higher in patients treated with psychostimulants or stimulant-like drugs in comparison to placebo (Figure 2). Heterogeneity was low but with large confidence intervals (0%-78%; Cochran's Q: $P > .05$). No outlier was detected (Figures A1 and A2 in Supplementary Material).

In order to define remission, a more stringent criterion was used, namely a drop in the scores of the main outcome measure below a nonclinical threshold. According to this criterion, the remission rate ranged from 11% to 29% in the placebo arm and from 12% to 55% in the active treatment arm. The results of the random-effects model (RR = 1.37 [1.06-1.77], $P = 0.02$; NNT = 16) indicated that psychostimulants or stimulant-like drugs were more likely than placebo to induce remission (Figure 3). The radial and the standardized residuals plot did not reveal outliers (Figures A3 and A4 in Supplementary Material). Heterogeneity was low but with large CIs (0%-73%; Cochran's Q: $P > .05$). Prediction interval from the random-effects model (95% CI of RR: 1.04-1.81) indicated that the result would hold in future studies.

Tolerability (dropout rates)

Data on dropout was available for the six studies. Percentage of dropout ranged from 16% to 34% in the placebo arm and from 9% to 30% in the active treatment arm. Results of the random-effects model (RR = 1.04 [0.91-1.18], $P = .50$) indicated that treatment with psychostimulants or stimulant-like drugs was not associated with a higher risk of dropout compared to placebo (Figure 4). Heterogeneity across studies was low (95 CI: 0%-17%; Cochran's Q: $P > .05$). No outliers were detected (Figures A5 and A6 in Supplementary Material).

Safety (side effects and anticipated termination of the trial because of adverse events)

Headache, insomnia, and hypomania were the most frequently reported side-effects in the included studies, followed by nausea and anxiety, which were reported in five studies (Table 3). Most side-effects or adverse events were equally likely in the experimental and the placebo arm group, with some exceptions (Table 4). There were two occurrences of acute urticarial or pruritic rash in the experimental group against none in the placebo group (NNTH = 7). Nausea was more likely in the experimental group, being reported by 35 participants out of 685 in 5 studies that recorded it, compared to 23 out of 686 in the placebo group (NNTH = 59). Conversely, dyspepsia was reported by 4 participants out of 58 in the placebo arm in 2 studies that recorded it as compared to none in the experimental group. People in the experimental group were

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Table 1. Main Characteristics of the Identified RCTs Studying the Use of Psychostimulants as add-on in the Treatment of Bipolar Depression

Study	Location	Drug (Dose/Day)	Criterion for Diagnosis	Definition of Resistance	Maintenance Treatment on Which Stimulants were Added	Main Outcome Measure	Criterion for Response	Criterion for Remission	Sample Size	Gender Ratio (m/f)	Mean age in the Sample (y)
Frye et al[47]	Five centers in two countries	Modafinil (100-200 mg; mean dose: 177 mg)	DSM-IV (SCID)	Inadequate response to maintenance medication	Mood stabilizer with or without concomitant antidepressant, at stables doses for at least 2 weeks prior to randomization (lithium, divalproex sodium, lamotrigine, carbamazepine, atypical antipsychotics)	IDS-C_{30}	50% drop in IDS-C_{30} scores	IDS-C_{30} scores <12	Treated: 41 Placebo: 44	37/48	42.4
Calabrese et al[48]	Four centers in four countries	Armodafinil (150 mg)	DSM-IV-TR (SCID)	Inadequate response to treatment with 1 or 2 of the base medication for ≥8 wk prior to screening	Lithium (plasma levels ≥0.6 mEq/L for ≥4 weeks prior to baseline), valproic acid (plasma levels ≥50 µg/ml for ≥4 wk prior to baseline), olanzapine (dose ≥5 mg/d for ≥4 prior to baseline)	IDS-C_{30}	50% drop in IDS-C_{30} scores	IDS-C_{30} scores <12	Treated: 128 Placebo: 129	117/140	43.7
Calabrese et al[11]	70 centers in 10 countries	Armodafinil (150 and 200 mg)	DSM-IV-TR (SCID)	Major depressive episode associated with bipolar I disorder despite stable doses of maintenance medications for at least 4 weeks prior to the onset of the depressive episode and during screening	Lithium, valproic acid, aripripazole, olanzapine, lamotrigine, risperidone, ziprasidone (ziprasidone only in combination with lithium or valproic acid, and if taking two maintenance medications, at least one had to be lithium or valproic acid)	IDS-C_{30}	50% drop in IDS-C_{30} scores	IDS-C_{30} scores <12	Treated 10 mg: 201 Treated 200 mg: 32 Placebo: 199	145/284	43.5
Frye et al[49]	84 centers in 13 countries	Armodafinil (150 mg)	DSM-IV-TR (SCID-CT)	Current depressive episode despite taking maintenance medication	Lithium, valproate, lamotrigine, olanzapine, quetiapine, aripiprazole, risperidone, or ziprasidone (ziprasidone only in combination with lithium, valproate, or lamotrigine, and if taking two mood stabilizers, one had to be lithium, valproate, or lamotrigine)	IDS-C_{30}	50% drop in IDS-C_{30} scores	IDS-C_{30} scores <12	Treated: 200 Placebo: 199	158/241	44.5
Ketter et al[29]	76 centers in 10 countries	Armodafinil (150 and 200 mg)	DSM-IV-TR (SCID)	Current major depressive episode despite maintenance treatment for bipolar I disorder	One or two of lithium, valproic acid, olanzapine, aripiprazole, risperidone, lamotrigine, or ziprasidone (ziprasidone only in combination with lithium or valproic acid)	IDS-C_{30}	50% drop in IDS-C_{30} scores	IDS-C_{30} scores <12	Treated 10 mg: 231 Treated 200 mg: 30 Placebo: 229	217/273	44.1

Table 1. *(Continued)*

Study	Location	Drug (Dose/Day)	Criterion for Diagnosis	Definition of Resistance	Maintenance Treatment on Which Stimulants were Added	Main Outcome Measure	Criterion for Response	Criterion for Remission	Sample Size	Gender Ratio (m/f)	Mean age in the Sample (y)
McElroy et al[50]	One center in Ohio	Lisdexamfetamine (20-70 mg; mean dose: 52.7 mg)	DSM-IV-TR (SCID)	Major depressive episode inadequately responsive to adequate mood stabilizer and/or antipsychotic therapy, with or without concomitant antidepressant therapy, received for at least 4 weeks	Mood stabilizer and/or antipsychotic therapy not specified	MADRS	50% drop in MADRS scores	MADRS ≤12	Treated: 11 Placebo:14	8/17	43.0

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; IDS-C_{30}, 30-item Inventory of Depressive Symptoms (IDS)—Clinician-rated; MADRS, Montgomery and Åsberg Depression Rating Scale; SCID, Structured Clinical Interview for DSM; SCID-CT, Structured Clinical Interview for DSM—Clinical Trials.

more likely to report a significant decrease (≥7%) in body weight (NNTH = 30) and less likely to experience a significant increase (≥7%) in body weight than those in the placebo arm (details in Tables 3 and 4).

Emergence or worsening of suicide ideation or manic switch was not more frequent in the experimental than in the placebo group (Table 4). Overall, LDX, modafinil, and armodafinil were reasonably free of side-effects at the prescribed doses.

Details on severe adverse effects were available for five studies including 772 patients treated with these agents and 771 under placebo. Percentage of anticipated termination of the trial because of adverse events ranged from 4% to 9% in the placebo arm and from 0% to 13% in the active treatment arm. Results of the random-effects (RR = 1.30 [0.81-2.10], $P = .20$) model indicated that there was not a higher risk of adverse events leading to an anticipated termination of trial in patients treated with the stimulants studied in comparison to placebo (Figure 5). The number needed to treat for an additional harmful outcome was 62, which is fairly safe. Heterogeneity was low but with large confidence interval (0%-71%; Cochran's Q: $P > .05$). No outliers were detected (Figures A7 and A8 in Supplementary Material).

Impact of moderators

The sample composition by sex or age did not influence outcome in any of the performed meta-analyses ($P > .05$ in all meta-regression). No effect was found for additional potential moderators, such as total sample size, duration of treatment, or the drug that was used in the trial.

Discussion

The current meta-analysis provides some evidence in support of the usefulness of LDX and the stimulant-like agents modafinil and armodafinil as an add-on to treatment as usual in bipolar depression. Treatment as usual refers to treatment used clinically that presents variable degrees of effectiveness.[46] The following outcomes were considered: response and remission, as defined by the authors in each study included in the meta-analysis; tolerability, as measured by dropout (anticipated termination of the trial for any cause); safety, as measured by side-effects and anticipated termination of trial because of adverse events.

The stimulants studied here were more likely to induce remission from an episode of resistant bipolar depression compared to placebo but did not differ from placebo in terms of response. Overall, they imported a greater risk of nausea (5.1% vs 3.3%) and a significant decrease in body weight (3.6% vs 0.3%). Side-effect frequency did not differ significantly between experimental and placebo arms of the trials. Interestingly, this report failed to show higher rates of emergence of hypomania or mania due to LDX, modafinil or armodafinil add-on to treatment-as-usual for resistant bipolar depression. Adding-on LDX, modafinil, and armodafinil did not result in more dropouts compared to placebo, neither was there a higher risk of adverse events or of emergence/worsening of suicide ideation, suggesting that these drugs offer a reasonably well-tolerated and safe treatment.

All three compounds enhance dopaminergic prefrontal transmission, through different mechanisms of action, however.

LDX, a prodrug of *d*-amphetamine, blocks the reuptake of norepinephrine (NE) and dopamine (DA) into the presynaptic neuron by reversing the direction of the dopamine and

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Table 2. Assessment of the Risk of Bias in the Included Studies According to the Cochrane Risk-of-Bias Tool for Randomized Trials and the Agency for Healthcare Research and Quality (AHRQ) Guidelines

	Frye et al[47]	Calabrese et al[48]	Calabrese et al[11]	Frye et al[49]	Ketter et al[29]	McElroy et al[50]
Random sequence generation	Low risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias
Allocation concealment	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias
Selective reporting	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Blinding of participants, personnel	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Blinding of outcome assessment	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Incomplete outcome data	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Other bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
AHRQ standards	Fair quality	Fair quality	Fair quality	Fair quality	Fair quality	Good quality

Abbreviation: AHRQ, Agency for Healthcare Research and Quality.

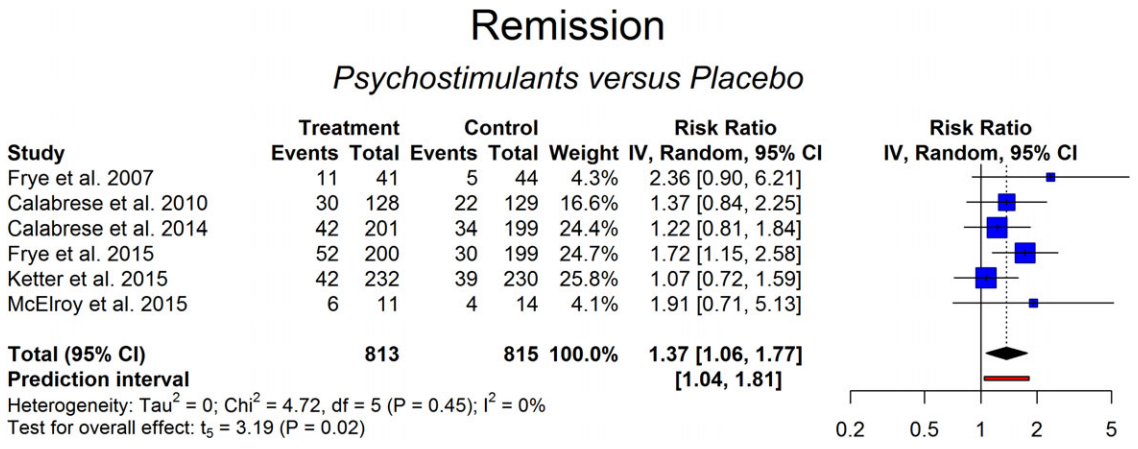

Figure 3. Remission achieved with psychostimulants vs placebo.

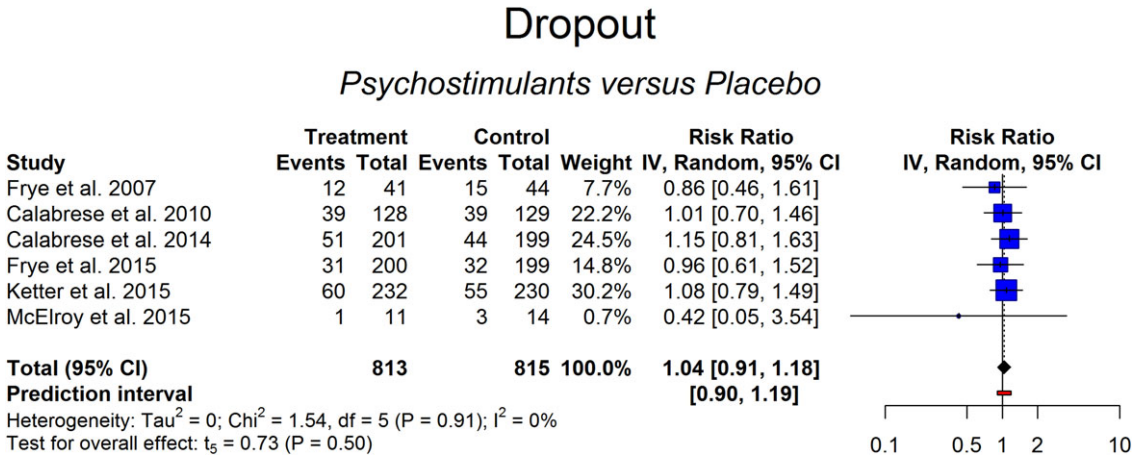

Figure 4. Dropouts in the psychostimulant vs placebo groups.

norepinephrine transporter pump (Dopamine Transporter [DAT] and Norepinephrine Transporter [NAT]) resulting in the active diffusion of neurotransmitters in the synaptic cleft. It also inhibits the vesicular monoamine transporter (VMAT-2) inside the cell favoring extracellular diffusion of DA.[51] More specifically, by targeting the trace amine-associated receptor 1 (TAAR1), which

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Table 3. Side or Adverse Events Across the Identified RCTs Studying the use of Psychostimulants as Add-On in the Treatment of Bipolar

Type of Side/Adverse Event	Frye et al[47]		Calabrese et al[30]		Calabrese et al[11]		Frye et al[49]		Ketter et al[29]		McElroy et al[50]	
	Modafinil vs placebo		Armodafinil vs placebo		Armodafinil vs placebo		Armodafinil vs placebo		Armodafinil vs placebo		Lisdexamfetamine vs placebo	
	TR.	PL.	TR.	PL.	TR.	PL.	TR.	PL.	TR.	PL.	TR.	PL.
	n = 41	n = 44	n = 128	n = 129	n = 201	n = 199	n = 200	n = 199	n = 232	n = 230	n = 11	n = 14
Headache	4 (10%)	1 (2%)	14 (11%)	13 (10%)	19 (9%)	20 (10%)	29 (14%)	15 (7%)	37 (16%)	30 (13%)	5 (45%)	2 (14%)
Nausea	1 (2%)	1 (2%)	–	–	11 (5%)	9 (4%)	12 (6%)	7 (3%)	9 (4%)	5 (2%)	2 (18%)	1 (7%)
Dry mouth	–	–	–	–	9 (4%)	4 (2%)	–	–	–	–	4 (36%)	0 (0%)
Infection	0 (0%)	1 (2%)	–	–	–	–	–	–	–	–	1 (9%)	1 (7%)
Dyspepsia	0 (0%)	2 (4%)	–	–	–	–	–	–	–	–	0 (0%)	2 (14%)
Insomnia	2 (5%)	0 (0%)	13 (10%)	10 (8%)	8 (4%)	8 (4%)	6 (3%)	4 (2%)	12 (5%)	7 (3%)	4 (36%)	1 (7%)
Diarrhea	–	–	13 (10%)	8 (6%)	13 (6%)	17 (8%)	–	–	12 (5%)	14 (6%)	1 (9%)	1 (7%)
Migraine	–	–	–	–	1 (0.5%)	0 (0%)	–	–	–	–	0 (0%)	1 (7%)
Fatigue	–	–	–	–	–	–	–	–	–	–	1 (9%)	2 (14%)
Palpitations	–	–	–	–	–	–	–	–	–	–	1 (9%)	1 (7%)
Decreased appetite	–	–	–	–	–	–	–	–	–	–	2 (18%)	2 (14%)
Significant increase in body weight	–	–	4 (3%)	8 (6%)	3 (1.5%)	9 (4.5%)	4 (2%)	9 (4.5%)	–	–	–	–
Significant decrease in body weight	–	–	4 (3%)	0 (0%)	8 (4%)	1 (0.5%)	–	–	–	–	–	–
Epididymal cyst	–	–	1 (0.8%)	0 (0%)	–	–	–	–	–	–	–	–
Acute urticaria/pruritic rash	–	–	1 (0.8%)	0 (0%)	1 (0.5%)	0 (0%)	–	–	–	–	–	–
Tremor	–	–	–	–	–	–	–	–	–	–	3 (27%)	0 (0%)
Sedation/somnolence	–	–	–	–	–	–	2 (1%)	2 (1%)	1 (0.4%)	3 (1%)	–	–
Restlessness/feeling jittery	–	–	8 (6%)	1 (0.8%)	1 (0.5%)	1 (0.5%)	–	–	–	–	4 (36%)	0 (0%)
Anxiety	–	–	5 (4%)	3 (2%)	7 (3.5%)	0 (0%)	8 (4%)	5 (2.5%)	2 (0.9%)	0 (0%)	2 (18%)	0 (0%)
Exacerbation of depression	0 (0%)	1 (2%)	2 (1.6%)	2 (1%)	0 (0%)	1 (0.5%)	–	–			–	–
Severe depression or hospitalization for it	1 (2%)	0 (0%)	1 (0.8%)	1 (0.8%)	0 (0%)	3 (1.5%)	–	–	3 (1%)	2 (0.9%)	–	–
Emergence/worsening suicide ideation	–	–	3 (2%)	3 (2%)	4 (2%)	2 (1%)	1 (0.5%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)
Hypomania	1 (2%)	4 (9%)	3 (2%)	1 (0.8%)	0 (0%)	1 (0.5%)	0 (0%)	1 (0.5%)	2 (0.9%)	0 (0%)	0 (0%)	0 (0%)
Severe mania or hospitalization for it	1 (2%)	1 (2%)	1 (0.8%)	5 (4%)	3 (1.5%)	2 (1%)	–	–	4 (2%)	0 (0%)	0 (0%)	0 (0%)
Psychotic breakdown	–	–	–	–	2 (1%)	0 (0%)	1 (0.5%)	0 (0%)	–	–	–	–

Abbreviations: PL., placebo; TR., treatment (active drug); –, unreported.

Table 4. Results of Random-Effects Models of Adverse Events Across the Identified RCTs Studying the Use of Psychostimulants as Add-On in the Treatment of Bipolar Depression

Type of side/adverse event	*k*	n. TR	n. PL	Random-effects	*p*	Tau	Cochrane's *Q*	I^2 (95% CI)
Headache	6	108/813	81/815	1.3 (0.9-2.0)	0.126	0.16	*Q* = 5.8; *P* = .32	14% (0%-78%)
Nausea	**5**	**35/685**	**23/686**	**1.5 (1.1-2-0)**	**0.017**	0.00	*Q* = 0.6; *P* = .95	0% (0%-0%)
Dry mouth	2	13/212	4/213	2.9 (0-7898)	0.330	0.34	*Q* = 1,1; *P* = .29	9% (-)
Infection	2	1/52	2/58	0.7 (0-2123)	0.729	0.00	*Q* = 0.3; *P* = .54	0% (-)
Dyspepsia	**2**	**0/52**	**4/58**	**0.2 (0.08-0.6)**	**0.035**	0.00	*Q* = 0.01; *P* = .94	0% (-)
Insomnia	6	45/813	30/815	1.5 (0.9-2.3)	0.081	0.00	*Q* = 2.9; *P* = .70	0% (0%-57%)
Diarrhea	4	39/572	40/572	0.9 (0.5-1.7)	0.895	0.00	*Q* = 2.2; *P* = .54	0% (0%-78%)
Migraine	2	1/212	1/213	1.1 (0-268740)	0.945	0.00	*Q* = 0.7; *P* = .38	0% (-)
Fatigue	1	1/11	2/14	0.6 (0.06-6.1)	0.695	–	–	–
Palpitations	1	1/11	1/14	1.3 (0.1-18)	0.859	–	–	–
Decreased appetite	1	2/11	2/14	1.3 (0.2-7.6)	0792	–	–	–
Significant increase in body weight	**3**	**11/529**	**26/527**	**0.4 (0.2-0.7)**	**0.019**	0.00	*Q* = 0.2; *P* = .89	0% (0%-10%)
Significant decrease in body weight	**2**	**12/329**	**1/328**	**8.3 (3.7-18)**	**0.019**	0.00	Q = 0.01; *P* = .94	0% (-)
Epididymal cyst	1	1/128	0/129	3.0 (0.1-73)	0.497	–	–	–
Acute urticaria/pruritic rash	**2**	**2/329**	**0/328**	**2.9 (2.7-3.3)**	**0.005**	0.00	*Q* = 0.0; *P* = .99	0% (-)
Tremor	1	3/11	0/14	8.8 (0.5-154)	0.135	–	–	–
Sedation/somnolence	2	3/432	5/429	0.6 (0.0-634)	0.543	0.00	*Q* = 0.5; *P* = .47	0% (-)
Restlessness/feeling jittery	3	13/340	2/342	5.0 (0.2-102)	0.147	0.00	*Q* = 1.8; *P* = .39	
Anxiety	5	24/772	8/771	2.2 (0.9-5.8)	0.074	0.00	*Q* = 2,9; *P* = .56	0% (0%-72%)
Exacerbation of depression	3	2/370	4/372	0.6 (0.1-3.2)	0.353	0.00	*Q* = 0.5; *P* = .77	0% (0%-58%)
Severe depression or hospitalization for it	4	5/602	6/602	1.0 (0.2-6.1)	0.963	0.00	*Q* = 2.4; *P* = .49	0% (0%-80%)
Emergence/worsening suicide ideation	4	8/772	6/771	1.3 (0.4-3.9)	0.513	0.00	*Q* = 1.3; *P* = .73	0% (0%-65%)
Hypomania	6	6/813	7/815	0.8 (0.1-4.9)	0.822	0.35	*Q* = 4.3; *P* = .36	7% (0%-80%)
Severe mania or hospitalization for it	4	9/613	8/616	1.1 (0.1-11)	0.898	0.87	*Q* = 4.5; *P* = .21	33% (0%-76%)
Psychotic breakdown	2	3/401	0/398	3.9 (0.1-96)	0.116	0.00	*Q* = 0.05; *P* = .82	0% (-)

Statistically significant results are in bold. Sample size varies according to the numerosity of the included studies.
Abbreviations: CI, confidence interval; n, number of events/sample size; PL., placebo; TR., treatment (active drug).

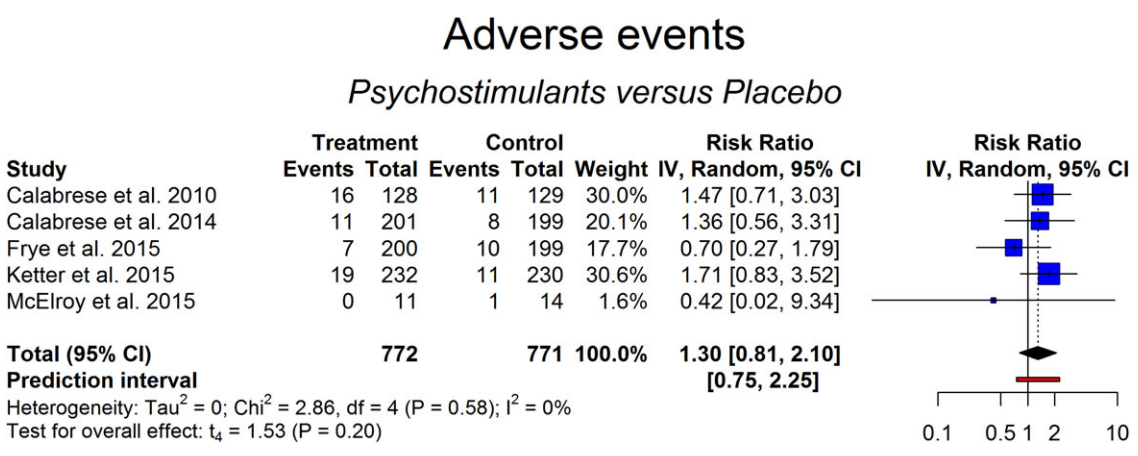

Figure 5. Adverse events analysis between subjects treated with add-on psychostimulants vs the placebo-treated group.

interacts with both presynaptic and post-synaptic D2 receptors to synergistically control the downstream signaling pathways, LDX increases synaptic concentrations of these catecholamine neurotransmitters in the prefrontal cortex, and in the striatum.[52] Amphetamines also enhance dopaminergic transmission not only in the reticular activating system and the prefrontal cortex, but also in the nucleus accumbens, which is responsible for their addictive potential and the worsening or emergence of tics. Abuse liability

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varies, however, with the delivery system used in these formulations.[53] Conversion of LDX to its active component requires enzymatic hydrolysis that results in a slow rise in serum *d*-amphetamine level, which possibly provides a reduced potential for abuse.[54] In a human abuse-liability study involving individuals with a history of drug abuse, lisdexamfetamine produced subjective responses that were significantly less than an equivalent oral dose of *d*-amphetamine immediate release.[55] Modafinil and armodafinil seem to act mostly at the suprachiasmatic nucleus in the hypothalamus and at the amygdala, both regions primarily involved in wakefulness. So, their interaction with the nucleus accumbens is believed to be less relevant than that of the amphetamines, hence allowing them to bear reduced addictive potential.[56]

It has also been debated that the stimulation of nucleus accumbens is involved in the induction of (hypo)manic switches, cycle acceleration, and psychosis, often related with the use of amphetamines.[57] Modafinil and its *R*-enantiomer armodafinil are stimulant-like agents promoting DA- and NE-related transmission. Differences with psychostimulants include their low affinity for the DAT.[58,59] In addition, modafinil increases noradrenergic transmission by directly acting as a partial agonist on alpha-1B adrenergic receptors, decreases gamma-amino-butyric Acid (GABA) release and increases glutamate release in various brain regions. It also activates orexigenic hypothalamic neurons and the histaminegic (H1) tuberomammillary nucleus.[60,61] Armodafinil is not a direct- or indirect-acting DA receptor agonist. However, *in vitro*, armodafinil is an antagonist to the DAT and inhibits DA reuptake, thus enhancing DA neurotransmission.[56]

The discrepancy between response and remission in patients with resistant bipolar depression treated with the three drugs studied may depend on them being able to affect only a subgroup of patients, possibly more sensitive to the action of the drug. As a consequence, when evaluated as a generic 50% drop in the outcome scores, the average effect was found to be similar in patients under the active treatment and patients receiving placebo. However, when a prespecified threshold is used, such as an IDS-C_{30} score < 12, as in most studies, more patients under the active treatment were found to achieve this threshold than patients receiving placebo.

Serotonin reuptake inhibition does not seem to play a major role for acute bipolar depression in contrast to unipolar depression, as antidepressants seem to be largely ineffective in the former.[9] Furthermore, it has been suggested that NE reuptake and 5-HT_{1A} agonism along with hypoactive NE and serotonin neurotransmission may play a central role in bipolar depression, and that NE rather than serotonin activity seems to be more important in bipolar depression.[62] Furthermore, evidence suggests that increased striatal DAT levels lead to reduced dopaminergic function and depression, postulating that a failure of DA receptor and transporter homoeostasis possibly underlies the pathophysiology of bipolar depression.[63] Currently, Food and Drug Admnistration (FDA)-approved treatments for bipolar depression are the olanzapine–fluoxetine combination, quetiapine, lurasidone, and cariprazine. They are all D2 and D3 antagonists, but cariprazine is a strong D3 partial agonist.[64] Cariprazine's binding affinity to the D3 receptors is higher than DA's affinity for this receptor, meaning that, at physiological doses, DA cannot reverse D3 binding.[65] With regard to the serotonin system, all four antipsychotics are antagonists at the $5HT_7$ receptors in the hypothalamus, and fluoxetine results in $5HT_7$ downregulation at the SCN[66]; lurasidone, quetiapine, and cariprazine are partial agonists at the 5-HT_{1A} receptors, and antagonists at the $5HT_{2A}$ receptors, whereas olanzapine is an antagonist at 5-HT_{1A} and an inverse agonist at $5HT_{2A}$ receptors.[67] Olanzapine, quetiapine and fluoxetine block the norepinephrine transporter (NET) and all antipsychotics in this group also enhance cortical cognitive function by exerting inhibitory effects at alpha-1 receptors.[68] All, except lurasidone inhibit muscarinic and H1 histamine receptors.[69] According to the model for antidepressant pathways in bipolar depression suggested by Fountoulakis et al,[62] serotonin reuptake is neither sufficient nor necessary as a condition for the antidepressant efficacy in bipolar depression. Moreover, no class effect seems to exist in the treatment of bipolar depression and this primarily concerns antidepressants.[70] NE activity, however, seems to be absolutely necessary in order to sustain the antidepressant effect.[62] Furthermore, it has previously been suggested that a regionally selective balance between the DA and serotonin systems may account for the mood-stabilizing properties of atypical antipsychotics such as quetiapine and olanzapine.[71] It is, therefore, possible that the psychostimulant and stimulant-like drugs studied here exert their antidepressant effect in bipolar depression by mediating increases in NE and DA in the extracellular space, in a similar way to the evidence-based treatments for bipolar depression.[17]

Implications for clinical practice

Our results replicate these of an earlier meta-analysis,[24] which examined the effects of dopaminergic agents used in ADHD and the dopamine agonist pramipexole used in Parkinson's disease, as add-on treatments in acute bipolar depression. Moreover, we also replicated the results of a more recent meta-analysis showing that, compared to placebo, augmentation with modafinil/armodafinil (MoArm) as adjunctive treatment for bipolar depression was associated with significantly greater rates of treatment response, with the all-cause discontinuation not differing from placebo and no evidence of mood switch or suicide attempts on MoArm treatment.[72]

Based on the above, in addition to using psychostimulants in comorbid ADHD and BD, it seems that using psychostimulants (and stimulant-like drugs) as an add-on to standard treatment in resistant bipolar depression may well have a place in clinical practice, not only in in-patients but in out-patients as well. Improvement in the symptoms of resistant bipolar depression translates into improvement in patient quality of life, decreased carer and family burden, lower cost for the health service and fewer lost days at work.[73]

The use of *S*-ketamine in resistant depression is being discussed extensively in recent years, and FDA approval for its use in treatment-resistant depression was granted in February 2019. *S*-ketamine, however, is complicated in its mode of administration, bears an addiction potential and is marketed as an expensive treatment that many health services around the globe are unable to offer to their patients. Furthermore, it appears to be less effective in bipolar compared to unipolar resistant depression.[74,75]

Nevertheless, our results should be further replicated by multicenter longitudinal randomized clinical trials, with a much larger number of participants diagnosed by strict consensus criteria for resistant bipolar depression, and with a more extended follow-up period to reflect the chronicity of bipolar depressive episodes. Moreover, the use of assessment tools and questionnaires to assess and follow-up symptomatology should be revised to include newer and more specific instruments, such as for example, the Koukopoulos Mixed Agitation Depression Rating Scale.[75] In addition, head-to-head trials comparing psychostimulant and stimulant-like medications with well-established approved effective treatments in resistant bipolar depression would also help to clarify the role of add-on stimulant medication further.

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Implications for research

Based on the results of this meta-analysis, further research should be aimed toward identifying the specific subsample of treatment-resistant bipolar depression patients for which add-on treatment with psychostimulants and stimulant-like medications is efficacious, if indeed such a subsample exists. Moreover, a better understanding of the mode of action of psychostimulants and stimulant-like medications in acute bipolar depression will inform further pharmacological hypotheses on the neurochemistry and the aetiology of depression in BD as well as on the possible causes of resistant depression in BD.

Conclusions

The current study provides some limited data concerning the usefulness of add-on stimulants in resistant bipolar depression. Remission but not response rates improve in comparison to placebo, suggesting a selective effect on a subgroup of patients. In view of the potential benefits of add-on psychostimulant and stimulant-like medication to treatment as usual in patients with acute bipolar depression, this study suggests a possible revision of treatment guidelines to include modafinil, armodafinil and LDX earlier in the therapeutic algorithm for resistant acute bipolar depression. To date, there is no study investigating the effectiveness of add-on psychostimulant and stimulant-like medication in comparison with an active compound. Therefore, further research is necessary in order to elucidate the usefulness of these and other similar compounds and their clinical applicability.

Supplementary Materials. To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S109285292000156X.

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