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Review

Meta-analysis of the effects of adjuvant drugs in co-occurring bipolar and substance use disorder

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ABSTRACT

Background: Individuals with bipolar disorder (BD) often have co-occurring substance use disorders (SUDs), which substantially impoverish the course of illness. Despite the importance of this dual diagnosis, the evidence of the efficacy and safety of adjuvant treatments is mostly unknown.
Objective: To perform a meta-analysis to evaluate the efficacy and safety of adjuvant drugs in patients with co-occurring BD and SUD.
Methods: We searched PubMed, Scopus, and Web of Knowledge until 30th April 2022 for randomized clinical trials (RCT) evaluating the efficacy and safety of adjuvant drugs compared to placebo in patients with a dual diagnosis of BD and SUD. We meta-analyzed the effect of adjuvant drugs on general outcomes (illness severity, mania, depression, anxiety, abstinence, substance craving, substance use, gamma-GT, adherence, and adverse events) and used the results to objectively assess the quality of the evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. For completeness, we also report the specific effects of specific adjuvant drugs in patients with specific substance disorders.
Results: We included 15 RCT studies (9 alcohol, 3 cocaine, 2 nicotine, and 1 cannabis) comprising 628 patients allocated to treatment and 622 to placebo. There was low-quality evidence that adjuvant drugs may reduce illness severity ($g = -0.25$, 95% CI: −0.44, −0.06), and very-low quality evidence that they may decrease substance use ($g = -0.23$, 95% CI: −0.44, −0.02) and increase substance abstinence ($g = 0.21$, 95% CI: 0.04, 0.38).

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Discussion: There is low-quality evidence that adjuvant drugs may help reduce illness severity, probably via facilitating abstinence and lower substance use. However, the evidence is weak; thus, these results should be considered cautiously until better evidence exists.
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Introduction

Bipolar disorder (BD) is a severe chronic mood disorder mainly characterized by episodes of abnormally elevated and depressed mood, affecting 2–3% of the population.[1,2] Beyond mood abnormalities, patients suffering from BD have an 8–10 times higher risk of alcohol and drug abuse.[3] For instance, 61% of patients with BD type I (which includes manic episodes, i.e., clinically severe mood elevations) and 48% with BD II (which includes hypomanic but not manic episodes) develop a substance use disorder (SUD).[2] Patients mostly abuse alcohol, with a lifetime prevalence of 58%,[2,4] followed by cocaine, with a lifetime prevalence of 15–39%.[4,5] The prevalence of tobacco smoking is also 2–3 times higher than among the general population.[6,7] And to add fuel to the fire, the co-occurrence of SUD substantially impoverishes the course of BD,[8,9] with longer mood episodes, higher hospitalization rates, and lower recovery rates,[10–12] higher aggression rates,[13,14] increased medical morbidity, and higher suicide risk,[9,15,16] worsened cognitive functioning,[17,18] and poorer treatment compliance.[8,9] Some studies have used machine-learning models to predict co-occurring SUD, finding increased risk in patients who had hypomania as the first affective episode or hetero-aggressive behavior.[19]

However, despite the aforementioned clinical relevance of co-occurring BD and SUD, the evidence about the efficacy and safety of treatments for this population is minimal, probably due to the challenges of studying this clinically complex population. Only a few randomized clinical trials (RCT) have evaluated the efficacy and safety of adjuvant drugs for this dual diagnosis. To shed some light on the topic, we systematically reviewed and meta-analyzed all RCTs that evaluated the efficacy and/or safety of adjuvant drugs in patients with a dual diagnosis of BD and SUD. We investigated the effect of adjuvant drugs on ten general outcomes (abstinence, adherence, adverse events, anxiety symptoms, depressive symptoms, functioning, illness severity, manic symptoms, quality of life, substance craving, and substance use), combining all medications and all substance use disorders. For completeness, we also report each specific effect of each specific adjuvant drug in patients with each specific substance disorder.

Methods

The protocol of this study was registered in PROSPERO (CRD42022304945) and the study was conducted according to it. Literature search and data extraction were carried out following the PRISMA 2020 guidelines[20] (see PRISMA checklists in the Supplement).

Inclusion criteria

Studies were eligible for inclusion if they: (a) included samples with only or mostly (≥75%) patients diagnosed with bipolar disorder (or schizoaffective disorder bipolar subtype) and substance use disorder established using the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD); (b) reported the results of an RCT evaluating the safety and/or efficacy in improving symptoms of an adjuvant drug against placebo (i.e., to establish safety and efficacy compared to no adjuvant therapy); (c) contained sufficient data for analyses. We decided only including RCT to provide better-quality evidence. We did not set language or age restrictions.

Search

We searched in Web of Knowledge, Scopus, and PubMed (last search on 30th April 2022) with the following keywords: "trial" AND "bipolar disorder" AND ("alcohol" OR "cocaine" OR "methamphetamine" OR "nicotine"). Search strings for each database can be found in the Supplement. After removing all duplicates, we screened titles and abstracts and, when required, the full text to select the studies according to our inclusion criteria. Of the 1366 studies identified, we excluded 1351 duplicates or irrelevant papers after screening titles, abstracts, and full text, thus including 15 studies. Two researchers conducted the search and inclusion of studies independently and resolved discrepancies by consensus with a third researcher.

Data extraction

For each study, we extracted the substance abused, the adjuvant drug in the treatment group, sample sizes, duration of the follow-up, mean age, sex distribution, diagnosis distribution (proportion of individuals with bipolar disorder type I/type II or not otherwise specified/schizoaffective, major depressive disorder or schizophrenia), the proportion of individuals with a manic or depressive episode or euthymic, the data required to assess the risk of bias (see below), and the following information regarding the clinical outcomes.

For binary outcomes (e.g., mania or depression remission, or drinking relapse), we extracted the number of events in each group and the odds ratio with its confidence interval and p-value when available. If the study reported both descriptive statistics (e.g., number of events in each group) and inferential statistics (e.g., 95% confidence interval of the odds ratio), we preferred the latter because the authors of the study may have controlled for the presence of potential confounders.

For numeric outcomes (e.g., a symptom scale score), we extracted the baseline mean, post-treatment mean, mean change, and their standard deviations in the two groups, as well as their difference, t-value, effect size, and p-value when available. Some studies only reported the post-treatment measures while others reported the changes from baseline; we preferred the latter because it is conceptually identical to the former but controls for baseline differences. For studies not reporting the standard deviations of the change, we imputed them from the standard deviations of the baseline and post-treatment measures assuming a correlation of $r = 0.5$ between baseline and post-treatment measures. Again, if the study reported both descriptive statistics (e.g., means and standard deviations in each group) and inferential statistics (e.g., 95% confidence interval of the mean changes), we preferred the latter because the authors of the study may have controlled for the presence of potential confounders.

Two researchers extracted all data independently and resolved disagreements by consensus with a third researcher.

Risk of bias assessment

We assessed the quality of the included studies using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[21] This tool evaluates five domains based on empirical evidence and theoretical considerations, through which bias might be introduced into the results. The five domains are: (1) bias arising from the randomization process; (2) bias due to deviation from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; and (5) bias in the selection of the reported results.

Meta-analysis of general outcomes

Given the heterogeneity of the specific outcomes reported in the papers (see below), we first grouped them into the following general categories, as specified in the protocol registered in PROSPERO:

- *Abstinence*: cumulative non-drinking days, no drinking days, no heavy drinking days, maximum consecutive non-drinking days, negative cocaine urine screen, negative methamphetamine urine screen, nicotine abstinence at 6 months, nicotine abstinence weeks ≥1, nicotine abstinence weeks ≥4, no heavy drinking relapse, non-drinking days per week, non-heavy drinking days per week, and proportion of negative cocaine urine screens.
- *Adherence*: pill counts, study completion, weeks in the study.
- *Adverse events*: specific adverse events (abnormal dreams, depressed mood), Psychobiology of Recovery from Depression-III Somatic Symptom Scale (SSS),[22] neuropsychiatric adverse events (NPSAEs), Abnormal Involuntary Movement Scale (AIMS),[23] Simpson-Angus Scale (SAS),[24] Barnes Akathisia Scale (BARS),[25] and Frequency of Side Effects Ratings/Global Rating of Side Effects Burden (FISER/GRSEB).
- *Anxiety*: Hamilton Anxiety Rating Scale (HAM-A).[26]
- *Depression*: 17-item Hamilton Rating Scale for Depression (HRSD-17),[27] 21-item Hamilton Rating Scale for Depression (HRSD-25),[28] HDRS-25 >7 (no remission), Inventory of Depressive Symptomatology – Clinician rating (IDS-C),[29] IDS-C >14 (no remission), Inventory of Depressive Symptomatology – Self-Report (IDS-SR),[29] Montgomery-Asberg Depression Rating Scale (MADRS),[30] and Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR).[31]
- *Functioning*: Global Assessment of Functioning (GAF),[32] (minus) Sheehan Disability Scale (SDS).[33]
- Gamma-GT.
- *Illness severity*: Clinical Global Impressions Scale (CGI)-mood, CGI-severity, and CGI-substance.[23]
- *Mania*: Bech-Rafaelsen Mania Scale (BRMS),[34] BRMS >7 (no remission), and Young Mania Rating Scale (YMRS).[35]
- *Memory*: Rey Auditory Verbal Learning Test (RAVLT) total, delayed recall, and alternative word list.[36]
- *Quality of life*: Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[37]
- *Substance craving*: Brief Substance Craving Scale (BSCS),[38] Cocaine Craving Questionnaire (CCQ),[39] and Obsessive Compulsive Drinking and Abstinence Scale (OCDS),[40] Penn Alcohol Craving Scale (PACS).[41]
- *Substance use*: cigarettes per day, cumulative heavy drinking days, drinks per day, drinks per drinking day, drinks per heavy drinking day, increased cigarette usage, increase in CO levels, and money spent on cocaine.

We applied simple transformations to some of the original specific outcomes to make them more homogenous, e.g., we transformed "proportion of heavy drinking days = 0" into "no heavy drinking days". In this regard, we transformed into "abstinence," those outcomes that involved no consumption days or negative screens.

We conducted a meta-analysis for each general outcome reported by at least three studies, combining all substances, all adjuvant drugs, and binary and numeric specific outcomes (for binary outcomes, we used the equivalent Hedges' *g* calculated for the specific substance–drug–outcome meta-analyses – see later – and imputed a variance that would lead to the same statistical significance). Some studies provided more than one specific outcome for the same general outcome (e.g., cumulative non-drinking days and maximum consecutive non-drinking for the general outcome "abstinence"). In these cases, we averaged the effect sizes of the specific outcomes and only used the average effect size in the meta-analysis. We also calculated the confidence intervals and the between-study heterogeneity statistic I^2 (values >50% are conventionally considered to indicate serious heterogeneity). We conducted a funnel plot and a meta-regression by the standard error (similar to Egger's test) to detect potential reporting or publication bias.

Finally, we graded the evidence of the efficacy of each intervention in improving each measure according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines.[42] Specifically, we assessed the risk of bias, inconsistency, indirectness, imprecision, and publication bias and derived the quality of the evidence from these assessments. To evaluate the risk of bias, we used the RoB 2 tool described above. We assessed inconsistency with the I^2 heterogeneity statistic complemented by the proportion of studies reporting contradictory findings (excluding small effects). Indirect evidence would refer to evidence from trials conducted in special population groups (e.g., due to strict exclusion criteria) or that had not measured the outcomes but surrogates (e.g., CO levels to infer substance use). To assess whether the trials were conducted in special population groups, we considered the exclusion criteria used in the studies. Meta-analyses were rated as imprecise if the 95% confidence interval included both null and large effects, or if they did not meet the optimal information size (i.e., the sample size required to detect small or medium effects with 80% statistical power). Specifically, we rated serious imprecision if the confidence interval included both null and large effects or if the overall number of individuals in each arm was inferior to 394. This number corresponds to the sample size required to detect small effects ($g = 0.2$) with 80% statistical power according to a standard formula (R function "power.t.test"). We rated very serious imprecision if the overall number of individuals in each arm was inferior to 394 and the confidence interval included both null and large effects, or if the overall number of individuals in each arm was smaller than 64. This number corresponds to the sample size required to detect medium effects ($g = 0.5$) with 80% statistical power. Finally, we rated likely potential publication bias when the corresponding test when the Egger test p-value <0.1 and the funnel plot confirmed the asymmetry.

To summarize and grade the quality of the evidence, we first gave each intervention four pluses, and subsequently, we subtracted one plus if there were serious limitations, one plus if there was serious inconsistency, two pluses if there was very serious inconsistency, one plus if there was serious imprecision, two pluses if there was very serious imprecision, and one plus if there was likely publication bias. We did not plan to five upgrades. Finally, if the final score was lower than one plus, we gave the intervention a final score of one plus.

We would have considered interventions with four pluses to have high-quality evidence (i.e., we would be very confident that the true effect is approximately the effect reported here). We considered interventions with three pluses to have moderate-quality evidence (the true effect is likely to be like the effect reported here,

but there is a possibility that it is substantially different). We considered interventions with two pluses to have low-quality evidence (the effect may differ substantially from the effect reported here). Finally, we considered interventions with one plus to have very low-quality evidence (the true effect is likely substantially different from the effect reported here).

Separate meta-analyses for specific substance–drug–outcomes

We also conducted a separate meta-analysis for each combination of a specific substance (e.g., alcohol), adjuvant drug (e.g., valproate), and outcome (e.g., change in a particular scale score). These small meta-analyses commonly included only one or two studies, which may be considered too few. Still, we conducted them with only a descriptive purpose. We did not aim to gather statistical power or to investigate between-study heterogeneity.

For binary specific outcomes (e.g., nicotine abstinence at 4 weeks), we conducted standard random-effects meta-analyses to derive the pooled odds ratio (OR) between the two groups and its *p*-value, along with the Hedges' *g* equivalent to the OR, as obtained using a standard formula.[43]

For numeric specific outcomes (e.g., YMRS), we conducted the meta-analyses with the MetaNSUE method, which imputes many times the non-statistically significant unreported effects (NSUEs) based on maximum likelihood estimates, conducts multiple standard random-effects meta-analyses and then pools their results using Rubin's rules.[44] The reason to use MetaNSUE is that some studies reported non-statistically significant differences in some outcomes but did not report other information required for a standard meta-analysis.[45–48] Excluding these studies with negative findings would bias the meta-analyses toward statistical significance, while including these studies assuming null effect sizes would bias the meta-analyses in the opposite direction. Conversely, MetaNSUE can include these studies unbiasedly.[49] We calculated the small sample-corrected standardized mean difference (Hedges' *g*) between the two groups and its *p*-value, along with the OR equivalent to the Hedges' *g*, as obtained using a standard formula.[43]

We conducted all analyses using R version 4.1.1 with the "curve2ipd" function and the "meta" and "metansue" packages.[44,49,50]

Results

The search yielded a total of 278 studies (see PRISMA flow diagram in the Supplement), of which 104 were excluded for being duplicates and 163 after title and abstract screening, leading to 11 studies for eligibility. From the eligible studies, we excluded two studies that had <75% of patients diagnosed with BD,[51,52] two that combined different SUDs,[53,54] and one that did not compare the treatment group against placebo[55] (see PRISMA flow diagram and reasons of exclusion in the Supplement). Together with the 9 studies included in a previous version, we included a total of 15 peer-reviewed studies (Table 1: 9 alcohol; 3 cocaine; 2 nicotine; 1 cannabis) comprising 628 patients allocated to treatment and 622 to placebo (funding sources for every studies can be found in the Supplement). The mean age ranged between 36 and 46 years (overall mean = 42 years). The proportion of females ranged between 25% and 68% except for one study[56] with only 5% females (overall percentage of females = 41%).

Twelve studies only included patients with bipolar disorder. Of the other three, one included 91% bipolar disorder/6% schizoaffective disorder/3% major depression,[57] another 86% bipolar disorder/14% schizoaffective disorder,[46] and the last 73% bipolar disorder/10% schizoaffective disorder/17% schizophrenia.[56] Overall, 80% of patients had a diagnosis of bipolar disorder type I, 18% bipolar disorder type II or not otherwise specified, 1% schizoaffective disorder, and 1% other disorders. Regarding the affective status, 16% patients had a manic or mixed episode, 71% a depressive episode, and 13% were in euthymia.

The adjuvant drugs used were acamprosate (for alcohol), bupropion (for nicotine), citicoline (for cocaine), disulfiram (for alcohol), gabapentin (for cannabis), lamotrigine (for cocaine), naltrexone (for alcohol), ondansetron (for alcohol), quetiapine (for alcohol), topiramate (for alcohol), valproate (for alcohol), and varenicline (for nicotine). One study[56] used naltrexone and disulfiram separately and combined. The duration of the follow-up ranged between 2 and 24 weeks (average 12 weeks).

For one study that reported the *p*-value of the survival analysis log-rank test comparing the time to relapse to sustained heavy drinking,[58] we estimated the equivalent numbers of heavy drinking relapses. Specifically, we derived the individual times from the Kaplan-Meier plot as detailed in.[59] We then conducted a Cox proportional hazards regression that yielded a 0.54 hazard ratio and assumed that the relative risk would be similar. Finally, we imputed the number of heavy drinking relapses in each group that matched that relative risk and the *p*-value reported in the paper.

Also, for one study that reported a statistically significant difference in an outcome but did not report other information required for our meta-analysis,[47] we conservatively assumed $p = 0.05$.

As shown in Fig. 1 (and detailed in the Supplement), the studies had a few limitations. Specifically, three studies presented some concerns in the randomization; two showed blindness' issues (patients were aware of their assigned intervention); there was potential bias due to missing data in three studies; the measurement of the outcome was uncertain in one study.

As detailed in the Supplement, most studies' exclusion criteria would have excluded a few patients (e.g., active suicidal or homicidal ideation). However, eight studies investigated a special population group with mild severity (e.g., absence of severe mood symptoms and psychiatric comorbidity).

General outcomes

Table 2 shows the GRADE evidence profile for efficacy and safety of adjuvant drugs for co-occurring bipolar and substance use disorder. There was low-quality evidence that adjuvant drugs improve illness severity ($g = -0.25$) and do not improve anxiety, manic symptoms, or substance craving.

For the remaining outcomes, the evidence had very low quality: a potential substance use reduction ($g = -0.23$) and abstinence increase ($g = 0.21$), and no effects on depressive symptoms, gamma-GT, adherence, or adverse events. We did not conduct meta-analyses of memory, functioning, and quality of life because they were reported in less than three studies.

We show the forest and funnel plots of all meta-analyses in the Supplement. Note that the blurred points in the funnel plots correspond to the effect sizes imputed by the meta-analysis.

Specific substance–drug–outcomes

In the following, we summarize the findings that reached statistical significance before correcting for multiple comparisons (none kept the statistical significance after the correction). We report these findings in Table 3, but we also provide a complete list of the results (i.e., including non-statistically significant associations) in the Supplement.

For alcohol, valproate showed a medium effect size in reducing the number of cumulative heavy drinking days (Hedges' $g = 0.6$), increasing the number of non-heavy drinking days per week ($g = 0.7$), reducing the levels of gamma-GT ($g = -0.6$), and increasing the time to relapse (OR = 3.1). Acamprosate showed a large

Table 1
Studies included in the meta-analysis of the efficacy and safety of adjuvant drugs for co-occurring bipolar and substance use disorder.

Study	Age	Fem.	Diagnosis				Mania	Depr.	Euth.	Substance	Study setting	Dose	Comparison (sample sizes)	Outcome	Weeks
			Bipolar disorder			Other psychiatric diagnosis									
			Total	I	II/NOS										
Brown 2007	41.4	48%	86%	92%	8%	14% SA	39%	50%	11%	Cocaine	Outpatients	500–2000 mg/d	Citicoline (23) vs. placebo (21)	Abstinence (negative cocaine urine screen) Adherence (pill counts, study completion, weeks in study) Adverse events (SSS) Declarative memory (RAVLT total, delayed recall, alternative word list) Depression (IDS-SR) Mania (YMRS)	12
Brown 2008	38.4	37%	100%	49%	51%	–	8%	82%	10%	Alcohol	Community	25–300 mg/d	Quetiapine (52) vs. placebo (50)	Abstinence (non-drinking days per week) Depression (HRSD-17) Mania (YMRS) Substance craving (PACS) Substance use (heavy drinking days per week)	12
Brown 2009	41.1	49%	100%	72%	28%	–	16%	84%	–	Alcohol	Outpatients	50 mg/d	Naltrexone (23) vs. placebo (27)	Abstinence (drinking days per week = 0, heavy drinking days per week = 0) Depression (HRSD-17) Gamma-GT Mania (YMRS) Substance craving (PACS) Substance use (drinks per drinking day)	12
Brown 2012	44.3	40%	100%	53%	47%	–	10%	90%	–	Cocaine	Outpatients	25–200 mg/d	Lamotrigine (55) vs. placebo (57)	Abstinence (proportion negative cocaine urine screen) Adherence (pill counts) Depression (HRSD-17, QIDS-SR) Mania (YMRS) Substance craving (CCQ) Substance use (money spent on cocaine)	10
Brown 2014	41.5	41%	100%	100%	0%	–	11%	89%	–	Alcohol	Outpatients	50–600 mg/QHS	Quetiapine (44) vs. placebo (44)	Abstinence (drinking days per week = 0, heavy drinking days per week = 0) Adverse events (SSS, glucose, cholesterol, weight, AIMS, SAS, BARS) Depression (HRSD-17, IDS-SR) Gamma-GT Mania (YMRS) Substance craving (PACS) Substance use (drinks per drinking day)	6–12

Table 1
(*Continued*)

Study	Age	Fem.	Diagnosis				Mania	Depr.	Euth.	Substance	Study setting	Dose	Comparison (sample sizes)	Outcome	Weeks
			Bipolar disorder			Other psychiatric diagnosis									
			Total	I	II/NOS										
Brown 2015	42.4	33%	100%	100%	–	–	2%	98%	–	Cocaine	Outpatients	500–2000 mg/d	Citicoline (61) vs. placebo (61)	Abstinence (negative cocaine urine screen) Adherence (opened bottles, study completion) Adverse events (number) Depression (HRSD-17, IDS-SR) Mania (YMRS) Substance craving (CCQ)	12
Brown 2021	44.9	40%	91%	47%	53%	6% SA 3% MDD				Alcohol	Outpatients	1–2 mg/d	Ondansetron (35) vs. placebo (35)	Abstinence (drinking days per week = 0, heavy drinking days per week = 0) Adherence (study completion) Adverse events (SSS) Depression (HRSD-17, IDS-SR) Gamma-GT Mania (YMRS) Substance craving (PACS) Substance use (drinks per drinking day)	12
Chengappa 2014	45.9	68%	100%	82%	18%	–	–	–	100%	Nicotine	Outpatients	0.5–2 mg/d	Varenicline (31) vs. placebo (29)	Abstinence (nicotine abstinence at 6 months, nicotine abstinence weeks $\geq$1, nicotine abstinence weeks $\geq$4) Adherence (study completion) Adverse events (depressed mood, abnormal dreams) Anxiety (HAM-A) Depression (MADRS) Mania (YMRS) Severity (CGI-severity) Substance use (increase in cigarette usage, increase of CO levels)	12–24
Heffner 2019	45.2	58%	100%	80%	20%	–				Nicotine	Outpatients	2 mg varenicline 300 mg bupropion	Varenicline (75) vs. placebo (59) Bupropion (86) vs. placebo (59)	Abstinence (nicotine abstinence at 3 and 6 months, nicotine abstinence weeks $\geq$4) Adverse events (NPSAEs) Anxiety (HADS-A) Depression (HADS-D)	12–24
Petrakis 2006	45.6	5%	73%			17% Sch 10% SA				Alcohol	Outpatients	50 mg naltrexone 250 mg disulfiram	Naltrexone (17) or disulfiram (17) or naltrexone + disulfiram (17) vs. placebo (15)	Abstinence (cumulative non-drinking days, maximum consecutive non-drinking days) Substance craving (OCDS) Substance use (cumulative heavy drinking days)	12

Prisciandaro 2021	37.6	50%	100%	55%	45%	–				Cannabis	Community	1200 mg/d	Gabapentin (11) vs. placebo (38)	Adherence (pill counts) Adverse events (number)	2
Salloum 2005	37.5	25%	100%	100%	–	–		79%	21% –	Alcohol	Community	750 mg/d	Valproate (27) vs. placebo (25)	Abstinence (heavy drinking days = 0, no heavy drinking relapse) Depression (HRSD-25, HDRS-25 >7) Functioning (GAF) Gamma-GT Mania (BRMS, BRMS >7) Substance use (drinks per heavy drinking day, cumulative heavy drinking days, heavy drinking days per week)	24
Stedman 2010	38.6	37%	100%	100%	–	–				Alcohol	Outpatients	300–800 mg/d	Quetiapine (159) vs. placebo (169)	Abstinence (non-drinking days per week) Anxiety (HAM-A) Depression (MADRS) Functioning (minus SDS) Gamma-GT Mania (YMRS) Quality of life (Q-LES-Q) Severity (CGI-severity) Substance craving (BSCS, OCDS) Substance use (cigarettes per day, drinks per day, heavy drinking days per week)	12
Sylvia 2016	43.6	42%	100%	–	–					Alcohol	Outpatients	150 mg/d	Topiramate (5) vs. placebo (7)	Abstinence (drinking days = 0, heavy drinking days = 0) Adherence (study completion) Adverse events (FISER/GRSEB) Depression (HRSD-25) Mania (YMRS) Quality of life (Q-LES-Q)	12
Tolliver 2012	42.3	37%	100%	43%	57%	–				Alcohol	Inpatients, outpatients and community	1998 mg/d	Acamprosate (14) vs. placebo (16)	Abstinence (non-drinking days per week) Depression (MADRS) Gamma-GT Mania (YMRS) Severity (CGI-mood, CGI-substance) Substance craving (OCDS) Substance use (heavy drinking days per week)	8

AIMS: Abnormal Involuntary Movement Scale (Guy, 1976); BARS: Barnes Akathisia Scale (Barnes, 1989); BSCS: Brief Substance Craving Scale (Somoza, Dyrenforth et al., 1995); BRMS: Bech-Rafaelsen Mania Scale (Bech, Bolwig et al., 1979); CCQ: Cocaine Craving Questionnaire (Tiffany, Singleton et al., 1993); CGI: Clinical Global Impressions Scale (Guy, 1976); Depr.: depressed; Euth.: euthymic; FISER/GRSEB: Frequency of Side Effects Ratings/Global Rating of Side Effects Burden (WISNIEWSKI, 2006); GAF: Global Assessment of Functioning (American Psychiatric Association, 2000); HAM-A: Hamilton Anxiety Rating Scale (Hamilton, 1959); HRSD-17: 17-item Hamilton Rating Scale for Depression (Hamilton, 1960); HRSD-25: 25-item Hamilton Rating Scale for Depression (Thase, Hersen et al., 1983); IDS-C: Inventory of Depressive Symptomatology – Clinician rating (Rush, Gullion et al., 1996); IDS-SR: Inventory of Depressive Symptomatology – Self-Report (Rush, Gullion et al., 1996); MADRS: Montgomery-Asberg Depression Rating Scale (Montgomery and Asberg, 1979); MDD: major depression disorder; NOS: not otherwise specified; NPSAEs: neuropsychiatric adverse events; OCDS: Obsessive Compulsive Drinking and Abstinence Scale (Anton, Moak et al., 1996); PACS: Penn Alcohol Craving Scale (Flannery, Volpicelli et al., 1999); QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report (Rush, Trivedi et al., 2003); Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire (Endicott, Nee et al., 1993); RAVLT: Rey Auditory Verbal Learning Test (Schmidt, 1996); SA: schizoaffective disorder; SAS: Simpson-Angus Scale (Simpson and Angus, 1970); Sch: schizophrenia; SDS: Sheehan Disability Scale (Sheehan, 1983); SSS: Psychobiology of Recovery from Depression-III Somatic Symptom Scale (Thase, Fava et al., 1996); YMRS: Young Mania Rating Scale (Young, Biggs et al., 1978).

Table 2
GRADE evidence profile for efficacy and safety of adjuvant drugs for co-occurring bipolar and substance use disorder.

Outcome (N of RCT)	Quality assessment					Summary of findings		Quality
	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	N of participants	Hedges' *g* (95% CI)	
Abstinence (14)	Serious limitations (some randomization concerns, blinding issues, and potential missing data bias)	No serious inconsistency (I^2 = 33%)	Serious indirectness (patients with mild severity)	No serious imprecision	Suspected (p = 0.027)	582 vs. 565	0.21 (0.04, 0.38) (p = 0.016)	⊕ (very low)
Adherence (7)	Serious limitations (some randomization concerns, blinding issues, and uncertain outcome measurement)	No serious inconsistency (I^2 = 0%)	Serious indirectness (patients with mild severity)	Serious imprecision (small overall sample size)	Undetected (p = 0.491)	221 vs. 221	0.04 (−0.18, 0.26) (p = 0.728)	⊕ (very low)
Adverse events (8)	Serious limitations (some randomization concerns, blinding issues, potential missing data bias, and uncertain outcome measurement)	Serious inconsistency (I^2 = 73% with 3/8 contradictory findings)	Serious indirectness (patients with mild severity)	Serious imprecision (small overall sample size)	Undetected (p = 0.439)	266 vs. 235	−0.09 (−0.46, 0.28) (p = 0.633)	⊕ (very low)
Anxiety (3)	No serious limitations	No serious inconsistency (I^2 = 0%)	Serious indirectness (patients with mild severity)	Serious imprecision (small overall sample size)	Undetected (p = 0.579)	215 vs. 193	0.00 (−0.23, 0.22) (p = 0.977)	⊕⊕ (low)
Depression (13)	Serious limitations (some randomization concerns and potential missing data bias)	No serious inconsistency (I^2 = 0%)	Serious indirectness (patients with mild severity)	No serious imprecision	Suspected (p = 0.067)	600 vs. 596	−0.11 (−0.24, 0.02) (p = 0.112)	⊕ (very low)
Gamma-GT (6)	Serious limitations (some randomization concerns and potential missing data bias)	Serious inconsistency (I^2 = 51% with 2/6 contradictory findings)	Serious indirectness (patients with mild severity)	Serious imprecision (small overall sample size)	Undetected (p = 0.731)	264 vs. 266	−0.04 (−0.34, 0.27) (p = 0.817)	⊕ (very low)
Illness severity (3)	No serious limitations	No serious inconsistency (I^2 = 0%)	Serious indirectness (patients with mild severity)	Serious imprecision (small overall sample size)	Undetected (p = 0.334)	202 vs. 214	−0.25 (−0.44, −0.06) (p = 0.011)	⊕⊕ (low)
Mania (12)	Serious limitations (some randomization concerns and potential missing data bias)	No serious inconsistency (I^2 = 0%)	Serious indirectness (patients with mild severity)	No serious imprecision	Undetected (p = 0.965)	525 vs. 537	−0.12 (−0.12, 0.02) (p = 0.083)	⊕⊕ (low)
Substance craving (9)	Serious limitations (some randomization concerns, blinding issues, and potential missing data bias)	No serious inconsistency (I^2 = 16%)	Serious indirectness (patients with mild severity)	No serious imprecision	Undetected (p = 0.103)	452 vs. 462	0.00 (−0.20, 0.20) (p = 0.978)	⊕⊕ (low)
Substance use (9)	Serious limitations (some randomization concerns, blinding issues, and potential missing data bias)	No serious inconsistency (I^2 = 30%)	Serious indirectness (patients with mild severity)	Serious imprecision (small overall sample size)	Suspected (p = 0.099)	379 vs. 385	−0.23 (−0.44, −0.02) (p = 0.029)	⊕ (very low)

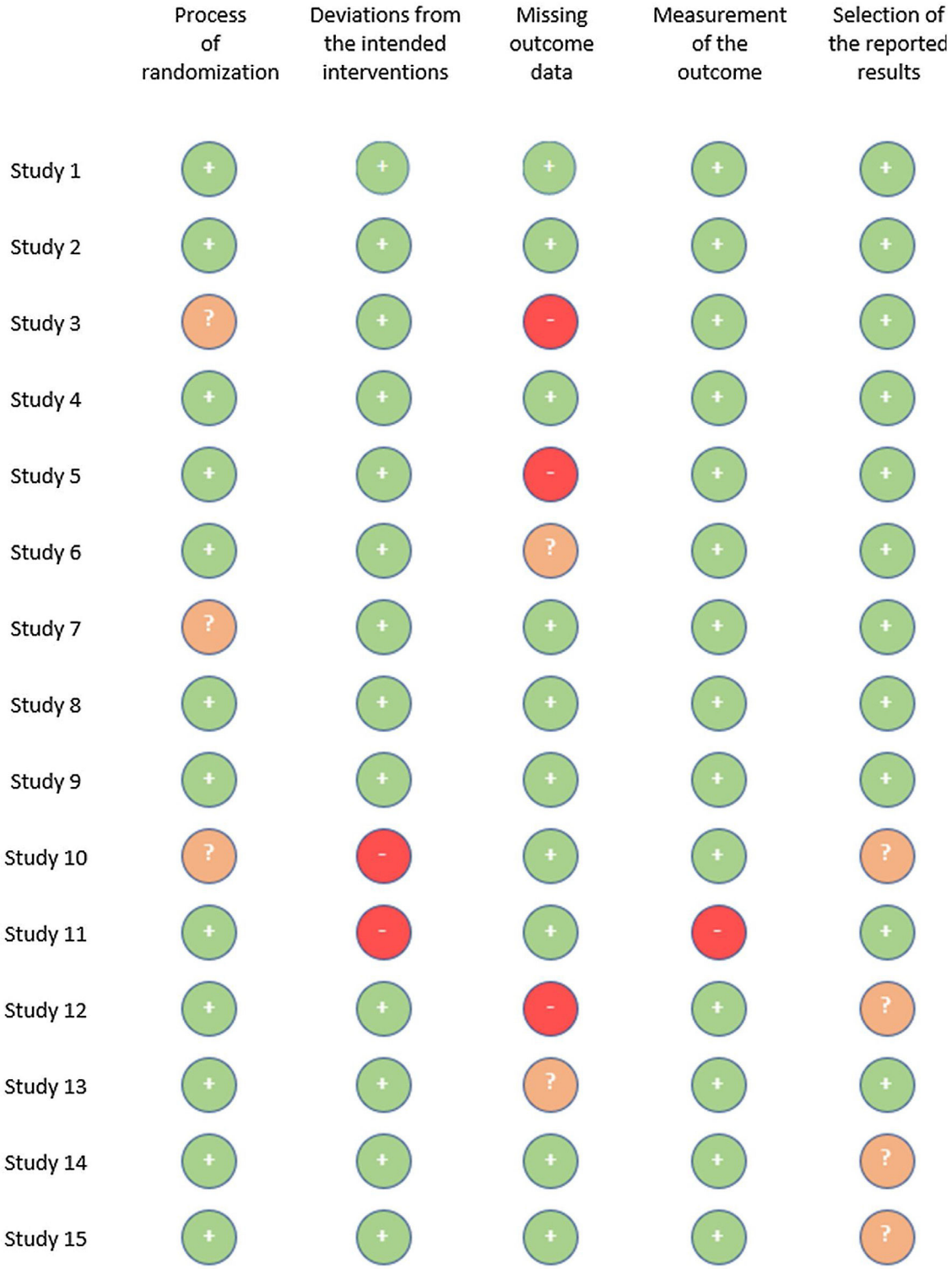

Figure 1. Risk of bias assessment of the included studies investigating efficacy and safety of adjuvant drugs for co-occurring bipolar and substance use disorder.

effect size in decreasing the substance use severity (CGI-substance $g = -0.8$). Naltrexone showed a large effect size in reducing alcohol craving (PACS $g = -1.0$), increasing the probability of abstinence (OR = 6.2), increasing the number of cumulative non-drinking days ($g = 0.8$), and reducing the number of cumulative heavy drinking days ($g = -0.8$), and a medium effect size in reducing the number of drinks per drinking day ($g = -0.6$) and manic symptoms (YMRS $g = -0.6$). The combination of naltrexone and disulfiram showed a large effect size in increasing the maximum number of consecutive non-drinking days ($g = 0.8$). Finally, quetiapine only showed adverse effects with a medium effect size: increased probability of akathisia (BARS) (OR = 2.8) and increased weight (OR = 2.9).

For cocaine, citicoline showed a large effect size in increasing declarative memory (RAVLT alternative word list $g = 0.86$). In addition, citicoline showed increased study adherence (OR = 2) and decreased adverse events (SSS score $g = -1.0$). Finally, lamotrigine

Table 3
Statistically significant specific substance use disorder × adjuvant drug × outcomes (see complete results in the t).

Substance	Drug and comparison (sample sizes)	Outcome	*k*	Hedges' *g*e	OR	*p*	I^2
Alcohol	Valproate (27) vs. placebo (25)	Non-heavy drinking days per week	1	0.67 (0.11, 1.23)	3.37	0.018	–
		Cumulative heavy drinking days	1	−0.56 (−1.12, −0.01)	0.36	0.046	–
		No heavy drinking relapse	1	0.63 (0.00, 1.27)	3.15	0.048	–
		Gamma-GT	1	−0.58 (−1.14, −0.02)	0.35	0.039	–
	Quetiapine (30) vs. placebo (25)	BARS at 6 weeks (adverse events)	1	0.56 (0.02, 1.10)	2.77	0.040	–
		Weight at 6 weeks (adverse events)	1	0.60 (0.05, 1.14)	2.94	0.030	–
	Acamprosate (14) vs. placebo (16)	CGI-substance (severity)	1	−0.78 (−1.53, −0.03)	0.24	0.037	–
	Naltrexone (15–23) vs. placebo (14–27)	YMRS (mania)	1	−0.61 (−1.22, 0.00)	0.33	0.049	–
		Drinking days per week = 0	1	1.01 (0.05, 1.98)	6.28	0.033	–
		Drinks per drinking day	1	−0.61 (−1.22, 0.00)	0.33	0.049	–
		PACS (substance craving)	1	−0.98 (−1.62, −0.34)	0.17	0.002	–
		Cumulative non-drinking days	1	0.83 (0.07, 1.60)	4.54	0.029	–
		Cumulative heavy drinking days	1	−0.75 (−1.47, −0.03)	0.26	0.038	–
		Maximum consecutive non-drinking days	1	0.77 (0.05, 1.49)	4.03	0.034	–
Cocaine	Citicoline (23–84) vs. placebo (21–82)	Study completion	2	0.37 (0.00, 0.74)	1.95	0.047	0%
		SSS (adverse events)	1	−1.05 (−1.68, −0.41)	0.15	0.001	–
		RAVLT alternative word list	1	0.86 (0.24, 1.48)	4.74	0.006	–
	Lamotrigine (55) vs. placebo (57)	Money spent on cocaine	1	−0.37 (−0.75, 0.00)	0.51	0.050	–
Nicotine	Varenicline (31–106) vs. placebo (29–88)	Nicotine abstinence weeks ≥1	1	1.16 (0.37, 1.94)	8.13	0.003	–
		Nicotine abstinence weeks ≥4	2	0.66 (0.08, 1.25)	3.08	0.040	0%
		Nicotine abstinence at 3 months	1	0.59 (0.07, 1.11)	2.93	0.025	–
		Abnormal dreams (adverse event)	1	0.62 (0.02, 1.22)	3.08	0.040	–

CGI: Clinical Global Impressions Scale (Guy, 1976); Depr.: depressed; Euth.: euthymic; NOS: not otherwise specified; OR: odds ratio; PACS: Penn Alcohol Craving Scale (Flannery, Volpicelli et al., 1999); RAVLT: Rey Auditory Verbal Learning Test (Schmidt, 1996); SSS: Psychobiology of Recovery from Depression-III Somatic Symptom Scale (Thase, Fava et al., 1996); YMRS: Young Mania Rating Scale (Young, Biggs et al., 1978). We calculated Hedges' *g* for continuous variables and OR for dichotomous variables, but we provide the Hedges' *g*- or OR-equivalents to allow comparisons between outcomes. Note that some outcomes have borderline statistical significance (e.g., confidence intervals including zero or *p*-values around 0.05).

showed a marginally statistically significant reduction in the money spent on cocaine ($g = -0.37$).

Finally, for nicotine, varenicline showed a large effect size in increasing the probability of nicotine abstinence longer than one week (OR = 8.1), four weeks (OR = 3.3), and three months (OR = 2.9). However, it also showed a medium effect size in increasing the probability of abnormal dreams (OR = 2.9).

Discussion

This is the first meta-analysis to investigate the efficacy of adjuvant drugs in improving affective symptoms and substance consumption in patients with a dual diagnosis of BD and SUD. We included 15 RCTs evaluating the efficacy of twelve drugs in patients with alcohol, cocaine, nicotine, or cannabis abuse. The main finding was that these drugs seem to slightly ameliorate illness severity (low-quality evidence, Hedges' $g = -0.25$, $p = 0.011$) and may decrease substance use (very low-quality evidence, Hedges' $g = -0.23$, $p = 0.029$) and increased abstinence (very low-quality evidence, Hedges' $g = 0.21$, $p = 0.016$), without increasing adverse events (very low-quality evidence, $p = 0.44$). Therefore, our study suggests that using adjuvant drugs may help improve the prognosis of patients with co-occurring BD and SUD. These drugs probably reduce substance consumption, likely leading to the amelioration of illness severity. Indeed, previous studies have reported that patients with co-occurring BD and SUD may have similar clinical and functional outcomes to never users after substance withdrawal.[16]

The studies investigated the effects of different adjuvant drugs in various SUDs using varying scales to measure affective symptoms and consumption. To provide insights into the specific outcomes of specific adjuvant drugs for specific substances, we conducted separate meta-analyses for specific substance–drug–outcomes. Given the paucity of studies in each of these separate meta-analyses, we recommend that the reader considers the following results with caution.

In patients with co-occurring BD and alcohol abuse, valproate, acamprosate, and naltrexone reduced consumption. The study investigating the effects of valproate also showed an increase in abstinence, the time to relapse, and a reduction in the levels of gamma-GT.[58] Similarly, the two studies investigating the effects of naltrexone showed an increase in abstinence and a reduction in alcohol craving and manic symptoms.[56,60] The increase in abstinence was also observed when combining naltrexone and disulfiram. Still, this combination failed to statistically significantly decrease substance use or craving. These results suggest that naltrexone alone may have better outcomes. Finally, disulfiram, ondansetron, quetiapine, and topiramate failed to show any statistically significant improvement, and quetiapine was associated with adverse events (akathisia and increased weight).[45,56,57,60–62]

In patients with co-occurring BD and cocaine addiction, citicoline improved declarative memory, decreased adverse effects (somatic symptoms such as stomach problems), and increased study adherence.[46,63] On the other hand, lamotrigine showed a marginally statistically significant reduction in consumption.[47]

In patients with co-occurring BD and nicotine addiction, varenicline showed an improvement in substance abstinence after one week of treatment, which remained significant until 3 months.[6,48] Varenicline also showed an increase in the frequency of abnormal dreams as a side-effect. Conversely, bupropion failed to show any statistically significant effects.[64]

We would like to highlight some limitations of our review. First, we included studies investigating the effects of different drugs in patients with various SUDs using different scales. Second, the number of studies investigating specific substance–drug–outcomes was tiny. In addition, we could not correct for multiple testing due to the large number of separate meta-analyses, for which a part of the results may likely be false positives. Given the latter two limitations, we recommend the reader consider the results of these separate meta-analyses with caution. Finally, in the first inclusion criterion. we defined that samples had to have ≥75% patients diagnosed with bipolar/schizoaffective disorder, but we acknowledge we could have used another cut-off, e.g., 50% or 80%. However,

we would have ended up including the same studies because the observed percentage of bipolar/schizoaffective in the included studies was ≥83%, while ≤28% or not reported in the studies excluded for this reason. To sum up, the use of adjuvant drugs in patients with a dual diagnosis of BD and any SUD seems to improve the severity, likely via decreased consumption and increased abstinence. However, the evidence for severity improvement is low quality, and the evidence for substance use and abstinence is very low quality; we recommend that the reader consider these results with caution. Even weaker is the evidence for the effects of individual drugs. Still, for the sake of reporting, we must stay that, to date, the drugs showing better outcomes are valproate and naltrexone for alcohol, citicoline for cocaine, and varenicline for nicotine. Taking the lack of high-quality evidence together, we strongly recommend the scientific community pursue the investigation of adjuvant drugs for this population, avoiding the limitations of previous studies. Increasing high-quality RCTs would allow improving the evidence needed to establish clinic recommendations that would benefit the patients.

Data availability

The data collection templates can be found in the Supplement.

Competing interests

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rpsm.2023.01.005.

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