Clinical practice guideline on pharmacological and psychological management of adult patients with bipolar disorder and comorbid substance use

Guía de práctica clínica para el tratamiento farmacológico y psicológico de los pacientes adultos con trastorno bipolar y un diagnóstico comórbido de trastorno por uso de sustancias

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Abstract

This review synthesizes the pharmacological and psychosocial interventions that have been conducted in comorbid bipolar disorder (BD) and substance use disorders (SUDs) while also providing clinical recommendations about which intervention elements are helpful for addressing substance use versus mood symptoms in patients with these co-occurring conditions. The best evidence from randomized controlled trials was used to evaluate treatment options. The strength of recommendations was described using the GRADE approach. Very few of the randomized trials performed so far have provided consistent evidence for the management of both mood symptoms and substance use in patients with a BD. No clinical trials are available for bipolar patients using cannabis. Some treatments have shown benefit for mood symptoms without benefits for alcohol or illicit substance use. Our results suggest that 1) we can (weakly) recommend the use of adjuvant valproate or naltrexone to improve symptoms of alcohol use disorder; 2) Lamotrigine add-on therapy seems to reduce cocaine-related symptoms and is therefore recommended (moderate strength); and 3) Varenicline is (weakly) recommended to improve nicotine abstinence. Integrated group therapy is the most-well validated and efficacious approach on substance use outcomes if substance use is targeted in an initial treatment phase.
Key words: Bipolar disorder; substance use; alcohol; cocaine; methamphetamine; psychostimulant; nicotine.

Resumen

Esta revisión resume las intervenciones farmacológicos y psicosociales que se han realizado en trastorno bipolar (TB) y un diagnóstico comórbido de trastorno por uso de sustancias (TUS) y además proporciona recomendaciones clínicas respecto de cuáles elementos de intervención son útiles para hacer frente a los síntomas del uso de sustancias versus los síntomas de estado de ánimo en pacientes con estas afecciones concurrentes. Se utilizó la mejor evidencia de ensayos controlados aleatorizados para evaluar las opciones de tratamiento. La fuerza de las recomendaciones se describió mediante el enfoque GRADE. Muy pocos de los ensayos aleatorizados realizados hasta la fecha han proporcionado evidencia consistente para el manejo tanto de los síntomas de estado de ánimo como del uso de sustancias en pacientes con TB. No hay disponibilidad de ensayos clínicos para pacientes con TB que utilizan el cannabis. Algunos tratamientos han mostrado beneficios para los síntomas de estado de ánimo sin beneficios para el uso de alcohol o sustancias ilícitas. Nuestros resultados sugieren que 1) podemos (débilmente) recomendar el uso de ácido valproico o naltrexona adyuvante para aliviar los síntomas del trastorno por consumo de alcohol; 2) el tratamiento complementario con lamotrigina parece reducir los síntomas relacionados con la cocaína y, por tanto, es recomendable (fuerza moderada); y 3) la vareniclina es recomendable (débilmente) para mejorar la abstinencia de la nicotina. La terapia grupal integrada es el enfoque con más validación y eficacia sobre los resultados en el uso de sustancias cuando este uso es abordado durante la fase inicial de tratamiento.
Palabras clave: Trastorno bipolar; uso de sustancias; alcohol; cocaína; metanfetaminas; psicoestimulantes; nicotina.

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The prevalence of bipolar disorder (BD) I and II is 1.1% and 1.2% respectively (Clemente et al., 2015). In these patients, drugs of abuse consumption or dependence are frequent comorbidities. According to the 2002 National Epidemiologic Survey on Alcohol and Related Conditions, the lifetime prevalence of comorbid alcohol use disorder and substance use disorder (SUD) in patients with bipolar I disorder was 58% and 38%, respectively (Grant et al., 2005). In the Epidemiological Catchment Area (ECA) study in which the lifetime prevalence of concurrent mental illness and SUD in 20,291 subjects was examined, history of SUD was present in 60.7% of patients with BD I and in 48% of those with BD II (Regier et al., 1990). Using data of the ECA survey, psychiatric diagnosis of mania was more likely to occur in alcohol abusers than in non-alcohol abusers (Odds Ratio, OR, 6.2) (Helzer & Pryzbeck, 1988). Tobacco consumption is the main preventable factor of mortality in smokers with BD, and any possible solutions are often blocked by prejudices over desire, and the possibilities and risks for these patients in giving up tobacco consumption (González-Pinto et al., 1998; Sarramea et al., 2019).

There is a large body of evidence indicating the clinical deleterious effects of comorbid SUD on BD and vice versa, including a high rate of relapse, slower recovery from episodes (González-Pinto et al., 2010), high impulsivity, poor adherence and response to treatment, higher risk for mixed episodes and suicide (González-Pinto et al., 2011a) , higher need of hospitalization, poorer functioning, and higher neuropsychological impact (Balanzá-Martínez, Crespo-Facorro, González-Pinto & Vieta, 2015; Colom, Vieta, Daban, Pacchiarotti & Sánchez-Moreno, 2006; Merikangas et al., 2007; Oquendo et al., 2010). In a naturalistic sample of BD I patients in which 10-year outcomes were examined, mixed-episode patients with alcohol or other substance use had an increased risk of hospitalization and suicidality compared with the non-mixed group (González-Pinto et al., 2010).

Given its prevalence and impact on public health, the comorbidity of BD and substance use disorders is one of the most relevant of dual diagnoses (Arias et al., 2017). So far, there is little information of the efficacy and safety of psychoactive drugs in dual diagnosis bipolar patients obtained from randomized controlled trials (RCTs) due to methodological difficulties, clinical complexity of the disorders, multiple associated variables and comorbidities. In this context, there is an increasing need for evidence-based recommendations for clinical decision-making in BD and co-occurring SUD.

Although several reviews and meta-analysis have reported outcomes of interventions in patients with BD and co-occurring SUD (Gold et al., 2018; Messer, Lammers, Müller-Siecheneder, Schmidt & Latifi, 2017; Post & Kalivas, 2013; Vornik & Brown, 2006; Yatham et al., 2018), to our knowledge, a clinical practice guideline with recommendations on the pharmacological and psychological management of these patients is lacking. Therefore, the aim of the present guideline is to provide healthcare professionals involved in the care of patients with dual diagnosis with clinical recommendations based on scientific evidence to assist in the decision-making process of their clinical practice.

Methods

Formulation of clinical questions

In accordance with evidence-based medicine principles, we used the 'PICO' structure (Patient-Intervention-Comparison-Outcomes [Oxman, Schünemann & Fretheim, 2006; Schünemann et al., 2008]) to formulate the following review question: "*What is the effect of a pharmacological and/or psychological intervention for the treatment of adult patients with a BD and a SUD?*". Patients older than 18 years diagnosed with a BD and a SUD (including cannabis, cocaine, alcohol and/or nicotine) were the target population of this clinical guideline. Opioid use disorder was not included because no systematic reviews with or without meta-analysis or randomized clinical trials were found.

Bibliographic search

We performed a comprehensive literature search in MEDLINE, PsycINFO, Embase, Scopus, Web of Science, Cochrane Library and Pubmed until May 2018. The following search terms were used:

- ((((“Bipolar Disorder”[Mesh] OR bipolar disorder*)) AND (substance abuse OR substance dependence OR substance use OR comorbidity OR misuse OR co-occurr* OR coexist* OR concurren* OR dual diagnosis OR dual disorder OR dual pathology OR “Diagnosis, Dual (Psychiatry)”[Mesh])) AND (“Alcohol Drinking”[Mesh] OR “Drinking Behavior”[Mesh] OR “alcohol use” OR “alcohol abuse” OR “nicotine use” OR “Marijuana Abuse”[Mesh] OR “Marijuana Smoking”[Mesh] OR “cannabis use” OR “Cocaine-Related Disorders”[Mesh] OR “cocaine use” OR “cocaine abuse”)) AND (“sertindole” [Supplementary Concept] OR sertindole OR “sultopride” [Supplementary Concept] OR amisulpride OR “zotepine” [Supplementary Concept] OR zotepine OR Asenapine OR “Asenapine” [Supplementary Concept] OR aripripazol OR “paliperidone palmitate” [Supplementary Concept] OR paliperidone OR “quetiapine” [Supplementary Concept] OR quetiapine OR “ziprasidone” [Supplementary Concept] OR ziprasidone OR “olanzapine” [Supplementary Concept] OR “olanzapine-fluoxetine combination” [Supplementary Concept] OR olanzapine OR “Risperidone”[Mesh] OR risperidone).

Limits: Review, Systematic Reviews, Meta-Analysis, Clinical Trial; Young Adult: 19-44 years; Middle Aged: 45-64 years.

- ((((“Bipolar Disorder”[Mesh] OR bipolar disorder*)) AND (substance abuse OR substance dependence OR substance use OR comorbidity OR misuse OR co-occurr* OR coexist* OR concurren* OR dual diagnosis OR dual disorder OR dual pathology OR “Diagnosis, Dual (Psychiatry)”[Mesh])) AND (“Alcohol Drinking”[Mesh] OR “Drinking Behavior”[Mesh] OR “alcohol use” OR “alcohol abuse” OR “nicotine use” OR “Marijuana Abuse”[Mesh] OR “Marijuana Smoking”[Mesh] OR “cannabis use” OR “Cocaine-Related Disorders”[Mesh] OR “cocaine use” OR “cocaine abuse”)) AND (“oxcarbazepine” [Supplementary Concept] OR oxcarbazepine OR “Carbamazepine”[Mesh] OR carbamazepine OR “lamotrigine” [Supplementary Concept] OR lamotrigine OR “Valproic Acid”[Mesh] OR valproate OR divalproex OR “Lithium”[Mesh] OR lithium).
  Limits Review, Systematic Reviews, Meta-Analysis, Clinical Trial; Young Adult: 19-44 years; Middle Aged: 45-64 years.
- ((((“Bipolar Disorder”[Mesh] OR bipolar disorder*)) AND (substance abuse OR substance dependence OR substance use OR comorbidity OR misuse OR co-occurr* OR coexist* OR concurren* OR dual diagnosis OR dual disorder OR dual pathology OR “Diagnosis, Dual (Psychiatry)”[Mesh])) AND (“Alcohol Drinking”[Mesh] OR “Drinking Behavior”[Mesh] OR “alcohol use” OR “alcohol abuse” OR “nicotine use” OR “Marijuana Abuse”[Mesh] OR “Marijuana Smoking”[Mesh] OR “cannabis use” OR “Cocaine-Related Disorders”[Mesh] OR “cocaine use” OR “cocaine abuse”)) AND (“Disulfiram”[Mesh] OR disulfiram OR “Naltrexone”[Mesh] OR naltrexone OR “acamprosate” [Supplementary Concept] OR acamprosate OR “topiramate” [Supplementary Concept] OR topiramate OR “Bupropion”[Mesh] OR bupropion OR nicotine replacement therapy OR “varenicline” [Supplementary Concept] OR varenicline OR “varenicline Ncarbamoylglucuronide” [Supplementary Concept] OR clozapine).
  Limits: Review, Systematic Reviews, Meta-Analysis, Clinical Trial; Young Adult: 19-44 years; Middle Aged: 45-64 years.

Evaluation of the quality of the evidence and formulation of recommendations

Evaluation of the quality of studies and summary of the evidence for each question was performed following the recommendations of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group (www.gradeworkinggroup.org) (Guyatt et al., 2011). Each paper was read in detail and critically appraised according to GRADE, then discussed between authors, resulting in an overall quality assessment score, subsequently revised per individual outcome. The whole process ended up in a clinical recommendation which was rated according to its strength. For clarity purposes, recommendations are here divided according to substance.

External review and evaluation

The evidence was evaluated using the AGREE II (Appraisal of Guidelines for Research and Evaluation) instrument (www.agreecollaboration.org).

A more detailed information on the methodology can be found in a previous paper by our group (Arranz et al., 2022).

Results

Study selection

Figure 1 outlines PRISMA flowchart leading to the study selection. The search yielded 194 studies. 59 studies were deemed eligible for further assessment. The final selection included 13 studies. Open-label, cohort or case-control studies, cross-sectional and observational studies, case reports, letters, posters and abstracts of presentations to specialist meetings and conferences were not included in the Guideline. Only articles published in English were included. Data were extracted from the included studies using a predefined template and the quality of each study was assessed using standard criteria. A summarized report of these studies can be found in Tables 1 to 3.

Patients with BD and alcohol use

Details about included studies are shown in Table 1.

PICO question 1. *Is adjuvant valproate therapy effective to reduce symptoms of BD, to reduce alcohol consumption or to improve pragmatic variables and functioning in patients with BD and alcohol consumption?*

One randomized controlled trial (RCT) evaluated adjuvant valproate *vs* placebo administered for 24 weeks in 52 acutely ill patients with diagnosis of BD I and alcohol dependence (Salloum et al., 2005). Levels of maniac symptoms decreased substantially in both treatment groups (78% in the valproate group, 80% in the placebo group). Bech-Rafaelsen Mania Scale (BRMS) scores decreased by approximately 60% (moderate quality of evidence). Likewise, remission for depression (25-item Hamilton Rating Scale for Depression, HAM-25) did not show significant differences between the study groups (moderate quality of evidence). The efficacy of valproate regarding alcohol use, heavy drinking days was reported by 44% of patients in the valproate group compared with 68% in the placebo group (low quality of evidence). Differences

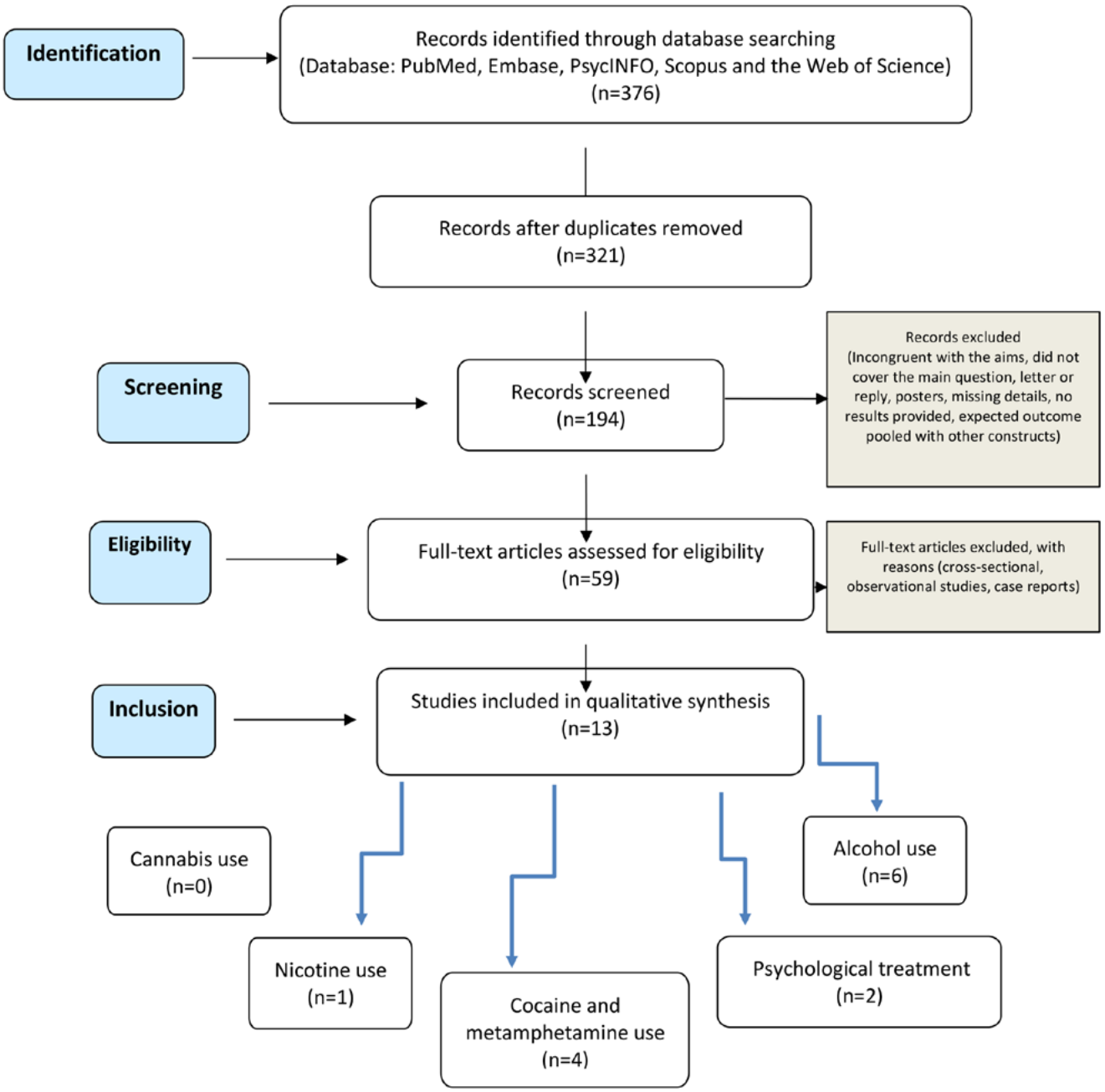

Figure 1. Flow chart of study selection process.

in the percentage of heavy drinking days and drinks per heavy drinking day were not found. The valproate group had significantly fewer cumulative heavy drinking days compared with the placebo group (mean reduction 7.1 days) (low quality of evidence). Valproate also prolonged the time to relapse to sustained heavy drinking to 93 days compared with 62 days in the placebo group but differences were not significant (low quality of evidence). Differences in mean scores of Global Assessment of Functioning (GAF) scale between valproate and placebo were not found.

- **Recommendations**
  - In patients with BD and co-occurring alcohol abuse disorder, the use of adjuvant valproate can be recommended to reduce the number of heavy drinking days (weak recommendation).
  - According to the Pharmacovigilance Risk Assessment Committee of the European Medicine Agency, valproate should not be prescribed for women of childbearing age who are not enrolled in a pregnancy prevention program, nor used in pregnancy. This is because of risk of malformations and developmental problems in babies who are exposed to valproate in the womb (https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances).

PICO question 2. *Is adjuvant quetiapine therapy effective to reduce symptoms of BD, to reduce alcohol consumption or to*

Table 1. *Bipolar disorder and alcohol use disorder*.

Author	Design	Diagnosis	Intervention	Sample size	Follow -up	Outcome variables (Clinical, consumption and pragmatic)	Limitations and bias
Petrakis 2006	RCT Double-blind Parallel Groups Outpatient Added treatment 3 centres	Psychotic spectrum disorders: - SP - SAD - BD AND Alcohol dependence VS Nonpsychotic spectrum disorders AND NO Alcohol Dependence	1. NTX. Dose not reported. 2. DIS 250 mg/day. 3. NTX + DIS. Dose not indicated. 4. DIS + placebo. Dose of 250 mg/day assumed. Patients with stable treatment: Lithium 15%, AS 35%, Typical AP 28.7%, Atypical AP, 15% intensive rehabilitative treatment, including home support.	N=66 - 48 (73%) BD - 7 (11%) SAD - 11 (16%) SP	12 weeks	Primary variables were alcohol consumption: - weekly Timeline Follow-Back Interview. - Craving: OCDS. - PANSS baseline and every 2 weeks. - Adverse effects: Hopkins Symptom Checklist. Weekly.	- Small sample. - No sub-analysis by diagnostic group. Since BD is the main one, all results assumed to be for this diagnosis, with the subsequent biases. - The two groups of DIS are open, not blind. - Post hoc analysis by Petrakis et al., Biol Psychiatry 2005. The article assesses the efficacy of the 4 lines of treatment in all patients with psychiatric disorders. In this article, the sample is subdivided into patients with psychotic and non-psychotic disorders and results are compared. - Four treatment groups. As analyses are performed in pairs, the groups are repeated for each treatment, thus creating a bias of assigning greater weighting to these samples.
Salloum 2005	RCT Double-blind Parallel Groups Added treatment Hospitalized (61%) and outpatient (39%). Single centre	Alcohol dependence and a concurrent affective episode of type I BD (manic, mixed, or depressive)	1. VAL 750 mg/day, increased as a function of tolerability to levels of 50-100 ug/ml 2. Placebo Lithium in all patients. subsequently randomized to added treatment. - Rescue medication: PFZ, BZT, SERT, TRZ - Psychosocial intervention.	N=59 Valproate = 29 Placebo = 30	24 weeks	Consumption variables: Time line follow-back method. - Proportion of days with high alcohol consumption (› 4 SDUs for women and › 5 SDUs for men). - Number of SDUs for each day of high consumption. - Proportion of days with alcohol consumption. - Number of SDUs for each day of alcohol consumption. - Time until relapse into continued high consumption Clinical variables: - Remission of mania (‹7 on BRMS) - Remission of depression (‹7 on HAM-25). - GGT and transaminase levels.	- Improvements in some consumption variables in the VAL group without improvement in affective variables. - Small sample size. - Heterogeneity of patients as they presented with different types of episode, but sample size is too small to allow sub-analysis based on type of episode. - High dropout rate: 62%. Only 20 subjects completed the study, 12 (44%) from the VAL group and 8 (32%) from the placebo group.
Sherwood Brown 2008	RCT Double-blind Parallel groups Added treatment Outpatient Single centre	BD - type I (50/102) - type II (52/102) AND alcohol abuse (3/102) dependence (99/102) in consumption during the 14 previous days	1. QUET up to 600 mg/day 2. Placebo 50% of QUET and 68% of placebo were not taking any concomitant medication. Among those that did: Lithium 13.5% and 4% respectively AS 25% and 18% AD 38.5% and 28% No concomitant psychotherapy or psychosocial treatment mentioned.	N=102 QUET=52 Placebo=50	12 weeks	Consumption variables: Time line follow-back method. Craving: PACS. Affective variables: HAM-D, YMRS. Adverse effects of antipsychotics: AIMS, SAS, BAS.	- No differences observed in consumption, only improvement in depressive symptoms. - Some sample heterogeneity with a majority of patients (approx. 80%) in depressive episode, around 10% in euthymia, and slightly less than 10% in manic or mixed episode. This may explain the improvement in depression variables improve and not those of manic symptoms. - The procedure for slow titration is described in detail. No data, however, on the actual final dose, mean dose, dropouts. - Complex statistical analysis: random regression analysis. - 50% of those on QUET and 68% of those on placebo were not taking any concomitant medication.

Table 1. *(cont.)*

Author	Design	Diagnosis	Intervention	Sample size	Follow -up	Outcome variables (Clinical, consumption and pragmatic)	Limitations and bias
Sherwood Brown 2009	RCT Double-blind Parallel groups Added treatment Outpatient Single centre	BD - type I (31/43) - type II (12/43), depressive/mixed AND Alcohol dependence, with consumption of at least 5 drinks in the previous 7 days	1. NTX 50 mg/day 2. Placebo Basic BD treatment: - Lithium: 9.3% - AS: 18.6% - VAL: 11.6% - LAM: 4.7% - OXC: 2.3% - AP: 11.6% - AD: 37.2% -Sedatives/hypnotics: 16.3% Concomitant medication following Texas algorithm. 16 CBT sessions	N=43 NTX=20 Placebo=23	12 weeks	- MINI Consumption variables: Time line follow-back method Used: - Days of consumption - Days of high consumption - Addiction Severity Index - Hepatic enzymes - PACS Affective variables: - IDS-SR30, HAM-D, YMRS, PRD-III	- Small sample size, which may have influenced the results in which a trend in favour of treatment is detected but without statistical significance (p = 0.10). - A single centre. - Complex statistical analysis: random regression analysis.
Stedman 2010	RCT Double-blind Parallel groups Added treatment Outpatient Multicentre (43 centres USA)	Type I BD (current episode manic, hypomanic, depressive, or mixed) AND Alcohol dependence with recent history of high consumption defined as a minimum of 4 SDUs/ day for women or 5 SDUs/ day for men in at least 10 of the 28 days prior to inclusion	1. QUET 300-800 mg/day 2. Placebo Concomitant treatments: - TRZ 50 mg/day - AC - PAR up to 25 mg/day - HAL All patients treated with lithium or VAL, and at therapeutic levels, from screening phase prior to randomization	N=328 QUET=159 Placebo=169	12 weeks	Consumption variables: Time line follow-back method Primary variable: change in the number of days of high consumption. Secondary variables: - change in the number of days of non-consumption - Mean SDUs/day - Time until the first 2 weeks of alcohol abstinence - Number of cigarettes/day - Change in GGT - OCDS - BSCS Affective variables: YMRS, MADRS, CGI-S, CGI-I, HAM-A Other variables: - Q-LES-Q, SDS	- Study with the largest sample size of those included, also multicentre. - Adequate control of concomitant treatments, both pharmacological (greater homogeneity) and psychotherapeutic (which cannot be started during the trial). - Heterogeneity in type of affective episodes, which could be of any type, although depressive or mixed episodes predominated (85%). - High dropout rate (57%) mainly due to adverse effects.
Tolliver 2012	RCT Double-blind Parallel groups Added treatment Outpatient	BD - type I (13/30) - type II (17/30) AND Alcohol dependence, with consumption in the previous 90 days.	1. ACAM 1998 mg/day 2. Placebo Stabilizing treatment unchanged for at least a month. Concomitant treatment: - Lithium: 7/30 - AS: 21/30 - AP: 15/30 - AD: 15/30 - BZD: 4/30 Brief weekly psychosocial intervention (counselling).	N=30 ACAM=14 Placebo=16	8 weeks	Consumption variables: Time line follow-back. Primary variables: - Time until the first day of consumption - Time until the first day of high consumption (defined as › 4 SDUs/day for women and› 5 SDUs/ day for men). Other variables: - OCDS: - Alcohol consumption biomarkers Affective and general variables: YMRS, MADRS, CGI-S, CGI-I	- Very small sample size. - Single centre. - High heterogeneity in the basic treatments. - Half of the sample were taking maintenance antidepressants. - Heterogeneity in subjects' affective state. Those with severe affective symptoms were excluded and had to undergo unchanged pharmacological treatment, which assumes a low level of affective symptoms, but without specifying episode or polarity. - No differences observed in results except in a secondary outcome, a post-hoc analysis of the improvement in CGI-substance use in the last week of the trial.

Note. AC: Anticholinergics; ACAM: Acamprosate; AD: Antidepressants; AIMS: Abnormal Involuntary Movement Scale; AP: antipsychotics; AS: Antiseizure; BAS: Barnes Akathisia Scale; BD: Bipolar Disorder; BRMS: Bech-Rafaelsen Mania Scale; BSCS: Brief Substance Craving Scale: BZD: Benzodiazepines; BZT: Benzotropin; CBT: Cognitive-behavioral therapy; CGI-I: Clinical Global Impression-Improvement; CGI-S: Clinical Global Impression-Severity; DIS: Disulfiram; GGT: gamma glutamyl-transferase; HAL: Haloperidol; HAM-A: Hamilton Rating Scale for Anxiety; HAM-25: 25-item Hamilton Rating Scale for Depression; HAM-D: 17-item Hamilton Rating Scale for Depression; IDS-SR30: Inventory of Depressive Symptomatology Self-Report 30-item version; LAM: Lamotrigine; MADRS: Montgomery-Asberg Depression Rating Scale; MINI: Mini International Neuropsychiatric Interview; NTX: Naltrexone; OCDS: Obsessive Compulsive Drinking and Abstinence Scale; OXC: Oxcarbazepine; PACS: Penn Alcohol Craving Scale; PANSS: Psychotic Positive and Negative Symptom Scale; PAR: Paroxetine; PFZ: Perphenazine; PRD-III: Psychobiology of Recovery in Depression III - Somatic Symptom Scale; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; QUET: Quetiapine; RCT: Randomized Clinical Trial; SAD: Schizoaffective Disorder; SAS: Simpson-Angus Scale; SDS: Sheehan Disability Scale; SERT: Sertraline; SP: Schizophrenia; TRZ: Trazodone; VAL: Valproate; YMRS: Young Mania Rating Scale.

improve pragmatic variables and functioning in patients with BD and alcohol consumption?

Two 12-week randomized placebo-controlled studies evaluated adjuvant treatment with quetiapine in outpatients with BD (Sherwood Brown, Garza & Carmody, 2008; Stedman et al., 2010). In the outcome of improvement of symptoms including manic symptoms assessed with the Young Mania Rating Scale (YMRS), depressive symptoms with the 17-item Hamilton Rating Scale for Depression (HAM-D), anxiety symptoms with the Hamilton Rating Scale for Anxiety (HAM-A) and Clinical Global Impression (CGI), no significant differences between quetiapine and placebo were found (moderate quality of evidence). In all outcomes of alcohol consumption, such as percent of heavy drinking days, reduction of the number of drinking days per week, percent of alcohol abstinence days, reduction of the number of drinks per day, changes in alcohol craving scales, and decrease of Obsessive Compulsive Drinking and Abstinence Scale (OCDS) score differences between quetiapine and placebo were not statistically significant (low/moderate quality of evidence). On the other hand, differences in pragmatic and functioning variables assessed with the Quality of Life Enjoyment Questionnaire (Q-LES-Q) and Sheehan Disability Scale (SD) were not significant (moderate quality of evidence).

- **Recommendations**
  - In patients with BD and co-occurring alcohol abuse disorder, adjuvant quetiapine treatment cannot be recommended to improve clinical symptoms, to reduce alcohol use or to improve functioning.

PICO question 3. *Is adjuvant treatment with acamprosate effective to reduce symptoms of BD, to reduce alcohol consumption or to improve pragmatic variables and functioning in patients with BD and alcohol consumption?*

In one RCT, 30 adults meeting criteria for BD I or II and current alcohol dependence were randomized to receive add-on acamprosate or placebo while concurrently maintained on mood stabilizing medications (Tolliver, Desantis, Brown, Prisciandaro & Brady, 2012). Patients were followed for 8 weeks. Improvements in maniac (YMRS) and depressive (Montgomery-Asberg Depression Rating Scale, MDRS) symptoms and changes in CGI scale were similar between the experimental and the control arms (very low quality of evidence). Statistically significant differences in the outcomes for assessing alcohol consumption (percent of abstinence days, percent of drinking days, reduction of OCDS score, gamma glutamyl-transferase levels (GGT) and CGI-substance scale score) were not found (very low quality of evidence).

- **Recommendations**
  - In patients with BD and co-occurring alcohol abuse disorder, add-on quetiapine therapy to improve clinical symptoms, to reduce alcohol use or to improve functioning cannot be recommended.

PICO question 4. *Is adjuvant treatment with naltrexone effective to reduce symptoms of BD, to reduce alcohol consumption or to improve pragmatic variables and functioning in patients with BD and alcohol consumption?*

In one RCT, 50 adult outpatients with BD I or II and current alcohol dependence with active alcohol use were randomized to 12 weeks of naltrexone (50 mg/day) add-on therapy or placebo (Sherwood Brown et al., 2009). Regarding maniac symptoms, decrease of the YMRS score was significantly greater in the naltrexone group and regarding depressive symptoms, decrease of the Hamilton Depression Rating Scale (HDRS) score was non significantly greater in the naltrexone group (very low quality of evidence). Statistically significant differences between naltrexone and placebo were found for the following alcohol outcome variables: zero drinking days at week 12 (33.1% *vs* 7.3%), reduction in the number of drinks per drinking day (63.4% *vs* 32.8%), reduction in GGT from baseline to week 12 (15.8% *vs* 3.7%), total abstinence days (12 times higher in the naltrexone group), and number of heavy drinking days (8.82 times lower in the naltrexone group) (very low/low quality of evidence). Differences between naltrexone and placebo in other variables, such as percentage of patients with zero drinking days, reduction of Penn Alcohol Craving Scale (PACS) craving scale at week 12, maximum number of consecutive days of abstinence, and final OCDS score were not found.

- **Recommendations**
  - In patients with BD and co-occurring alcohol abuse disorder, adjuvant treatment with naltrexone to improve maniac or depressive symptoms cannot be recommended.
  - The use of adjuvant naltrexone to improve symptoms of alcohol abuse disorder can be recommended (weak recommendation).

PICO question 5. *Is adjuvant treatment with disulfiram effective to reduce symptoms of BD, to reduce alcohol consumption or to improve pragmatic variables and functioning in patients with BD and alcohol consumption?*

A 12-week RCT of 251 patients with major Axis I disorder (66 patients with psychotic spectrum disorder, 48 (73%) of which had BD) and alcohol dependence was identified (Petrakis, Nich & Ralevski, 2006). Randomization included open randomization to disulfiram 250 mg or no disulfiram and randomization to naltrexone 50 mg or placebo in a double-blind fashion, which resulted in the following

groups: naltrexone alone, placebo alone, disulfiram and naltrexone, or disulfiram and placebo. Primary outcomes were measures of alcohol use. There were no significant differences between disulfiram and placebo in maximum number of consecutive abstinent days, total days of abstinence, number of heavy drinking days (≥ 5 standard drinking units [SDU]), and OCDS score (very low quality of evidence).

- **Recommendations**
  - In patients with BD and co-occurring alcohol abuse disorder, the use of adjunct disulfiram to improve symptoms of alcohol dependence cannot be recommended.

PICO question 6. *Is adjuvant treatment with disulfiram and naltrexone effective to reduce symptoms of BD, to reduce alcohol consumption or to improve pragmatic variables and functioning in patients with BD and alcohol consumption?*

Data of the same RCT analysed for adjuvant disulfiram *vs* placebo on measures of alcohol use (Petrakis et al., 2006) was extracted to determine effectiveness of disulfiram and naltrexone *vs* placebo. Maximum consecutive days of abstinence was higher in the disulfiram and naltrexone group as compared with placebo (very low quality of evidence). However, results for total days of abstinence, number of days of heavy drinking days (≥ 5 SDU), and OCDS scores were similar (very low quality of evidence).

- **Recommendations**
  - In patients with BD and co-occurring alcohol abuse disorder, there is insufficient evidence to recommend the use of adjunct disulfiram and naltrexone to improve symptoms of alcohol abuse.

PICO question 7. *Is adjuvant treatment with naltrexone vs disulfiram effective to reduce symptoms of BD, to reduce alcohol consumption or to improve pragmatic variables and functioning in patients with BD and alcohol consumption?*

The comparison of the arms of naltrexone *vs* disulfiram of the aforementioned 12-week RCT of patients with BD and alcohol dependence (Petrakis et al., 2006), showed no significant differences between the two drugs in the outcomes of alcohol consumption, including total days of abstinence, number of heavy drinking days (≥ 5 SDU), and OCDS scores (very low quality of evidence).

- **Recommendations**
  - In patients with BD and co-occurring alcohol abuse disorder, the use of disulfiram over naltrexone and vice versa to improve symptoms of alcohol abuse cannot be recommended.

PICO question 8. *Is adjuvant treatment with naltrexone vs disulfiram and naltrexone effective to reduce symptoms of BD, to reduce alcohol consumption or to improve pragmatic variables and functioning in patients with BD and alcohol consumption?*

The comparison of the arms of naltrexone *vs* disulfiram combined with naltrexone in the 12-week RCT of patients with BD and comorbid alcohol dependence (Petrakis et al., 2006) did not show statistically significant differences for the outcome of alcohol consumption (maximum consecutive days of abstinence, total days of abstinence, number of heavy drinking days, and OCDS score) (very low quality of evidence).

- **Recommendations**
  - In patients with BD and co-occurring alcohol abuse disorder, the use of naltrexone *vs* disulfiram and naltrexone to improve symptoms of alcohol abuse cannot be recommended.

PICO question 9. *Is adjuvant treatment with disulfiram vs disulfiram and naltrexone effective to reduce symptoms of BD, to reduce alcohol consumption or to improve pragmatic variables and functioning in patients with BD and alcohol consumption?*

Based on data of the 12-week RCT of patients with BD and comorbid alcohol dependence (Petrakis et al., 2006), the comparison of the arms of disulfiram *vs* disulfiram plus naltrexone for improvement of alcohol consumption outcomes (maximum consecutive days of abstinence, total days of abstinence, number of heavy drinking days, and OCDS score) did not show statistically significant differences (very low quality of evidence).

- **Recommendations**
  - In patients with BD and co-occurring alcohol abuse disorder, the use of disulfiram *vs* disulfiram and naltrexone to improve symptoms of alcohol abuse cannot be recommended.

Patients with BD and cocaine, methamphetamine or psychostimulant use

Details about included studies are shown in Table 2.

PICO question 10. *Is adjuvant treatment with citicoline effective to reduce symptoms of BD, to reduce cocaine consumption or to improve pragmatic variables and functioning in patients with BD and cocaine consumption?*

The effectiveness of citicoline add-on therapy *vs* placebo in patients with BD and cocaine dependence was assessed in one 12-week trial conducted in 44 outpatients (depressive 22, maniac/hypomaniac 17, euthymic 5) (Sherwood Brown, Gorman & Hynan, 2007). The primary outcome was to examine memory but mood and cocaine use were also assessed. Outcomes were measured with the Inventory of Depressive Symptomatology-Self-Report (IDS-SR), YMRS, cocaine urine testing, and the Rey Auditory Verbal Learning (RAVLT) instruments. Differences between the groups of citicoline and placebo in scores of depression or maniac symptom scales were not found (very low quality of evidence). Regarding cocaine consumption, the group of citicoline showed an improvement of urine drug testing

Table 2. *Bipolar Disorder and Stimulant Use Disorder.*

Author	Design	Diagnosis	Intervention	EXP(N)/ COMP(N)	Follow-up	Outcome variables (Clinical, consumption and pragmatic)	Limitations and bias
Sherwood Brown 2007	RCT Double-blind Parallel groups Added treatment Outpatient Single centre	BD I (35/44) BD II (3/44) SAD, bipolar type (6/44) AND Cocaine abuse or dependence, in early recovery (1-12 weeks abstinence). 17 in (hypo)mania 22 in depression and 5 euthymics.	1. Citicoline 2000 mg/d (progressive titration reaching this dose in week 6) 2. Placebo Concomitant medication is not specified, but drugs that were modified throughout the trial are.	N=44 Citicoline=23 Placebo=21	12 weeks	Consumption variables: - Urinanalysis - Reported consumption Affective variables: - IDS-SR, YMRS Other variables: -Rey Auditory Verbal Learning Test (RAVLT) - Adverse effects: PRD-III	- Small sample size. - Single centre. - Differences between groups despite randomization: more patients entered the depressive phase in the citicoline group than in the placebo group (15 vs 7). - Heterogeneity in affective state of the patients included. - The results are striking due to the clear and positive response, both in terms of consumption and in a cognitive variable.
Sherwood Brown 2012	RCT Double-blind Parallel groups Added treatment Outpatient Single-centre	BD I (59/112) BD II (42/112) Non-specific BD (11/112) current depressive/mixed episode (90% entered depression) AND Cocaine dependence, with active use (in the previous 14 days)	1. Lamotrigine 200 mg/day (standard titration) 2. Placebo Concomitant treatment but not mandatory: - Lithium: 7 - AD: 20 - AP: 4 - Sedatives/anxiolytics: 9	N=112 Lamotrigine=55 Placebo=57	10 weeks	Consumption variables: Timeline follow-back method. Main variable: Urinanalysis CCQ Affective variables: - HAM-D, QIDS-S, YMRS, PRD-III. Treatment variables: Adverse effects: PRD-III Pill count.	- Single centre. - 70% use cocaine in the form of “Crack”. - Randomization and calculation of the sample size are properly specified. - Many patients did not receive basic treatment for BD, and in particular, low number of patients receiving lithium or PC. - Complex statistical analysis: random regression analysis. - The positive result is in a secondary variable (spending on cocaine) reported by the patient. However, the main variable and the affective variables were not positive.
Sherwood Brown 2012	RCT Double-blind Parallel groups Added treatment Outpatient Single-centre	BD I (6/48) BD II (4/48) Non-specific BD (7/48), current depressive / mixed episode MMD (31/48) AND Methamphetamine dependence, with use in the previous 2 weeks.	1. Citicoline 2000 mg/d (in progressive titration in 6 weeks). 2. Placebo Concomitant medication, mostly antidepressants, 2 lithium, 4 AS, 1 AP	N = 48 Citicoline = 28 Placebo = 20	12 weeks	Consumption variables: - Urinanalysis - Reported consumption Affective variables: - IDS-C Cognitive variables: - Memory: Hopkins Auditory Verbal Learning Test-	- Small sample size. - Single centre. - Very important limitation: Only 1/3 of the sample with BD. - High dropout rate, although higher in placebo group (14% of placebo and 41% of citicoline completed). - Citicoline group received more antidepressants at baseline, which could explain result of improvement in depressive symptoms in that group, although doses of these antidepressants were not increased. - A positive result would perhaps have been more plausible in the cognitive aspect, but was not, and instead occurred in depressive symptoms.
Nejtek 2008	RCT Double-blind Parallel groups Added treatment Outpatient Two centres	BD tipo I: 79/94 BD tipo II: 15/94 Current manic, hypomanic, or mixed episode (YMRS › 9) AND Cocaine or methamphetamine dependence, with craving (SCQ-10 ›10).	1. QUET: 100-600 mg/day 2. RIS: 1-6 mg/day -6/94 with stabilizer -13/94 stabilizer + AD	N = 80 Quetiapine = 42 Risperidone = 38	20 weeks	Consumption variables: - Urinanalysis (weekly) - SCQ-10 Affective variables: - YMRS - IDS-C Treatment variables: - Adverse effects: PRD-III:	- Sample too small (no potency analysis) to detect significant differences between two active treatments. - No placebo control to adequately interpret the effects of the intervention. - Low inclusion of subjects: 651 pass the screening, but only 80 are randomized and take at least one dose of treatment. - Very high dropout rate: only 15% of subjects completed 20 weeks of treatment. - Astra-Zeneca provided the Quetiapine.

Note. AD: Antidepressants; AP: Antipsychotics; AS: Antiseizure; BD: Bipolar Disorder; CCQ: Cocaine craving questionnaire; IDS-C: Inventory of Depressive Symptomatology- Clinician Rated; IDS-SR30: Inventory of Depressive Symptomatology Self-Report 30-item version; MDD: Major Depressive Disorder; PRD-III: Psychobiology of Recovery in Depression III - Somatic Symptom Scale; QIDS-S: quick inventory of depressive symptomatology-SR; QUET: Quetiapine; RCT: Randomized Clinical Trial; RIS: Risperidone; SAD: Schizoaffective Disorder; SCQ-10: Substance craving questionnaire ; YMRS: Young Mania Rating Scale;

for cocaine (very low quality of evidence). Also, there were no significant differences between citicoline and placebo in results of the RAVLT (total number of words, alternative word list and delayed recall) test (very low quality of evidence).

- **Recommendations**
  - In patients with BD and co-occurring cocaine abuse disorder, the use of citicoline add-on therapy to improve mood symptoms, cocaine use-related symptoms or pragmatic or functioning variables cannot be recommended.

PICO question 11. *Is adjuvant treatment with citicoline effective to reduce symptoms of BD, to reduce consumption of methamphetamines or to improve pragmatic variables and functioning in patients with BD and methamphetamine consumption?*

Methamphetamine use disorders are common and persons with mood disorders, particularly BD, have high rates of methamphetamine dependence. In one RCT, 48 outpatients with BD I and II, unspecified affective disorder, schizoaffective disorder depressive type or major depressive disorder and methamphetamine dependence were randomized to citicoline (2000 mg/day) or placebo for 12 weeks (Sherwood-Brown & Gabrielson, 2012a). Mood was assessed using Inventory of Depressive Symptomatology-Clinician Version (IDS-C) and cognition with the Hopkins Verbal Learning Test (HVLT). Drug use was determined by urine drug screens. In the IDS-SR scale, the mean score was 6.9 times lower in the citicoline group vs placebo (very low quality of evidence). Regarding methamphetamine use, the group of citicoline showed an improvement of urine drug testing for methamphetamine (very low quality of evidence). Significant differences between citicoline and placebo in scores of the HVLT test were not found (very low quality of evidence).

- **Recommendations**
  - In patients with BD and co-occurring methamphetamine abuse disorder, citicoline add-on therapy to improve mood symptoms, methamphetamine use-related symptoms or pragmatic or functioning variables cannot be recommended.

PICO question 12. *Is adjuvant treatment with lamotrigine effective to reduce symptoms of BD, to reduce consumption of cocaine or to improve pragmatic variables and functioning in patients with BD and cocaine consumption?*

Lamotrigine appears to be useful for depressive symptoms and relapse prevention in BD. A 10-week RCT of lamotrigine was conducted in 120 outpatients with BD, depressed or mixed mood state, and cocaine dependence (Sherwood Brown, Sunderajan, Hu, Sowell & Carmody, 2012b). Cocaine use was quantified weekly by urine drug screens and the Time Line Follow Back (TLFB) method. Mood was quantified with the HDRS, Quick Inventory of Depressive Symptomatology-SR (QIDS-SR), and YMRS. Cocaine craving was assessed with the cocaine-craving questionnaire. Adherence was assessed by pills dispensed and returned. Differences between lamotrigine and placebo regarding maniac or depressive symptoms were not found (moderate quality of evidence). Percentage of cocaine-positive urine drug screens and the Cocaine Craving Questionnaire (CCQ) scores did not differ between groups. However, dollars spent on cocaine showed a significant between-group difference on both initial and by-week effect (moderate quality of evidence). Adherence was 92% with lamotrigine and 93% with placebo (moderate quality of evidence).

- **Recommendations**
  - In patients with BD and co-occurring cocaine abuse disorder, lamotrigine add-on therapy to reduce cocaine use-related symptoms may be recommended (moderate strength recommendation).

PICO question 13. *Is adjuvant treatment with quetiapine vs risperidone effective to reduce symptoms of BD, to reduce consumption of psychostimulants or to improve pragmatic variables and functioning in patients with BD and psychostimulant consumption?*

A RCT was conducted in 80 outpatients with BD (type I, type II current maniac episode, hypomaniac or mixed) and concurrent cocaine or methamphetamine dependence, treated with add-on quetiapine (100-600 mg/day) or risperidone (1-6 mg/day) (Nejtek et al., 2008). Patients were followed for 20 weeks. Both quetiapine and risperidone (control group) improved depressive and maniac symptoms assessed with the IDS-30 and YMRS instruments but differences were not statistically significant (very low quality of evidence). Also, differences between quetiapine and risperidone in improvement of psychostimulant consumption assessed by drug urine testing were not observed (low quality of evidence). Side effects evaluated with the Psychobiology of Recovery in Depression III—Somatic Symptom Scale (PRD-III) were also similar (very low quality of evidence).

- **Recommendations**
  - In patients with BD and co-occurring psychostimulant abuse disorder, quetiapine or risperidone add-on therapy to reduce mood symptoms, psychostimulant-related symptoms or to improve pragmatic variables and functioning cannot be recommended.

Patients with BD and nicotine use

Details about included studies are shown in Table 3.

Table 3. *Bipolar disorder and Nicotine use disorder.*

Author	Design	Diagnosis	Intervention	EXP(N)/ COMP(N)	Follow-up	Outcome variables (Clinical, consumption and pragmatic)	Limitations and bias
Chengappa 2014	RCT Double-blind Parallel groups Added treatment Outpatient Two centres	BD type I (49/60) BD type II (5/60) BD NS (6/60), in euthymia (MADRS and YMRS <9), or without changes in drug treatment in the previous 8 weeks, and without decompensation in the previous 6 months AND Smoker › 10 cig/day and expired CO › 10 ppm.	1.Varenicline. Standard titration 2. Placebo No data on concomitant treatments 15 minutes of each visit with counselling to quit smoking for all participants	N =60 Varenicline = 31 Placebo = 29	12 weeks of treatment AND up to 24 weeks of follow-up I	Primary variable: Onset of abstinence: 7 days without smoking, reported by the patient and verified by expired CO levels <10 ppm at 12 weeks. Other variables: - 4 consecutive weeks of abstinence (also reported and verified by CO levels). - Maintenance of abstinence at 24 weeks among those who gave up smoking in the 12 weeks.	- Short-term efficacy data are very favourable for varenicline, but not so good mid-term: 9 out of 15 patients who quit smoking with varenicline relapsed. At 24 weeks, there were no significant differences between the groups. - Sample size is small for studying possible adverse effects, especially the appearance of psychopathological decompensation (although a tendency towards the appearance of depressive symptoms is already detected). 31 patients treated with varenicline. - Conducted in 2 centres.

Note. BD: Bipolar disorder; CO: Carbon monoxide; MADRS: Montgomery-Asberg Depression Rating Scale; NS: Not specified; RCT Randomized clinical trial YMRS: Young Mania Rating Scale.

PICO question 14. *Is adjuvant treatment with varenicline effective to reduce symptoms of BD, to reduce nicotine consumption or to improve pragmatic variables and functioning in patients with BD and nicotine consumption?*

In one RCT the efficacy of varenicline *vs* placebo administered for 12 weeks in 69 euthymic bipolar subjects motivated to quit smoking was examined (Chengappa et al., 2014). In the outcome of improvement of depressive symptoms (MDRS), anxiety (HAM-A), mania (YMRS), and CGI scores, differences in favour of varenicline were not reported (low quality of evidence). The primary outcome of the study was nicotine abstinence defined as 7 days of abstinence evaluated by self-report and confirmed by exhaled Carbon Monoxide (CO) levels < 10 ppm at 12 weeks. Statistically significant differences in the primary outcome between the groups of varenicline and placebo were found. Significant differences were also observed for 4-week abstinence and reduction of CO levels (moderate quality of evidence). Significant differences between varenicline and placebo in abstinence at 24 weeks or reduction of the number of cigarettes in the last week were not found (low quality of evidence). Abnormal dreams occurred significantly more often in varenicline-treated subjects than in those receiving placebo (moderate quality of evidence). Differences in withdrawal rates were not found (moderate quality of evidence).

- **Recommendations**
  - In patients with BD and co-occurring nicotine abuse disorder, the use of varenicline to improve nicotine abstinence can be recommended (weak recommendation).

PICO question 15. *Is psychological treatment effective to reduce symptoms of BD, to reduce consumption of drugs of abuse or to improve pragmatic variables and functioning in patients with BD and SUD?*

Two RCTs evaluated behavioural treatment in patients with BD and SUD (Weiss et al., 2007; Weiss et al., 2009). One RCT compared 20 sessions of integrated group therapy that addresses the two disorders simultaneously with group drug counselling. Thirty-one patients were included in each treatment group and followed for 3 months. Outcomes were the number of days of substance use during treatment and the number of days of substance use (Weiss et al., 2007). In the other RCT, 61 patients with BD and substance dependence were randomized to a briefer version of 12 sessions of integrated group therapy (n = 31) or group drug counselling (n = 30). The same main outcomes of interest were evaluated. Patients were followed for 3 months (Weiss et al., 2009).

In the RCT of 20 sessions of group therapy (Weiss et al., 2007), overall, substance use decreased during treatment, but substance use remained significantly lower in integrated group therapy patients as compared to baseline. This difference was maintained at 3 months. In relation to improvement of mood symptoms, scores of the HDRS and YMRS decreased significantly in integrated group therapy as compared to baseline. In the RCT of a brief version of integrated group therapy (Weiss et al. 2009), substance use decreased significantly in both the integrated group therapy and drug counselling group with statistically significant differences for within-group comparisons from baseline to the last month of treatment, and from baseline to the last months of follow-up. The between-group

difference in risk for mood episodes during treatment was marginally significant, with a 1.8 times greater decline for patients on integrated group therapy vs drug counselling group.

- **Recommendations**
  - In patients with BD and co-occurring SUD, integrated group therapy can be recommended (weak recommendation).

Discussion

This review synthesizes the pharmacological and psychosocial interventions that have been conducted in comorbid BD and SUDs while also providing clinical recommendations about which intervention elements are helpful for addressing substance use versus mood symptoms in patients with these co-occurring conditions.

Very few of the randomized trials performed so far have provided consistent evidence for the management of both mood symptoms and substance use in patients with a BD. Surprisingly, no clinical trials are available for bipolar patients using cannabis. Some treatments have shown benefit for mood symptoms without benefits for alcohol or illicit substance use. Our results suggest that 1) we can (weakly) recommend the use of adjuvant valproate or naltrexone to improve symptoms of alcohol use disorder; 2) Lamotrigine add-on therapy seems to reduce cocaine-related symptoms and is therefore recommended (moderate strength); and 3) Varenicline is (weakly) recommended to improve nicotine abstinence.

Quitting substance abuse in BD is of the highest importance due to the outcome improvement after quitting. In a study done in first psychotic episodes that included both schizophrenia and affective bipolar patients it was found that quitting cannabis improved considerably the prognosis in the long-term (González-Pinto et al., 2011b). The same has been proven in large European samples diagnosed with BD (Zorrilla et al., 2015). Both cannabis and alcohol are especially difficult to quit when there is a depressive polarity (González-Pinto et al., 2010; González-Ortega et al., 2015). Therefore, managing depressive symptoms and doing more clinical trials in patients with BD and substance abuse are mandatory. Regarding nicotine use, in real-world clinical settings it is feasible and safe to help patients with BD to quit smoking (García-Portilla et al., 2016). It should be important to investigate the relation between quitting drugs and the use of lithium, the gold standard of BD treatment, with effectiveness in treating depressive symptoms in the real world (González-Pinto, López-Peña, Bermúdez-Ampudia, Vieta & Martinez-Cengotitabengoa, 2018).

At present, Integrated group therapy is the most-well validated and efficacious approach on substance use outcomes if substance use is targeted in an initial treatment phase. For a subsequent phase, additional psychosocial BD treatments may be needed for mood and functioning benefits.

Our review highlights the need for more research in this area and for larger, multisite studies with generalizable samples to provide more definite guidance for clinical practice.

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Conflict of interests

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