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

Guía de práctica clínica para el tratamiento farmacológico y psicológico de los pacientes adultos con un trastorno de ansiedad 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 anxiety disorders and SUDs while also providing clinical recommendations about which intervention elements are helpful for addressing substance use versus anxiety 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. Clinical trials are only available for posttraumatic stress disorder (PTSD) and for social anxiety. Concerning the comorbid substance use, all the studies have included patients with alcohol use, none of them have dealt with cocaine, cannabis or nicotine use. Although some treatments have shown benefit for anxiety symptoms without benefits for alcohol or other substance use, only limited pharmacological approaches have been

Resumen

Esta revisión resume las intervenciones farmacológicos y psicosociales que han sido llevadas a cabo en trastornos de ansiedad con un diagnóstico comórbido de trastorno por uso de sustancias y además proporciona recomendaciones clínicas respecto de cuáles elementos de intervención son útiles para hacer frente a los síntomas del uso de sustancias y los síntomas de ansiedad 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. Hay ensayos clínicos disponibles únicamente para el trastorno por estrés postraumático (TEPT) y para el trastorno de ansiedad. En cuanto al diagnóstico comórbido de trastorno por uso de sustancias, todos los estudios han incluido pacientes con consumo de alcohol, ninguno de ellos ha abordado el consumo de cocaína, cannabis o nicotina.

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assayed (sertraline, desipramine, paroxetine, buspirone, naltrexone and disulfiram). Our results suggest that 1) we can (weakly) recommend the use of desipramine over paroxetine to alleviate symptoms of anxiety in patients with a PTSD and alcohol use; 2) In these patients, the use of naltrexone to reduce symptoms of anxiety is also recommended (weak strength); and 3) SSRI antidepressants vs placebo can be recommended to reduce alcohol use (weak recommendation). 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.
Keywords: Anxiety; posttraumatic stress disorder; alcohol; selective serotonin reuptake inhibitors; desipramine; naltrexone; disulfiram.

Aunque algunos tratamientos han mostrado beneficios para los síntomas de ansiedad sin beneficios para el consumo de alcohol u otras sustancias, solo se han ensayado enfoques farmacológicos limitados (sertralina, desipramina, paroxetina, buspirona, naltrexona y disulfiram). Nuestros resultados sugieren que 1) podemos (débilmente) recomendar el uso de desipramina sobre la paroxetina para aliviar los síntomas de ansiedad en pacientes con un TEPT y consumo de alcohol; 2) en estos pacientes, el uso de naltrexona para reducir los síntomas de ansiedad es también recomendable (fuerza débil); y 3) se pueden recomendar antidepresivos ISRS frente a placebo para reducir el consumo de alcohol (recomendación débil). Nuestra revisión pone de relieve la necesidad de realizar más investigaciones en esta área y de estudios más grandes, multisitio con muestras generalizables para proporcionar evidencia más definitiva para la práctica clínica.
Palabras clave: Ansiedad; trastorno por estrés postraumático; alcohol; inhibidores selectivos de la recaptación de serotonina; desipramina; naltrexona; disulfiram.

According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, anxiety disorders (AD) include disorders that share features of excessive fear and anxiety and related behavioural disturbances (American Psychiatric Association, 2013). AD can be classified according to the cause of the fear: generalized anxiety disorder (everyday situations), obsessive-compulsive disorder (repetitive thoughts and behaviours), panic disorder (panic attacks), post-traumatic stress disorder (previous traumatic events), social anxiety disorder (negative judgements by others) and specific phobia (specific objects or situations).

Analyses from the epidemiological survey focused on comorbidity, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; N=43,093), has revealed striking rates of co-occurring anxiety and substance use disorders (Compton, Thomas, Stinson & Grant, 2007; Hunt, Siegfried, Morley, Sitharthan & Cleary, 2013). AD increase vulnerability to drug abuse (María-Ríos & Morrow, 2020; Vorspan, Mehtelli, Dupuy, Bloch & Lépine, 2015), being the estimated US lifetime prevalence rate for AD of 14.6% and the odds of having at least one substance use disorder (SUD) of 1.7 (Smith & Book, 2008). Also, nicotine, alcohol and cannabis users with comorbid anxiety disorder showed an increased risk from transition to dependence (Lopez-Quintero et al., 2011). Regarding alcohol use, clinical studies have provided evidence for both the self-medication hypothesis, with a short-term anxiolytic effect of alcohol and a toxic effect of prolonged alcohol consumption that increases anxiety and induces anxiety symptoms among other withdrawal symptoms (María-Ríos & Morrow, 2020; Vorspan et al., 2015).

Studies have consistently shown that the co-occurrence of PTSD and SUD makes each individual condition more severe and difficult to treat (Clark, Masson, Delucchi, Hall & Sees, 2001). Patients with comorbid PTSD and SUD have with a more complex and costly clinical course when compared with either disorder alone, including poorer mental health functioning, increased chronic physical health problems, poorer treatment adherence and response, more inpatient hospitalizations, more interpersonal problems and higher rates of suicide attempts (Brady, Killeen, Brewerton & Lucerini, 2000; Driessen et al., 2008; McCauley, Killeen, Gros, Brady & Back, 2012).

In clinical practice, management of an AD with a SUD is based on the use of treatment strategies effective for each condition separately (Ipser, Wilson, Akindipe, Sager & Stein, 2015; Sáiz et al., 2014). Integrated treatment puts the treatment focus on two or more conditions simultaneously and uses multiple treatments such as the combination of psychotherapy and pharmacotherapy. The logic for integrated treatment is that multiple approaches are more comprehensive in treating a condition that is really an interaction of disorders. So far, the superiority of the integrated approach versus single focused treatments in patients with depressive disorders and substance use has been reported (Hesse, 2009). However, evidence-based psychotherapeutic treatment for co-morbid anxiety and substance use disorders is not empirically supported (Iqbal, Levin & Levin, 2019; Vorspan et al., 2015). This review synthesizes the pharmacological and psychosocial interventions that have been conducted in comorbid anxiety disorder SUDs, while also providing clinical recommendations about which intervention elements

are helpful for addressing substance use versus anxiety symptoms in patients with these co-occurring conditions.

Methods

Formulation of clinical questions

In accordance with evidence-based medicine principles, we used the 'PICO' structure (Patient-Intervention-Comparison-Outcomes (Guyatt et al., 2008; Oxman, Schünemann & Fretheim, 2006) to formulate the following review question: "*What is the effect of a pharmacological and/or psychological intervention for the treatment of adult patients with Anxiety Disorder and a SUD?",* being Patients: Adult patients with Anxiety Disorder and coexisting/co-occurring substance / alcohol / cannabis / cocaine /nicotine use disorder; Interventions: Any Pharmacological OR any Psychological Treatment; Comparator: Placebo OR any pharmacological treatment OR any psychological treatment and Outcomes: Reduction of clinical symptoms of anxiety disorder; Improved Substance Use Disorder and Improved pragmatic and functional measures. The target population of these clinical guidelines are patients older than 18 years diagnosed with an AD and a SUD (including cannabis, cocaine, alcohol and/or nicotine). 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:

- Pubmed (pharmacological intervention)

((((“Stress Disorders, Post-Traumatic”[Mesh] OR “Obsessive-Compulsive Disorder”[Mesh] OR “Panic Disorder”[Mesh] OR “Anxiety Disorders”[Mesh] OR posttraumatic stress disorder* OR obsessive compulsive disorder* OR panic disorder* OR anxiety 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 (varenicline OR “varenicline”[Supplementary Concept] OR nicotine replacement therapy OR “Bupropion”[Mesh] OR bupropion OR “topiramate”[Supplementary Concept] OR topiramate OR “acamprosate”[Supplementary Concept] OR acamprosate OR “Naltrexone”[Mesh] OR naltrexone OR anticraving OR “Cyanamide”[Mesh] OR cyanamide OR “Disulfiram”[Mesh] OR disulfiram OR antidipsotropic OR “Antipsychotic Agents”[Mesh] OR antipsychotics OR “Benzodiazepines”[Mesh] OR benzodiazepines OR lamotrigine OR “lamotrigine”[Supplementary Concept] OR valproate OR “Valproic Acid”[Mesh] OR divalproex OR “Lithium”[Mesh] OR lithium OR “Serotonin Uptake Inhibitors”[Mesh] OR “Serotonin Uptake Inhibitors”[Pharmacological Action] OR “duloxetine”[Supplementary Concept] OR duloxetine OR ssris OR “Antidepressive Agents, Tricyclic”[Mesh] OR “Antidepressive Agents, Tricyclic”[Pharmacological Action] OR tricyclic antidepressant OR nsri).

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

((((“Stress Disorders, Post-Traumatic”[Mesh] OR “Obsessive-Compulsive Disorder”[Mesh] OR “Panic Disorder”[Mesh] OR “Anxiety Disorders”[Mesh] OR posttraumatic stress disorder* OR obsessive compulsive disorder* OR panic disorder* OR anxiety 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 (“Lithium”[Mesh] OR “Lithium Chloride”[Mesh] OR “Lithium Carbonate”[Mesh] OR lithium OR “Valproic Acid”[Mesh] OR valproate OR “lamotrigine 2-N-glucuronide”[Supplementary Concept] OR lamotrigine OR carbamazepine OR oxcarbazepine OR mood stabilizer*).

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

((((“Stress Disorders, Post-Traumatic”[Mesh] OR “Obsessive-Compulsive Disorder”[Mesh] OR “Panic Disorder”[Mesh] OR “Anxiety Disorders”[Mesh] OR posttraumatic stress disorder* OR obsessive compulsive disorder* OR panic disorder* OR anxiety 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 (“Benzodiazepines”[Mesh] OR benzodiazepines).

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

((((“Stress Disorders, Post-Traumatic”[Mesh] OR “Obsessive-Compulsive Disorder”[Mesh] OR “Panic Disorder”[Mesh] OR “Anxiety Disorders”[Mesh] OR posttraumatic stress disorder* OR obsessive compulsive disorder* OR panic disorder* OR anxiety 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 (“Antipsychotic Agents”[Mesh] OR antipsychotic*).

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

((((“Stress Disorders, Post-Traumatic”[Mesh] OR “Obsessive-Compulsive Disorder”[Mesh] OR “Panic Disorder”[Mesh] OR “Anxiety Disorders”[Mesh] OR posttraumatic stress disorder* OR obsessive compulsive disorder* OR panic disorder* OR anxiety 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 (varenicline OR “varenicline”[Supplementary Concept] OR nicotine replacement therapy OR “Bupropion”[Mesh] OR bupropion OR “topiramate”[Supplementary Concept] OR topiramate OR “acamprosate”[Supplementary Concept] OR acamprosate OR “Naltrexone”[Mesh] OR naltrexone OR anticraving OR “Cyanamide”[Mesh] OR cyanamide OR “Disulfiram”[Mesh] OR disulfiram OR antidipsotropic).

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

((((Stress Disorders, Post-Traumatic[Mesh] OR “Obsessive-Compulsive Disorder”[Mesh] OR “Panic Disorder”[Mesh] OR “Anxiety Disorders”[Mesh] OR posttraumatic stress disorder* OR obsessive compulsive disorder* OR panic disorder* OR anxiety 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 (“behavioral therapy” Or therapy OR “cognitive therapy” OR “social skills” OR “contingency management” OR “time out” OR “reinforcement programs” OR “token economy” OR self-help OR “motivational interview” OR mindfulness OR “cue exposure” OR self-control OR psychoeducation OR psychotherapy).

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

(((Stress Disorders, Post-Traumatic[Mesh] OR “Obsessive-Compulsive Disorder”[Mesh] OR “Panic Disorder”[Mesh] OR “Anxiety Disorders”[Mesh] OR posttraumatic stress disorder* OR obsessive compulsive disorder* OR panic disorder* OR anxiety disorder*) AND (“Alcohol Drinking”[Mesh] OR “Drinking Behavior”[Mesh] OR alcohol [Title/Abstract] OR nicotine [Title/Abstract] OR “Marijuana Abuse”[Mesh] OR “Marijuana Smoking”[Mesh] OR marijuana[Title/Abstract] OR “cannabis”[Title/Abstract] OR “Cocaine-Related Disorders”[Mesh] OR cocaine[Title/Abstract] OR “substance abuse”[Title/Abstract] OR “substance dependence”[Title/Abstract] OR “substance use”[Title/Abstract] OR misuse[Title/Abstract] OR dual diagnosis[Title/Abstract] OR “dual disorder”[Title/Abstract] OR “dual pathology”[Title/Abstract] OR “Diagnosis, Dual (Psychiatry)”[Mesh]))).

- Limits: Systematic review, Meta-Analysis; +19 years.

(((Stress Disorders, Post-Traumatic[Mesh] OR “Obsessive-Compulsive Disorder”[Mesh] OR “Panic Disorder”[Mesh] OR “Anxiety Disorders”[Mesh] OR posttraumatic stress disorder* OR obsessive compulsive disorder* OR panic disorder* OR anxiety disorder*) AND (“Alcohol Drinking”[Mesh] OR “Drinking Behavior”[Mesh] OR alcohol [Title/Abstract] OR nicotine [Title/Abstract] OR “Marijuana Abuse”[Mesh] OR “Marijuana Smoking”[Mesh] OR marijuana[Title/Abstract] OR “cannabis”[Title/Abstract] OR “Cocaine-Related Disorders”[Mesh] OR cocaine[Title/Abstract] OR “substance abuse”[Title/Abstract] OR “substance dependence”[Title/Abstract] OR “substance use”[Title/Abstract] OR misuse[Title/Abstract] OR dual diagnosis[Title/Abstract] OR “dual disorder”[Title/Abstract] OR “dual pathology”[Title/Abstract] OR “Diagnosis, Dual (Psychiatry)”[Mesh]))) AND (Meta-Analysis[ptyp] OR systematic[sb] OR meta-analysis[ti] OR metaanalysis [ti] OR systematic review [ti]).

(((Stress Disorders, Post-Traumatic[Mesh] OR "Obsessive-Compulsive Disorder"[Mesh] OR "Panic Disorder"[Mesh] OR "Anxiety Disorders"[Mesh] OR posttraumatic stress disorder* OR obsessive compulsive disorder* OR panic disorder* OR anxiety disorder*) AND ("Alcohol Drinking"[Mesh] OR "Drinking Behavior"[Mesh] OR alcohol [Title/Abstract] OR nicotine [Title/Abstract] OR "Marijuana Abuse"[Mesh] OR "Marijuana Smoking"[Mesh] OR marijuana[Title/Abstract] OR "cannabis"[Title/Abstract] OR "Cocaine-Related Disorders"[Mesh] OR cocaine[Title/Abstract] OR "substance abuse"[Title/Abstract] OR "substance dependence"[Title/Abstract] OR "substance use"[Title/Abstract] OR misuse[Title/Abstract] OR dual diagnosis[Title/Abstract] OR "dual disorder"[Title/Abstract] OR "dual pathology"[Title/Abstract] OR "Diagnosis, Dual (Psychiatry)"[Mesh])))).

- Limits: Randomized Controlled Trial; +19 years.

Evaluation of the quality of the evidence and formulation of recommendations

Given the wide variation in the methodology of studies, outcomes reported and the limited numbers of original research reports that focused on each pharmacological or psychological treatment, we based this report in a qualitative synthesis of all available evidence. Evaluation of the quality of evidence for each PICO question was performed following the recommendations of the GRADE working group (Grading of Recommendations Assessment, Development and Evaluation) (www.gradeworkinggroup.org) (Guyatt et al., 2008; Guyatt et al., 2011; Mustafa et al., 2013). 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. Factors reducing the quality of evidence were study design, inconsistency, indirectness, imprecision and publication bias, while factors increasing the quality of evidence were large magnitude of effect and dose response gradient. The Summary of Findings tables corresponding to each PICO are available upon request.

The whole process ended up in a clinical recommendation which was rated according to its strength, so as to reflect the degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects. Recommendations in the present document were formulated according to the quality of evidence and the balance of benefits and harms. Patient values and preferences and cost analyses were not included. For clarity purposes, recommendations are here divided according to substance.

External review and evaluation

External review and evaluation was performed by an independent group of experts using the AGREE II (Appraisal of Guidelines for Research and Evaluation) instrument (Gopalakrishna, Langendam, Scholten, Bossuyt & Leeflang, 2013) (www.agreecollaboration.org). The AGREE II instrument consists in 23 items included in six evaluable Domains: Scope and purpose, stakeholder involvement, rigour and development, clarity and presentation, applicability and editorial independence. Comments raised by the reviewers were included in the revised study.

A more detailed information on the methodology can be found in previous publications (San & Arranz, 2016).

Results

Study selection

Figure 1 outlines PRISMA flowchart leading to the study selection. The search yielded 204 studies. 39 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 Table 1.

PICO question 1. *Are selective serotonin reuptake inhibitor (SSRI) antidepressants effective to reduce symptoms of anxiety in patients with PTSD and co-occurring alcohol abuse disorder? and Are SSRI antidepressants effective to reduce alcohol use in patients with PTSD and co-occurring alcohol abuse disorder?*

Three RCTs evaluated the effect of sertraline plus cognitive behavioural therapy (CBT) versus placebo during 12 weeks in patients with PTSD and alcohol use (Back, Brady, Sonne & Verduin, 2006; Brady, Sonne & Roberts, 1995; Labbate, Sonne, Randal, Anton & Brady, 2004), two of them being the same study (Back et al., 2006; Labbate et al., 2004). None of the studies described random sequence generation, allocation concealment or study protocol. Number and average number of drinks per day as well as number of heavy drinking days were higher in the sertraline group (moderate quality of evidence) (Brady et al., 1995).

One RCT carried out in 94 patients who met criteria for PTSD and comorbid alcohol dependence assessed paroxetine and clinical management/compliance enhancement therapy *vs* desipramine and management/compliance enhancement therapy with or without naltrexone in the two arms, for measure of PTSD severity as the primary outcome (Petrakis et al., 2012). PTSD symptom severity was assessed with the Clinician-Administered PTSD Scale (CAPS) and the duration of treatment was 12 weeks. In CAPS total score and CAPS subscales of re-experience,

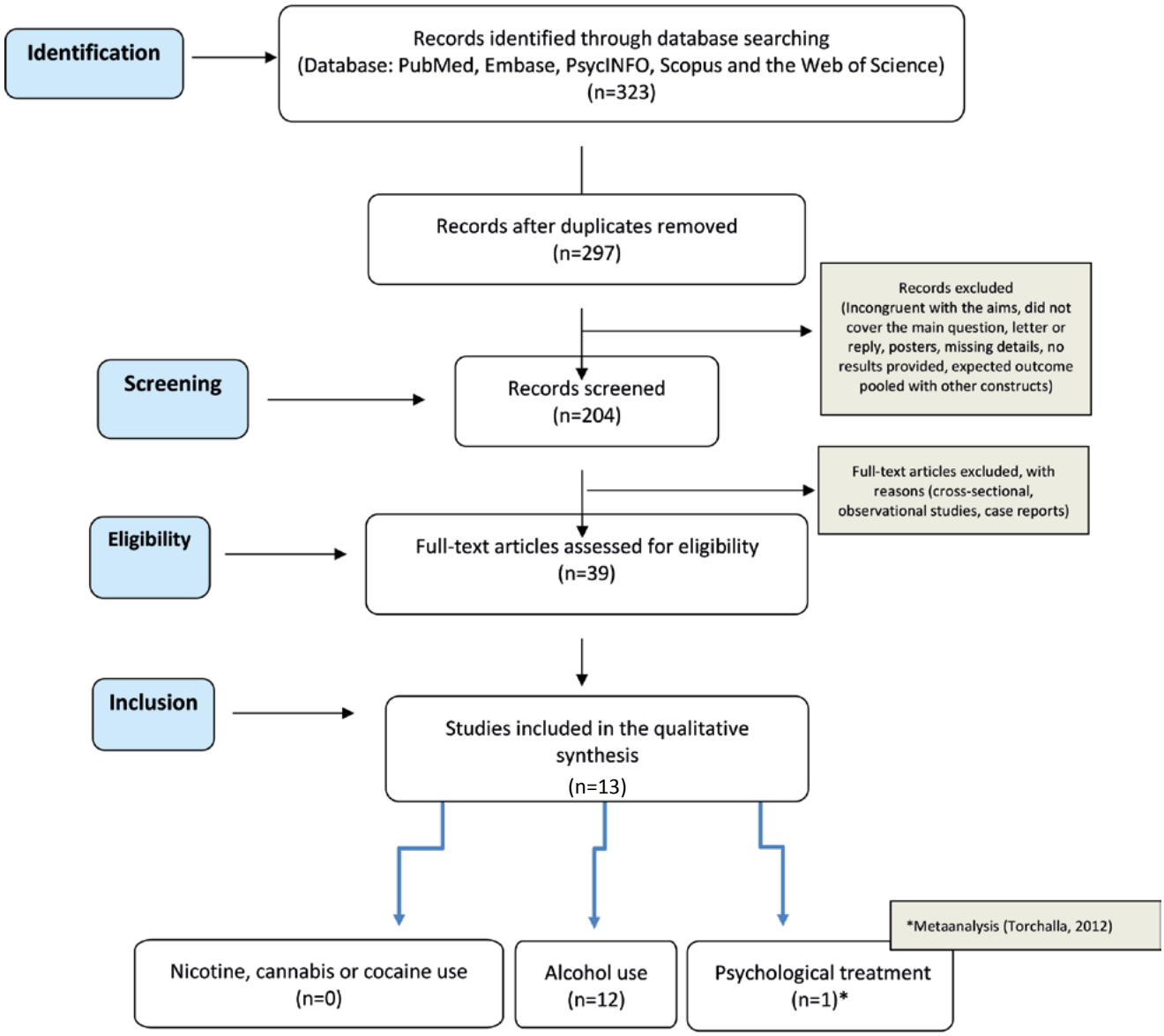

Figure 1. Flow chart of study selection process.

avoidance and hyperarousal, mean scores were higher in the paroxetine group (moderate quality of evidence).

- **Recommendations**
  - In patients with PTSD and comorbid alcohol abuse disorder, the use of SSRI to alleviate symptoms of anxiety or to reduce alcohol consumption cannot be recommended (weak recommendation).

PICO question 2. *Is desipramine effective to reduce symptoms of anxiety in patients with PTSD and co-occurring alcohol abuse disorder? and Is desipramine effective to reduce alcohol use in patients with PTSD and co-occurring alcohol abuse disorder?*

In the same RCT described in PICO question #1, the effect of desipramine *vs* paroxetine to alleviate symptoms of anxiety in 94 patients who met criteria for PTSD and comorbid alcohol dependence was evaluated (Petrakis et al., 2012). Patients treated with paroxetine as compared to those treated with desipramine scored 3.82 times in total CAPS score, 0.94 times higher in CAPS re-experience subscale, 1.6 times higher in CAPS avoidance subscale, and 3.82 times higher n CAPS hyperarousal subscale (moderate quality of evidence).

- **Recommendations**
  - In patients with PTSD and comorbid alcohol abuse disorder, the use of desipramine over SSRI (paroxetine) to alleviate symptoms of anxiety can be recommended (weak recommendation).
  - Desipramine over SSRI (paroxetine) cannot be recommended to reduce alcohol consumption (weak recommendation).

PICO question 3. *Is naltrexone effective to reduce symptoms of anxiety in patients with PTSD and co-occurring alcohol abuse disorder? and Is naltrexone effective to reduce alcohol use in patients with PTSD and co-occurring alcohol abuse disorder?*

Table 1. *Anxiety Disorder and Alcohol Use Disorder.*

AUTHOR	METHODS	INTERVENTIONS	DIAGNOSIS	TREATMENT (N) / CONDITION (N)	FOLLOW UP	RESULTS	BIAS
Labbate, 2004 Brady, 2005 Back, 2006	RCT	SERT 50-150 mg/d versus placebo	PTSD Alcohol dependence (DSM-IV)	49 / 45	12 weeks	CAPS Alcohol intake (TLFB)	Sequence generation methods not described (not applicable for Brady et al., 2005). Allocation concealment not described. Study protocol not described.
Petrakis, 2012	RCT	PAR 25-200 mg/d versus DESI 25-200 mg por día NTX 25-50 mg/d versus placebo	PTSD Alcohol dependence (DSM-IV)	PAR + NTX (22) PAR + placebo (20) DESI + NTX (22) DESI + placebo (24)	12 weeks	CAPS Alcohol intake (TLFB) OCDS GGT Scores	Sequence generation method not described. Allocation concealment not described. Study protocol not described.
Foa, 2013	RCT	NTX 50-100 mg/d versus placebo	PTSD Alcohol dependence (DSM-IV)	82 / 83	24 weeks	PSS-I Alcohol intake (TLFB)	Sequence generation method not described. Allocation concealment not described. Study protocol not described.
Petrakis, 2006	RCT	NTX 50 mg/d versus placebo DIS 250 mg/d versus placebo	PTSD Alcohol dependence (DSM-IV)	93 PTSD/ 161 No PTSD	12 weeks	CAPS Alcohol intake (TLFB) OCDS GGT Scores	Sequence generation method not described. Allocation concealment not described. Study protocol not described.
Book, 2008 Thomas, 2008	RCT	PAR 10-60 mg/d versus placebo	Generalized Social Anxiety Alcohol Abuse or Dependence (DSM-IV)	20 /22	16 weeks	LSAS CGI SPIN Alcohol intake (TLFB) Alcohol consumption related to social situations	Not detected.
Randall, 2001	RCT	PAR 20-60 mg/d versus placebo	Social Anxiety Alcohol Abuse or Dependence (DSM-IV)	6/9	8 weeks	LSAS SPIN CGI ADS Alcohol intake (TLFB)	Few patients included.
Kranzler, 1994	RCT	BUS 15-60 mg/d versus placebo	Alcohol dependence (DSM-III) With HAM-A › 15	31/30	12 weeks	HAM-A Alcohol intake (TLFB, ASI)	Sequence generation method not described. Allocation concealment not described. Study protocol not described.
Malcolm, 1992	RCT	BUS 15-60 mg/d versus placebo	Alcohol dependence (DSM-III R) With HAM-A › 18	33/34	24 weeks	HAM-A SAS Alcohol intake (TLFB, ASI)	Allocation concealment not described. The study protocol not described.
Tollefson, 1992	RCT	BUS 15-60 mg/d versus placebo	GAD Alcohol Abuse / Dependence (DSM-III) With HAM-A › 18	26 / 25	24 weeks	HAM-A HSCL-90 Alcohol intake (ASI)	The sequence generation method not described. Allocation concealment not described. The study protocol not described.

ADS: Alcohol Dependence Scale; ASI: Addiction Severity Index; BUS: Buspirone; CAPS: Clinician administered PTSD Scale; CGI: Clinical Global Impression; DESI: Desipramine; GAD: Generalized Anxiety Disorder; GGT: Gamma-glutamyl transpeptidase; HAM-A: Hamilton Anxiety Rating Scale; HSCL-90: The Hopkins symptom checklist; LSAS: Liebowitz Social Anxiety Scale; NTX: Naltrexone; OCDS: Obsessive Compulsive Drinking Scale; PAR: Paroxetine; PSS-I: PTSD Symptom Scale-Interview; PTSD: Post Traumatic Stress Disorder; PTSD Symptom Scale-Interview; RCT: Randomized Controlled Trial; SPIN: Social Phobia Inventory; SAS: State Anxiety Scale; SERT: Sertraline; TLFB: Time line follow back.

Two RCTs carried out by the same group (Petrakis et al., 2006) (Petrakis et al., 2012) evaluated 12-week treatment with naltrexone *vs* placebo associated with clinical management/compliance enhancement therapy in both arms to relieve symptoms of anxiety (CAPS questionnaire) and to reduce alcohol consumption. Naltrexone-treated patients showed lower scores in total CAPS score and CAPS subscales of re-experience, avoidance and hyperarousal (moderate quality of evidence). In the measures of alcohol consumption, results were more favourable in the naltrexone group *vs* placebo: 19.9 times higher for the maximum mean number of days on abstinence, 4.4 times higher for percentage of abstinent days, 4.2 times lower for heavy drinking days, 6 times higher for mean abstinence during the study period, and 1.3 times lower scores in the total score of the Obsessive Compulsive Drinking Scale (OCDS) (moderate quality of evidence). Gamma-glutamyl transferase levels (GGT) were 3.5 times higher levels in the naltrexone group (moderate quality of evidence).

- **Recommendations**
  - In patients with PTSD and comorbid alcohol abuse disorder, the use of naltrexone to reduce symptoms of anxiety can be recommended (weak recommendation).
  - Naltrexone cannot be recommended to reduce alcohol consumption (weak recommendation).

PICO question 4. *Is disulfiram effective to reduce symptoms of anxiety in patients with PTSD and co-occurring alcohol abuse disorder? and Is disulfiram effective to reduce alcohol use in patients with PTSD and co-occurring alcohol abuse disorder?*

One RCT with 93 patients compared 12-week treatment of naltrexone *vs* placebo and disulfiram *vs* placebo plus clinical management/compliance enhancement therapy (Petrakis et al., 2006). Total CAPS scores and scores in CAPS subscales were higher in the disulfiram group than in the placebo group (moderate quality of evidence). Regarding alcohol consumption, the maximum mean number of consecutive days abstinent was 8 times higher, the percentage of heavy drinking days was 7.4 lower, the mean abstinence during the study period was 11 times higher, the mean total OCDS score was 3.8 lower, and the mean GGT levels were 24.5 times higher in the disulfiram group as compared with placebo (moderate quality of evidence).

- **Recommendations**
  - In patients with PTSD and comorbid alcohol abuse disorder, the use of disulfiram *vs* placebo to reduce symptoms of anxiety cannot be recommended (weak recommendation).
  - Disulfiram *vs* placebo cannot be recommended to reduce alcohol consumption (weak recommendation).

PICO question 5. *Is naltrexone plus disulfiram effective to reduce symptoms of anxiety in patients with PTSD and co-occurring alcohol abuse disorder? and Is naltrexone plus disulfiram effective to reduce alcohol use in patients with PTSD and co-occurring alcohol abuse disorder?*

In the RCT of Petrakis et al. (Petrakis et al., 2006) of 93 patients with PTSD and comorbid alcohol consumption treated for 12 weeks, one of the study groups was naltrexone and disulfiram, with placebo as the comparator. Total CAPS scores and scores in CAPS subscales were higher in the naltrexone and disulfiram group than in the placebo group (moderate quality of evidence). In relation to alcohol consumption, the maximum mean number of consecutive days abstinent was 18.5 times higher, the percentage of abstinent days was 8.1 times higher, the percentage of heavy drinking days was 7.9 times lower, the mean abstinence during the study period was 6 times higher, the mean total OCDS score was 4.2 times lower, and the mean GGT levels were 10.9 times higher in the naltrexone and disulfiram group as compared with placebo (moderate quality of evidence).

- **Recommendations**
  - In patients with PTSD and comorbid alcohol abuse disorder, the use of naltrexone plus disulfiram *vs* placebo to reduce symptoms of anxiety cannot be recommended (weak recommendation).
  - Naltrexone plus disulfiram *vs* placebo cannot be recommended to reduce alcohol consumption (weak recommendation).

PICO question 6. *Are SSRI antidepressants effective to reduce symptoms of anxiety in patients with social anxiety disorder and co-occurring alcohol abuse disorder? and Are SSRI antidepressants effective to reduce alcohol use in patients with social anxiety disorder and co-occurring alcohol abuse disorder?*

Three RCTs addressed the comparison of paroxetine *vs* placebo in patients with social anxiety disorder and comorbid alcohol abuse disorder (Book, Thomas, Randall & Randall, 2008; Randall et al., 2001; Thomas, Randall, Book & Randall, 2008), but in two of them (Book et al., 2008; Randall et al., 2001) the outcomes of interest were not analyzed. In a 16-week RCT including 93 patients (Thomas et al., 2008), there were no differences between paroxetine and placebo in drinks per day of alcohol consumption, percentage of abstinent days or percentage of heavy drinking days (moderate quality of evidence). However, the percentage of alcohol consumption before social situations was 24 times lower and during social situations was 13 times lower in the paroxetine group (moderate quality of evidence).

- **Recommendations**
  - In patients with social anxiety disorder and co-occurring alcohol abuse disorder, ISSRI antidepressants *vs* placebo to reduce symptoms of anxiety cannot be recommended (weak recommendation).
  - SSRI antidepressants *vs* placebo can be recommended to reduce alcohol use (weak recommendation). This recommendation assigns a relatively high value to reduction of alcohol consumption related to social anxiety, and a relatively low value to reduction of drinking in general.

PICO question 7. *Is buspirone effective to reduce symptoms of anxiety in patients with an anxiety disorder and co-occurring alcohol abuse disorder? and Is buspirone effective to reduce alcohol use in patients with an anxiety disorder and co-occurring alcohol abuse disorder?*

One RCT assessed treatment with buspirone vs placebo for 12 weeks in 61 patients with an anxiety disorder and comorbid alcohol abuse disorder (Kranzler et al., 1994). The mean scores of the HAM-A questionnaire were 1.5 lower in the buspirone group than in the placebo group (moderate quality of evidence). Also, mean days of alcohol consumption was 6 times lower, drinks per day of alcohol consumption 3.9 times lower and number of drinks per

day of alcohol use 4.6 times lower in the buspirone group *vs* placebo (moderate quality of evidence).

- **Recommendations**
  - In patients with an anxiety disorder and co-occurring alcohol abuse disorder, the use of buspirone to reduce symptoms of anxiety or to reduce alcohol consumption cannot be recommended (weak recommendation).

PICO question 8. *Is psychological treatment effective to reduce symptoms of posttraumatic stress disorder (PTSD) or to reduce consumption of drugs of abuse in patients with PTSD and SUD*

A meta-analysis of nine RCTs evaluated the impact of psychotherapeutic integrated *vs* non-integrated treatment programs in patients with PTSD and concurrent SUD (Hesse, 2009; Torchalla, Nosen, Rostam & Allen, 2012). Most of the interventions included a combination of social support, psychoeducation and CBT, the building of problem-solving, interpersonal and emotional regulation skills, development of strategies to cope with trauma- and substance-related stimuli, and integrated smoking cessation programs. There were no significant differences between integrated treatment programs and comparators for change of PTSD symptoms or improvement of SUD (very low quality of evidence).

Recommendations

In patients with PTSD and co-occurring SUD, no recommendations can be made regarding which is the most effective psychological intervention to improve PTSD symptoms and to reduce substance use.

Conclusions

This review synthesizes the pharmacological and psychosocial interventions that have been conducted in comorbid anxiety disorders, including social anxiety, panic disorder, agoraphobia, simple phobia, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, and PTSD, and SUDs, while also providing clinical recommendations about which intervention elements are helpful for addressing substance use versus anxiety symptoms in patients with these co-occurring conditions.

The paucity of randomized studies in individuals with co-occurring anxiety disorders and SUD remains a concern, given the enormous burden that they pose. Very few of the randomized trials performed so far have provided consistent evidence for the management of both anxiety and substance use. Clinical trials are only available for PTSD and for social anxiety. Concerning the comorbid substance use, all the studies have included patients with alcohol use, none of them have dealt with cocaine, cannabis or nicotine use. Although some treatments have shown benefit for anxiety symptoms without any profit for alcohol or other substance use, only limited pharmacological approaches have been assayed (sertraline, desipramine, paroxetine, buspirone, naltrexone and disulfiram).

Our results suggest that 1) we can (weakly) recommend the use of desipramine over paroxetine to alleviate symptoms of anxiety in patients with a PTSD and alcohol use; 2) In these patients, the use of naltrexone to reduce symptoms of anxiety is also recommended (weak strength); and 3) ISSRI antidepressants *vs* placebo can be recommended to reduce alcohol use (weak recommendation). This recommendation assigns a relatively high value to reduction of alcohol consumption related to social anxiety, and a relatively low value to reduction of drinking in general.

During the course of the present recommendations, Gimeno et al. (2017) reported a narrative review of the scientific evidence and recommendations for treatment of patients with an alcohol dependence and an anxiety disorder. Their recommendations are not in agreement with ours because of several methodological differences in both studies. In our study the quality of evidence was rated following the GRADE system, which is a more structured and rigid procedure, and evaluated using the AGREE II instrument. Secondly, Gimeno et al. (2017), included some open and retrospective studies, which were not included in our study. Furthermore, some of their recommendations were based on studies performed in Major Depression with anxiety symptoms, or in patients with alcohol disorder in which anxiety symptoms (not anxiety disorder) were rated.

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. This research should ensure adequate randomization, the use of an active comparator, and long-term follow ups, so as to establish the sustainability of treatment outcomes.

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Conflict of interests

None of the authors report any conflict of interest related to this manuscript.

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