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

Pilar A Sáiz1,*, Gerardo Florez1**, Manuel Arrojo1***, Miquel Bernardo1****, Ana González-Pinto1*****, José Manuel Goikolea1*******, Inaki Zorrilla1*******, Ruth Cunill1*******, Xavier Castells1********, Elisardo Becoña1********, Ana López1*********, Marta Torrens1*********, Francina Fonseca1*********, Judit Tirado-Muñoz1*********, Belén Arranz1*********, Marina Garriga1*********, Luis San1*********.

1These authors have equally contributed to this work.

*Universidad de Oviedo, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Servicio de Salud del Principado de Asturias (SESPA), Oviedo, Spain.

**Unidad de Conductas Adictivas, Complejo Hospitalario de Ourense, CIBERSAM, Ourense, Spain.

***Servicio de Psiquiatría. EOXI de Santiago de Compostela, Spain.

****Hospital Clinic, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). Universitat de Barcelona, CIBERSAM, Spain.

*****Instituto de Investigación Sanitaria BIOARABA. OSI Araba. Hospital Universitario. CIBERSAM, UPV/EHU, Vitoria, Spain.

******Parc Sanitari Sant Joan de Deu, CIBERSAM, Universitat de Barcelona, Spain.

*******Grupo de investigación TransLab, Departamento de Ciencias Médicas, Universitat de Girona, Spain.

********Unidad de Tabaquismo y Trastornos Adictivos. Facultad de Psicología. Universidad de Santiago de Compostela, Santiago de Compostela, Spain.

*********Institut de Neuropsiquiatria i Adiccions (INAD). Parc de Salut Mar, RTA, Barcelona, Spain.

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.

Received: April 2020; Accepted: December 2020.

Send correspondence to:
Manuel Arrojo, MD. Hospital Psiquiátrico de Conxo. Plaza Martin Herrera 2. 15706, Santiago de Compostela, Spain.
E-mail: manuel.arrojo.romero@usc.es
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.

A

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=43,095), 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 & Lacerini, 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)


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

- Limits: Review, Systematic Reviews, Meta-Analysis, Clinical Trial; Young Adult: 19-44 years; Middle Aged: 45-64 years
Clinical practice guideline on pharmacological and psychological management of adult patients with an Anxiety Disorder and comorbid substance use


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


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

Pubmed (exhaustive)

- Pubmed (psychological intervention)

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

Pubmed (exhaustive)
Are selective serotonin reuptake inhibitor antidepressants effective to reduce alcohol use in patients with PTSD and comorbid alcohol abuse disorder? and Are SSRI antidepressants effective to reduce symptoms of anxiety in patients with PTSD and co-occurring alcohol abuse disorder?

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 pre-defined template and the quality of each study was assessed using standard criteria. A summarized report of these studies can be found in Table 1.

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

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
Table 1. Anxiety Disorder and Alcohol Use Disorder.

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

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.

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).

ADICCIONES, 2021 · VOL. xx NO. x
**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, SSRI 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.

Acknowledgements

Servicio Gallego de Salud, SERGAS; Sociedad Española de Psiquiatría Biológica (SEPB), Pla Director de Salut Mental i Adiccions, Barcelona

Conflict of interests

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

References


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

of Anxiety Disorders, 22, 310–318. doi:10.1016/j.janxdis.2007.03.001.


