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

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

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## Abstract

Co-occurrence of depression and a substance use disorder (SUD) in patients who present dual diagnoses has been long recognized as an important consideration in clinical practice. This review synthesizes the evidence of pharmacological and psychosocial interventions for comorbid depressive disorders and SUDs while providing clinical recommendations about the best interventions to address these patients. The best evidence from randomized controlled trials was used to evaluate treatment options. The strength of recommendations was described using the GRADE approach. Our results suggest that 1) In patients with depression and alcohol consumption, the administration of non-selective serotonin reuptake inhibitor (SSRI)

## Resumen

La concurrencia de depresión y un trastorno por uso de sustancias (TUS) en pacientes que presentan patología dual ha sido reconocida desde hace mucho tiempo como una consideración importante en la práctica clínica. Esta revisión sintetiza la evidencia de intervenciones farmacológicas y psicosociales para trastornos comórbidos de depresión y uso de sustancias y además proporciona recomendaciones clínicas respecto de las mejores intervenciones para tratar a estos pacientes. 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. Nuestros resultados sugieren que: 1) en pacientes con depresión y consumo de

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antidepressants instead of SSRI is recommended for improvement of depressive symptoms (strong recommendation). Neither SSRI (strong recommendation) nor non-SSRI (weak recommendation) antidepressants are recommended for reduction in alcohol consumption. 2) In patients with depression and cannabis use, the use of venlafaxine is not recommended (weak recommendation). 3) In patients with depression and cocaine consumption, the use of SSRI antidepressants for improving depressive symptoms (weak recommendation) or to reduce cocaine use is not recommended (strong recommendation). The use of non-SSRI antidepressants is only recommended for improving depressive symptoms (strong recommendation). 4) The administration of bupropion to reduce nicotine consumption is not recommended (strong recommendation). 5) Regarding psychological treatment, in patients with depression and co-occurring alcohol disorder, both pharmacotherapy and cognitive behavioural therapy have positive effects on internalizing symptoms and in reducing alcohol consumption (weak recommendation). Our review suggests the need for more research in this area and for larger, multisite, randomized studies to provide more definite evidence.

*Keywords:* Depression; substance use disorder; alcohol; cocaine; cannabis; nicotine; antidepressants; selective serotonin reuptake inhibitors.

alcohol, se recomienda la administración de antidepresivos inhibidores de la recaptación de serotonina (ISRS) no selectivos en lugar de los ISRS para mejorar los síntomas depresivos (recomendación fuerte). No se recomiendan antidepresivos ISRS (recomendación fuerte) ni antidepresivos no ISRS (recomendación débil) para reducir el consumo de alcohol; 2) en pacientes con depresión y consumo de cannabis, no se recomienda el uso de venlafaxina (recomendación débil); 3) en pacientes con depresión y consumo de cocaína, no se recomienda el uso de antidepresivos ISRS para mejorar los síntomas depresivos (recomendación débil) o para reducir el consumo de cocaína (recomendación fuerte). El uso de antidepresivos no ISRS solo se recomienda para mejorar los síntomas depresivos (recomendación fuerte); 4) no se recomienda la administración de bupropión para reducir el consumo de nicotina (recomendación fuerte), y 5) en cuanto al tratamiento psicológico, en pacientes con depresión y trastorno de alcohol concurrente, tanto la farmacoterapia como la terapia cognitivo-conductual tienen efectos positivos en la internalización de los síntomas y en la reducción del consumo de alcohol (recomendación débil). Nuestra revisión sugiere la necesidad de realizar más investigaciones en esta área y de estudios aleatorizados, multisitio y más grandes para proporcionar más evidencia definitiva.

*Palabras clave:* Depresión; trastorno por uso de sustancias; alcohol; cocaína; cannabis; nicotina; antidepresivos; inhibidores selectivos de la recaptación de serotonina.

Co-occurrence of depression and a substance use disorder (SUD) in dual diagnoses patients has been long recognized as an important consideration in clinical practice (Iqbal, Levin & Levin, 2019). This strong association between SUD and major depression has been confirmed in several meta-analysis of epidemiological surveys published between 1990 and 2014 (odds ratio [OR] 3.80) (Lai, Cleary, Sitharthan & Hunt, 2015) and between 1990 and 2019 (Hunt, Malhi, Lai & Cleary, 2020). Studies concur on a prevalence of depression ranging from 15% in the general population to 80% in otherwise selected clinical samples from both mental health and addiction settings (Caetano, Vaeth & Canino, 2019; Compton, Thomas, Stinson & Grant, 2007; Torrens, Rossi, Martínez-Riera, Martínez-Sanvisens & Bulbena, 2012; Vázquez, Torres, Otero & Díaz, 2011). By substances, comorbidity between major depression and SUD has a prevalence of 20% for Alcohol Use Disorder (AUD) (Boschloo et al., 2011; Carton et al., 2018), ranging between 16% and 34% for cocaine use (Alías-Ferri et al., 2021; Vergara-Moragues et al., 2012), 13.5% and 38% for Cannabis Use Disorder (CUS) (Cuenca-Royo, Torrens, Sánchez-Niubó, Suelves & Domingo-Salvany, 2013) and 43.2%-61.2% for tobacco consumption (Jiménez-Treviño et al., 2019). Based on epidemiological and clinical studies, comorbid major depression is two-fold more frequent in women with SUD than in the general population and the presence of this comorbidity is more frequent in women than in men (Farré, Tirado-Muñoz & Torrens, 2017; Tirado-Muñoz, Farré, Mestre-Pintó, Szerman & Torrens, 2018).

Comorbidity between depression and SUD can be explained in causal terms, with the presence of one disorder increasing the likelihood of the other to occur (Khantzian, 1985). Comorbidity could also be caused by substance use revealing a latent predisposition toward depression in high-risk individuals (Schuckit, 2006). Finally, shared predisposing factors such as biological, social or environmental factors and exposure to early adverse life events in the form of child abuse and/or neglect may increase the likelihood of depression and SUD (Rappeneau & Bérod, 2017).

Compared with patients with a single disorder, the comorbidity of depression and SUD is commonly associated with an inaccurate diagnosis, worsened clinical course, greater functional impairment, lower medication adherence, a greater relapses to substance use, as well as a greater risk of suicidal behaviour (Torrens et al., 2011; Torrens et al, 2012). In addition, mental health and SUD treatment professionals are confronted with the difficulties of providing effective care to patients whose problems overlap two health care

specialties. In this respect, treatment of SUD should be integrated into the management strategies of depressive disorders unrelated to SUD, combining pharmacological and appropriate psychotherapeutic interventions (Tirado-Muñoz et al., 2018). Cautious selection of pharmacological treatment assessing effectiveness, safety, potential drug interactions and adherence-related problems is crucial in patients with depressive disorders and SUD. So far, systematic reviews and meta-analysis have reported outcomes of interventions in patients with co-occurring SUD and mood disorders (Agabio, Trogu & Pani, 2018; Carey, 2019; Conner, Pinquart & Holbrook, 2008; Conner, Pinquart & Gamble, 2009; Tirado-Muñoz et al., 2018; Torrens, Fonseca, Mateu & Farre, 2005).

This review synthesizes the pharmacological and psychosocial interventions that have been conducted in comorbid depressive disorder and a co-occurring alcohol, cocaine, nicotine or cannabis use. It also provides healthcare professionals involved in the care of these patients with clinical recommendations based on scientific evidence to assist in the decision-making process in their clinical practice.

## Methods

### *Formulation of clinical questions*

In accordance with evidence-based medicine principles, we used the 'PICO' structure (Patient-Intervention-Comparison-Outcomes) (Guyatt et al., 2011; 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 Depression and a SUD?*". Patients older than 18 years diagnosed with a Depression and a SUD (including cannabis, cocaine, alcohol and/or nicotine) were the target population of this clinical guideline. Opioid use disorder was out of the scope of this review given no systematic reviews with or without meta-analysis or randomized clinical trials were identified.

### *Search strategy*

The following databases were searched for relevant studies published until December 2015: MEDLINE, PsycINFO, Embase, Scopus, Web of Science, Cochrane Library and Pubmed with an update search to May 2016. Table 1 describes the search strategy employed and the different terms used.

### *Eligibility criteria*

Studies were eligible for inclusion if 1) they were meta-analysis, cochrane reviews, systematic reviews or clinical trials (randomized, double-blind, and placebo-controlled) of any pharmacological and psychological treatment, 2) patients diagnosed with a major depressive disorder and a substance use disorder (alcohol, cannabis, cocaine, or nicotine), and 3) the outcome was substance use (decrease or withdrawal)

Table 1. *Description of search terms.*

| Topic | Keywords | Limitations applied |
|---|---|---|
| Depression | dysthymic disorder; depressive disorder; depressive disorder, major; mood disorders | |
| Comorbidity | substance abuse, substance dependence, substance use, comorbidity, misuse, co-occurr*, coexist*, concurren* dual diagnosis dual disorder, dual pathology | |
| Alcohol | alcohol drinking, drinking behavior, alcohol use, alcohol abuse | |
| Cocaine | cocaine-related disorders, cocaine use, cocaine abuse | |
| Cannabis | cannabis use, marijuana Abuse marijuana Smoking | |
| Nicotine | nicotine use | |
| Pharmacological treatment (Antidepressants) | antidepressive agents, tricyclic; tricyclic antidepressant, SSRI | Human, 18 years or older, RCT OR Review, Systematic Reviews, Meta-Analysis |
| Pharmacological treatment | oxcarbazepine, oxcarbazepine, carbamazepine, carbamazepine, lamotrigine, lamotrigine, valproic acid, valproate, divalproex, lithium | |
| Pharmacological treatment | benzodiazepines | |
| Pharmacological treatment | varenicline, nicotine replacement therapy, bupropion, topiramate, acamprosate, naltrexone, anticraving, cyanamide, disulfiram, antidipsotropic | |
| Psychological treatment | behavioral therapy, therapy, cognitive therapy, social skills, contingency management, time out, reinforcement programs, token economy, self-help, motivational interview, mindfulness, cue exposure, self-control, psychoeducation, psychotherapy | |

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and/or depressive symptoms. Selected studies included participants with a single SUD (alcohol, cocaine, cannabis or nicotine) depending of the substance of interest.

### 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., 2008). 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 (Gopalakrishna, Langendam, Scholten, Bossuyt & Leeflang, 2013) (www.agreecollaboration.org).

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

## Results

Figure 1 outlines PRISMA flowchart leading to the study selection. The search yielded 741 studies. 84 studies were deemed eligible for further assessment. The final selection included 32 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
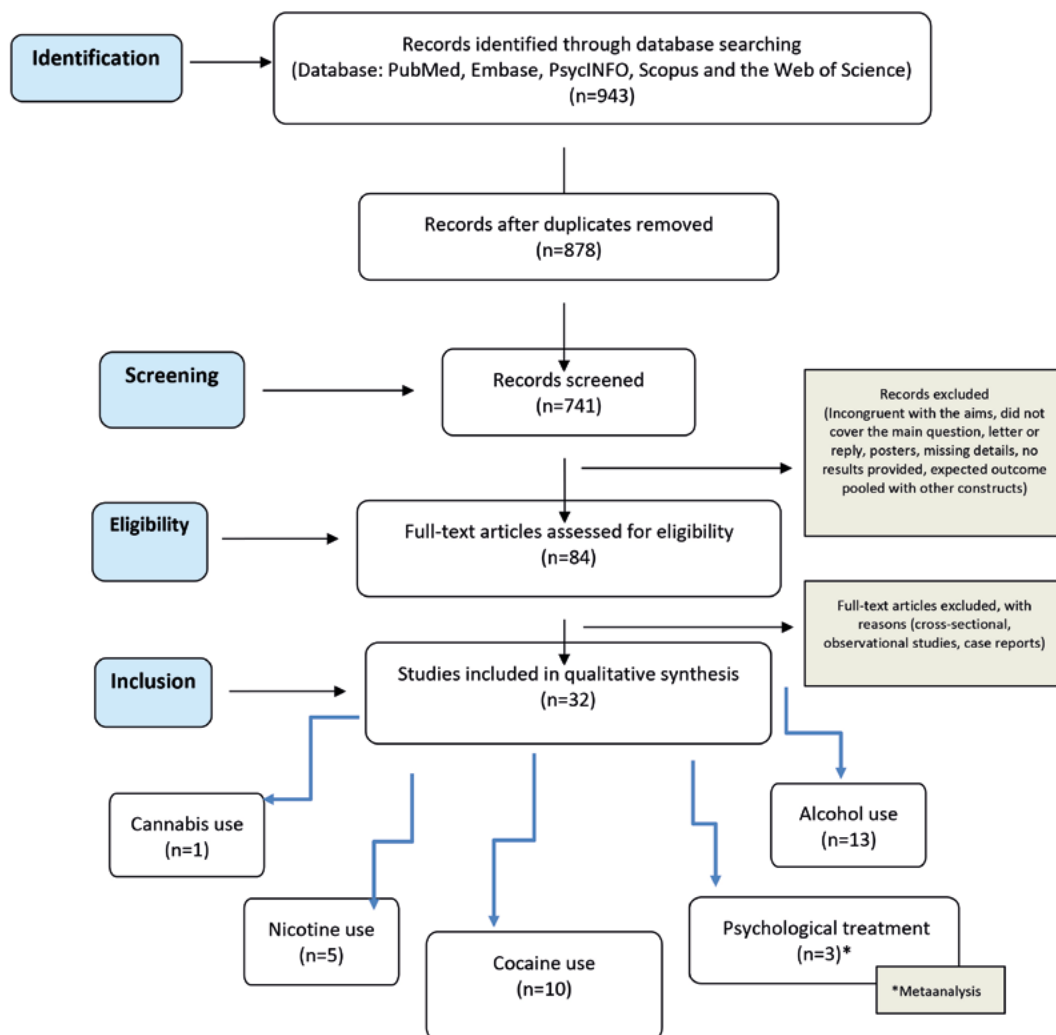


*Figure 1.* Flow chart of study selection process.

study was assessed using standard criteria. A summarized report of these studies can be found in Tables 2 to 5. For psychological interventions, only metaanalyses were included.

### Patients with Depressive Disorder and alcohol use

Details about included studies are shown in Table 2.

*PICO question 1. Is the administration of selective serotonin reuptake inhibitors (SSRIs) effective to reduce symptoms of depression, to reduce alcohol consumption or to improve pragmatic and functioning variables in patients with depression and alcohol consumption?*

Seven RCTs assessed the efficacy of SSRI (mainly fluoxetine and sertraline) in reducing depressive symptoms (Cornelius et al., 1997; Gual et al., 2003; Kranzler et al., 2006; Moak et al., 2003; Pettinati et al., 2001, 2010; Roy, 1998). In six RCTs (Gual et al., 2003; Kranzler et al., 2006; Moak et al., 2003; Pettinati et al., 2001, 2010), differences between SSRI and placebo at 12 weeks using the Hamilton Depression Rating Scale (HAMD) were not found (n = 498) (low quality of evidence). Using the Beck Depression Inventory (BDI), no differences were found either in four RCTs (Cornelius et al., 1997; Moak et al., 2003; Pettinati et al., 2001; Roy, 1998) (n = 184) (moderate quality of evidence).

Table 2. *Depression and alcohol use disorder.*

| AUTHORS | DRUG USED MG/DAY | DIAGNOSIS/ INSTRUMENT | CASE/ CONTROL | CONSUMPTION AT START OF RCT | WEEKS | CONCOMITANT THERAPY | OUTCOME VARIABLE |
|---|---|---|---|---|---|---|---|
| Altamura 1990 | Viloxazina (400) Placebo | DSM-III-R/NA (distimia ≥ 18 en HRSD) | 14/13 | 7 days abstinent | 12 | 4 weeks in hospital followed by outpatient treatment | TLFB: Both groups improve alcohol use without significant differences. HAMD: Significant improvement in the viloxazine group (5 vs. 21, p ‹ 0.01). |
| Mc Grath 1996 | Imipramina (150–300) Placebo | DSM-III-R/SCID | 27/29 | Current consumption | 12 | Individual CBT and relapse prevention | TLFB: No overall effect on alcohol use (last 4 weeks abstinent). In patients with improvements in mood, alcohol use decreased more in those treated with imipramine HAMD: significantly lower values in the imipramine (9.4 ± 7.7) than the placebo group (12.4 ± 9,7) (p ‹0.03). |
| Mason 1996 | Desipramina (200) Placebo | DSM-III-R/NA | 12/10 | ≥7 days abstinent | 24 | Alcoholics anonymous | TLFB: Desipramine patients showed a longer period of abstinence than the P group (mean: 109 vs 65 days) (p = 0.03). HAMD: Desipramine group decreased scores significantly compared to placebo (mean: 8 vs. 20) (p ‹0.01). |
| Cornelius 1997 | Fluoxetine ( 20) Placebo | DSM-III-R/SCID | 25/26 | ≥9 days abstinent | 12 | Supportive psychotherapy | TLFBI: Total alcohol use was significantly lower in the fluoxetine group than in the placebo group. HAMD: Significant improvement in depressive symptoms in the fluoxetine group compared to the placebo group. |
| Roy 1998 | Sertraline (100) Placebo | DSM-III-R/NA | 10/5 | ≥14 days abstinent | 6 | Hospitalisation followed by intensive day hospital | Consumption: Not assessed BDI, HAMD: the sertraline group had significantly lower scores in HAMD (12.7 ± 9.1) and in BDI (18.5 ± 12.5) compared to placebo (16.3 ± 7.5 and 23.1 ± 10.2) (p ‹ 0.003 and p ‹ 0.03). |
| Roy-Byrne 2000 | Nefazodone (460 ± 75) Placebo | DSM-III-R/SCID | 20/11 | Current consumption | 12 | Groups CBT | TLFBI: non-significant decrease in the mean number of daily alcoholic drinks in nefazodone (3) vs. group P (4) HAMD: significant improvement with nefazodone (12) compared to placebo (16) (p ‹0.1). |
| Pettinati 2001 | Sertraline (200) Placebo | DSM-III-R/SCID | 12/17 | ≥3 days abstinent | 14 | 12-step therapy | TLFB: non-significant differences in %age decrease of drinking days and weeks to relapse between sertraline and the placebo group. BDI, HAMD: non-significant differences in decrease in HAMD and BDI scores between sertraline (6.8 and 7.2 respectively) and placebo groups (8.8 y 9.1). |

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| AUTHORS | DRUG USED MG/DAY | DIAGNOSIS/ INSTRUMENT | CASE/ CONTROL | CONSUMPTION AT START OF RCT | WEEKS | CONCOMITANT THERAPY | OUTCOME VARIABLE |
|---|---|---|---|---|---|---|---|
| Gual 2003 | Sertraline (50–150) Placebo | DSM-IV/ NA | 24/22 | ≥14 days abstinent | 24 | 2 weeks of abstinence after detoxification | Non-significant differences in relapse rates in the sertraline group (31.8%) versus the placebo group (23.1%). HAMD/MADRS: non-significant differences in response rates between the sertraline group (44%) and the placebo group (39%). When patients were stratified into severe (MADRS ≥ 26) and moderate (MADRS ‹26) depression, significant improvement with sertraline treatment observed in the first group. |
| Moak 2003 | Sertraline (186) Placebo | DSM-III-R/PRISM | 38/44 | ≥3 days abstinent | 12 | Individual CBT for alcohol and depression | TLFB: fewer drinks per day in the sertraline group than the placebo group (2.3 vs 3.5, p = 0.027). No other differences. HAMD, BDI: Lower depression in women treated with sertraline: HAMD = 6.9 vs 9.3 (p = 0.041) and in BDI = 7.9 vs 10.4 (p = 0.005) than the placebo group. |
| Hernández-Àvila 2004 | Nefazodone (200-600) Placebo | DSM-IV / SCID | 21/20 | ≥18 drinks/week in men or 14 drinks/week in women | 10 | Supportive psychotherapy | TLFB: More nefazodone-treated subjects (n = 7, 33.3%) were abstinent, compared to placebo-treated subjects (n = 3, 15.0%). No statistical significance (p = 0.17). HAMD: No differences between the groups (p = 0.82). |
| Kranzler 2006 | Sertraline (200) Placebo | DSM-IV / PRISM Group A*: HDRS≥17 | 89/100 | ≥18 drinks/week in men or 14 drinks/week in women | 10 | Not reported | TLFB/HAMD: Both alcohol use and depressive symptoms decreased substantially over time in both groups. There were no differences between the groups. |
|  |  | Group B*: HDRS≤16 | 70/69 |  |  |  |  |
| Cornelius 2009 | Fluoxetine (20) Placebo | DSM-IV/ K-SADS-PL+ SCID | 24/26 | At least 10 drinks prior to baseline assessment | 12 | CBT and motivational therapy | TLFB: Significant decrease of alcohol use in subjects in fluoxetine and placebo groups. HAMD: Significant improvement in depressive symptoms in fluoxetine and placebo groups. |
| Pettinati 2010 | Sertraline (200) Naltrexone (100) Sertraline (200) +Naltrexone (100) Placebo | DSM-IV-R/ SCID + questionnaire to differentiate induced from primary | 40 49 42 39 Placebo | 12 or more alcoholic drinks per week | 14 | Weekly CBT | TLFB: Combination of sertraline + naltrexone produced higher alcohol withdrawal rate (53.7%, p = 0.001, OR = 3.7) than the other treatment groups: naltrexone (21.3%), sertraline (27.5%), or placebo (23.1%). HAMD: patients on sertraline + naltrexone were less depressed at the end of treatment (83.3%, p = .014, OR = 3.6) compared to other groups. |

*Note.* BDI: Beck Depression Inventory; CBT: Cognitive Behavioral Therapy; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders; HAMD: Hamilton depression scale; K-SADS-PL: The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version; MADRS: Montgomery-Asberg Depression Rating Scale; OR: Odds Ratio; PRISM: Psychiatric Research Interview for Substance Use Disorders; RCT: Randomized clinical trial; SCID: Structured Clinical Interview for DSM Disorders; TLFB: Time line follow back.

Five RCTs focused on alcohol consumption as the outcome of interest using the time line follow back (TLFB) calendar method (Cornelius et al., 1997; Gual et al., 2003; Kranzler et al., 2006; Pettinati et al., 2001; Sobell & Sobell, 1992). In these five RCTs, differences between SSRI and placebo were not found (n = 431) (moderate quality of evidence). In three RCTs (Cornelius et al., 1997; Gual et al., 2003; Kranzler et al., 2006), differences regarding time to relapse were not found either (n = 163) (very low quality of evidence).

Four RCTs assessed pragmatic variables, such as treatment drop-out from due to side effects using the Modified Systematic Assessment for Treatment and Emergent Events (SAFTEE) instrument and treatment retention (Gual et al., 2003; Moak et al., 2003; Pettinati et al., 2010; Roy, 1998). In one RCT (Pettinati et al., 2010), differences between SSRI and placebo in the SAFTEE score were not found (n = 79) (low quality of evidence). Regarding treatment retention assessed in three RCTs (Gual et al., 2003; Moak et al., 2003; Roy, 1998) differences between SSRI and placebo were not observed (n = 201) (moderate quality of evidence).

- **Recommendations**
  · The administration of SSRI antidepressants for improving depressive symptoms is not recommended (strong recommendation).

· The administration of SSRI antidepressants to reduce alcohol consumption is not recommended (strong recommendation). No recommendation can be made for the outcome "time to relapse" (weak recommendation).

· Regarding pragmatic variables (treatment retention and drop-out from treatment due to side effects) no recommendations can be made (weak recommendation).

*PICO question 2. Is the administration of antidepressants other than SSRI effective to reduce symptoms of depression, to reduce alcohol consumption or to improve pragmatic and functioning variables in patients with depression and alcohol consumption?*

Five studies were included in the revision, two of them evaluating the efficacy of tricyclic antidepressants (Mason, Kocsis, Ritvo & Cutler, 1996; McGrath et al., 1996), one viloxazine (Altamura, Mauri, Girardi & Panetta, 1990) and two evaluating nefazodone (Hernandez-Avila, Modesto-Lowe, Feinn & Kranzler, 2004; Roy-Byrne et al., 2000).

Three RCTs evaluated the efficacy of antidepressants other than SSRI vs placebo in reducing depressive symptoms using the HAMD scale (Mason et al., 1996; McGrath et al., 1996; Roy-Byrne et al., 2000) and showed significant differences in favour of the active treatment at 12 weeks (n = 107), with the highest efficacy for desipramine (Mason et al., 1996) (low quality of evidence).

Four RCTs studied reduction of alcohol consumption as the outcome of interest using the TFLB (Hernandez-Avila et al., 2004; Mason et al., 1996; McGrath et al., 1996; Roy-Byrne et al., 2000). At 12 weeks, differences between antidepressants other than SSRI and placebo were not found (n = 150) (moderate quality of evidence).

Three RCTs compared other depressants with placebo regarding pragmatic variables (Hernandez-Avila et al., 2004; Mason et al., 1996; Roy-Byrne et al., 2000). In two RCTs (Mason et al., 1996; Roy-Byrne et al., 2000), differences in the SAFTEE score or self-reported side effects were not observed (n = 86) (moderate quality of evidence). Treatment retention was assessed in two RCTs (Hernandez-Avila et al., 2004; Roy-Byrne et al., 2000) and

differences between other antidepressants and placebo were not significant (n = 105) (low quality of evidence).

- **Recommendations**

· In patients with depression and alcohol consumption, administration of non-SSRI, mainly tricyclic antidepressants is recommended (strong recommendation).

· The administration of non-SSRI antidepressant to reduce alcohol consumption is not recommended (weak recommendation).

· Recommendations cannot be made regarding the effect of non-SRRI antidepressants on pragmatic variables (drop-out from treatment due to side effects and treatment retention) (weak recommendation).

## Patients with Depressive Disorder and cannabis use

Details about included studies are shown in Table 3.

*PICO question 3. Is the administration of antidepressants other than SSRI effective to reduce symptoms of depression, to reduce cannabis consumption or to improve pragmatic and functioning variables in patients with depression and cannabis consumption?*

One RCT evaluated the effect venlafaxine on the outcome of reduction of depressive symptoms at 12 weeks using the HAMD scale (Levin et al., 2013), and differences were not found (n = 103) (moderate quality of evidence). This RCT (Levin et al., 2013) also evaluated the effect of venlafaxine for reducing cannabis consumption assessed by quantitative urine tetrahydrocannabinol (THC) levels. At 12 weeks, differences in favour of placebo were observed (n = 103) (moderate quality of evidence).

The same RCT (Levin et al., 2013) assessed pragmatic variables, and differences between non-SRRI antidepressants and placebo in the outcomes of drop-out from treatment at 12 weeks due to side effects (n = 103) (low quality of evidence) and treatment retention (n = 103) (moderate quality of evidence) were not found.

- **Recommendations**

· In patients with depression and cannabis consumption, the administration of venlafaxine to

Table 3. *Depression and cannabis use disorder.*

| AUTHORS | DRUG USED MG/DAY | DIAGNOSIS/ INSTRUMENT | CASE/ CONTROL | CONSUMPTION AT START OF RCT | WEEKS | CONCOMITANT THERAPY | OUTCOME VARIABLE |
|---|---|---|---|---|---|---|---|
| Levin 2013 | VEN-XR (375) Placebo | DSM-IV/SCID | 51/52 | Current consumption | 12 | CBT and relapse prevention | TLFB/UC: Proportion of patients achieving abstinence was significantly worse in VEN-XR (11.8%) compared to placebo (36.5%) (x1 (2) = 7.46, p ‹0.01; OR = 4.51). HAMD: Proportion of patients with clinically significant improvement in mood did not differ between the VEN-XR (63%) and placebo (69%) groups (P = 0.49). |

*Note.* CBT: Cognitive Behavioral Therapy; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders; HAMD: Hamilton Depression Scale; OR: Odds Ratio; SCID: Structured Clinical Interview for DSM Disorders; TLFB: Time line follow back; UC: Urine Controls; VEN-XR: venlafaxine extended release.

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reduce depressive symptoms is not recommended (weak recommendation).

· The use of venlafaxine to reduce cannabis consumption is not recommended (weak recommendation).

· It is not possible to make any recommendation regarding the effect of venlafaxine on pragmatic variables (drop-out from treatment due to side effects and treatment retention) (weak recommendation).

### Patients with Depressive Disorder and cocaine use

Details about included studies are shown in Table 4.

*PICO question 4. Is the administration of SSRIs antidepressants effective to reduce symptoms of depression, to reduce cocaine consumption or to improve pragmatic and functioning variables in patients with depression and cocaine consumption?*

Table 4. *Depression and cocaine use disorder.*

| AUTHORS | DRUG USED MG/DAY | DIAGNOSIS/ INSTRUMENT | CASE/ CONTROL | CONSUMPTION AT START OF RCT | WEEKS | CONCOMITANT THERAPY | OUTCOME VARIABLE |
|---|---|---|---|---|---|---|---|
| Ziedonis 1991 | Desipramine (150) or Amantadine (300) Placebo | DSM-III-R/SCID | 30/33 31 | 3 days abstinent | 12 | MMP | UC: Increase in %age of negative UCs in the last 2 weeks in the desipramine group (42%) compared to Placebo group (6%) (p ‹0.01). BDI: Better BDI results in desipramine group (mean: 9) than placebo group (mean: 15). |
| Nunes 1995 | Imipramine (150–300) Placebo | DSM-III-R/SCID | 38/31 | Current consumption | 12 | Individual counselling | UC: non-significant increase in negative UC for three consecutive weeks in imipramine (26%) vs. placebo (13%). HDRS: No effect in treating depression. |
| Cornelius 1998 | Fluoxetine (20) Placebo | DSM-III-R/SCID | 8/9 | ±9 days abstinent | 12 | Supportive therapy | UC, ASI, TLFB, AR: No significant differences observed in intra- or intergroup cocaine use. BDI: Mean BDI score down 2.2 points on placebo and up 3.9 points on fluoxetine, statistically not significant. |
| Schmitz 2001 | Fluoxetine (40) Placebo | DSM-IV/SCID | 34/34 | Current consumption | 12 | CBT and relapse prevention | UC: No significant differences in negative UC at the end of treatment between both groups. HAMD: Depressive symptoms decrease as a function of treatment time, without significant differences. |
| Mc Dowell 2005 | Desipramine (300) Placebo | DSM-III-R /SCID, consulta con 2 expertos | 55/56 | Current consumption | 12 | CBT and relapse prevention | TLFB, UC: Treatment groups showed no difference in response rate. CGI, HAMD: Desipramine was associated with higher response rate in depressive symptoms (51%, 28/55) than placebo (32%, 18/56) (p ‹0.05). |
| Ciraulo 2005 | Nefazodone (200) Placebo | DSM-IV | 34/ 35 | Current consumption | 8 | Counseling | UC: Benzoylecgonine weekly average decreased more rapidly in nefazodone group than in placebo group. Both groups had equivalent improvement in mood. |
| Asphar 2012 | Mirtazapine (45) Placebo | DSM-IV | 11/13 | Current consumption | 12 | Relapse prevention | UC/AR: Cocaine use during treatment period did not differ significantly between mirtazapine and placebo groups. HAMD: Significant reduction at week 1 in HAMD scores, both for mirtazapine [p = 0.002] and for placebo groups [p = 0.005]. |
| Oliveto 2012 | Sertraline (200) Placebo | DSM-IV (SCID) | 32/27 | Current consumption | 12 | CBT | UC/AR: Reduction in use in 19 (70.3%) placebo and 17 (53.1%) sertraline subjects. HAMD: Scores decreased significantly over time (p ‹0.0001), but with no difference between groups (p = 0.77). |
| Mancino 2014 | Sertraline (200) Placebo | DSM-IV (SCID) | 23/27 | Current consumption | 12 | CBT | UC: Sertraline subjects had a significantly lower overall percentage of positive urine samples compared to placebo. HAMD: depression scores decreased significantly over time, regardless of treatment group. |
| Raby 2014 | Venlafaxine (300) Placebo | DSM-IIIR/ SCID | 66/66 | Current consumption | 12 | Relapse prevention | UC: No differences found between treatment groups. Proportion of patients achieving 3 or more consecutive weeks of confirmed abstinence in urine was low (venlafaxine: 16%; placebo: 15%). HAMD: Improvement in mood was 41% (26/64) in venlafaxine group, and 33% (22/66) in placebo. |

*Note.* AR: Self-reported cocaine use; ASI: addiction severity index; BDI: Beck Depression Inventory; CBT: Cognitive Behavioral Therapy; CGI: Clinical Global Impression Scale; CM: Contingency management; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders; HAMD: Hamilton depression rating scale; MMP: Methadone Maintenance Program; RCT: Randomized clinical trial; SCID: Structured Clinical Interview for DSM Disorders; TLFB: time-line follow-back; UC: urine control.

One RCT assessed improvement of depressive symptoms at 12 weeks using the HAMD scale (Schmitz et al., 2001), and there were no significant differences between SSRI antidepressants and placebo (n = 68) (low quality of evidence).

Three RCTs (Mancino et al., 2014; Oliveto et al., 2012; Schmitz et al., 2001) compared SSRI antidepressant with placebo for the outcome of decrease in cocaine consumption at 12 weeks using cocaine urine testing, and significant differences were not encountered (n = 177) (low quality of evidence).

One RCT (Schmitz et al., 2001) compared SSRI antidepressant and placebo for treatment retention and differences were not found (n = 68) (very low quality of evidence).

- **Recommendations**
  · In patients with depression and cocaine consumption, the use of SSRI antidepressants for improving depressive symptoms is not recommended (weak recommendation). Recommendations regarding the use of non-SSRI antidepressant cannot be made.
  · The administration of SSRI antidepressant to reduce cocaine consumption is not recommended (strong recommendation).
  · The administration of SSRI antidepressants to improve treatment retention is not recommended (weak recommendation).

*PICO question 5. Is the administration of antidepressants other than SSRI effective to reduce symptoms of depression, to reduce cocaine consumption or to improve pragmatic and functioning variables in patients with depression and cocaine consumption?*

A total of six RCTs evaluated the efficacy of non-SSRI antidepressants, three of them evaluated tricyclic antidepressants (McDowell et al., 2005; Nunes et al., 1995; Ziedonis & Kosten, 1991); one nefazodone (Ciraulo et al., 2005); one mirtazapine (Afshar et al., 2012); and one venlafaxine (Raby et al., 2014).

Three RCTs (McDowell et al., 2005; Nunes et al., 1995; Raby et al., 2014) evaluated the effect of non-SSRI antidepressants vs placebo on reduction of depressive symptoms at 12 weeks using HDMA. Differences in favour of the active treatment were found (n = 310), with desipramine as the most effective intervention (Nunes et al., 1995) (moderate quality of evidence). In relation to severity of depression assessed with the Clinical Global Impression (CGI) scale, differences between non-SSRI antidepressants and placebo were not found (n = 259) (low quality of evidence).

Five RCTs assessed the outcome of reduction of cocaine consumption. In four RCTs (McDowell et al., 2005; Nunes et al., 1995; Raby et al., 2014; Ziedonis & Kosten, 1991), no differences between non-SSRI antidepressants and placebo in decrease in cocaine consumption at 12 weeks as

confirmed by urine testing were found (n = 324) (moderate quality of evidence). Also, in two RCTs (Afshar et al., 2012; McDowell et al., 2005) no significant differences were found in cocaine craving using the Conceptual Craving Scale (CCS) (n = 129) (very low quality of evidence). For the outcome "days of week taking cocaine" analyzed in three RCTs (Afshar et al., 2012; McDowell et al., 2005; Raby et al., 2014), significant differences were not observed (n = 259) (moderate quality of evidence).

Drop-out from treatment due to side effects was assessed in three RCTs (McDowell et al., 2005; Nunes et al., 1995; Raby et al., 2014), and there were no significant differences between non-SSRI antidepressants and placebo (n = 354) (very low quality of evidence). In relation to treatment retention assessed in two RCTs (McDowell et al., 2005; Raby et al., 2014), differences were not found (n = 241) (low quality of evidence).

- **Recommendations**
  · The use of antidepressants other than SSRI, mainly tricyclic antidepressants, for improving depressive symptoms is recommended (strong recommendation).
  · The use of antidepressants other than SSRI to improve cocaine consumption (abstinence) is not recommended (strong recommendation).
  · The use of antidepressants other than SSRI to reduce craving is not recommended (weak recommendation).
  · The use of antidepressants other than SSRI for improving treatment retention or reducing drop-out from treatment due to side effects is not recommended (weak recommendation).

### *Patients with Depressive Disorder and nicotine use*
Details about included studies are shown in Table 5.

*PICO question 6. Is the administration of antidepressants other than SSRIs effective to reduce nicotine consumption in patients with depression and nicotine consumption?*

Three RCTs have compared the effectiveness of non-SSRIs (bupropion) vs placebo on smoking cessation measured by exhaled carbon monoxide levels (Catley et al., 2005; Evins et al., 2008; Schnoll et al., 2010). Differences between the two study groups were not found (n = 306) (moderate quality of evidence).

- **Recommendations**
  · The administration of non-SSRIs (bupropion) to reduce nicotine consumption is not recommended (strong recommendation).

### *Psychological treatment*

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Table 5. *Depression and nicotine use disorder.*

| AUTHORS | DRUG USED MG/DAY | DIAGNOSIS/ INSTRUMENT | CASE/ CONTROL | CONSUMPTION AT START OF RCT | WEEKS | CONCOMITANT THERAPY | OUTCOME VARIABLE |
|---|---|---|---|---|---|---|---|
| Brown 2007 | Bupropion (150) Placebo | CES-D | 108/157 | Current consumption | 12 | CBT | CMC: Bupropion showed better results for smokers in both intensive group treatments. |
| Catley 2005 | Bupropion (150) Placebo | CES-D | 78/83 | Current consumption | 7 | Counselling and quit smoking guide | CMC: (self-reported/CO): No significant differences found between the groups. Placebo group had greater nicotine use reduced. |
| Evins 2008 | Bupropion (150) + NRT (21) / Placebo | DSM-IV/SCID | 45/45 | Current consumption | 13 | CBT | TLFB/CO: Abstinence rates at the end of the trial were 36% (37/97) in bupropion + NRT + CBT group and 31% (32/102) in placebo + NRT + CBT group. Not statistically significant. |
| Thorndike 2008** | Bupropion (150) Placebo | BDI | 21/32 | Current consumption | 12 | CBT | CMC: Smokers with low BDI scores are more likely to maintain abstinence than those with high BDI scores at 3 months of follow-up (37% vs 15%; OR 3.02) and at 12 months of follow-up (27% vs 10%; OR 3.77). |
| Schnoll 2010 | Bupropion + NRT / placebo. | CES-D | 28/27 | Current consumption | 9 | Counseling + NRT | CMC: No main effect of bupropion versus placebo on withdrawal (OR 1.36). Patients with depression symptoms reported significantly lower abstinence rates compared to patients without depression symptoms (OR = 0.14) |

*Note.* BDI: Beck Depression Inventory; CBT: Cognitive Behavioral Therapy; CES-D: Center for Epidemiologic Studies Depression Scale; CMC: Carbon Monoxide Concentration; CO: Carbon monoxide; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders; NRT transdermal patch; OR: Odds ratio; RCT: Randomized clinical trial; SCID: Structured Clinical Interview for DSM Disorders; TLFB: time-line follow-back.
** Secondary analyses.

*PICO question 7. Is psychological treatment effective to reduce depressive symptoms or to reduce alcohol consumption in patients with depression and alcohol consumption?*

The meta-analysis of Hobbs et al. (Hobbs, Kushner, Lee, Reardon & Maurer, 2011) reports the effects from 15 published RCTs trials examining the impact of supplementing alcohol use disorder treatment with a pharmacological treatment vs cognitive behavioural therapy (CBT) for improvement of co-occurring internalizing symptoms (anxiety or depression). CBT intervention had a pooled estimate of effect size of Cohen's $d = 0.66$, while medication yielded a smaller estimate pooled effect size of $d = 0.24$ (quality of evidence very low). The meta-analysis of Riper et al. (2014) carried out in 12 studies assessed the effectiveness of combining CBT and motivational interviewing (MI) (CBT/MI) to treat comorbid alcohol use disorder and major depression as compared with usual care in a total of 1721 patients (experimental group 1026, control group 695). The effects of CBT/MI on decrease of depression symptoms over controls were small but significant at post-test (Hedge's $g = 0.27$, 95% CI 0.13–0.41, $p < 0.001$). When the impact of CBT/MI on depressive symptoms was assessed at follow-up (6-12 months post-treatment), a similar effect size was found ($g = 0.26$, 95% CI -0.01 to 0.54) (moderate quality of evidence).

In the study of Hobbs et al. (2011) with a total of three studies for the analysis of the alcohol outcome, the effect size for decreasing alcohol consumption was higher for CBT ($d = 0.29$) than for pharmacological treatment ($d$ = 0.17) but differences were not significant (low quality of evidence). In the meta-analysis of Riper et al. (2014), CBT/MI showed a small but significant effect on reduction of alcohol consumption ($g = 0.17$). At 6-12 months follow-up the effect was $g = 0.31$ (moderate quality of evidence).

- **Recommendations**
  · In patients with depression and co-occurring alcohol abuse disorder, both pharmacotherapy and cognitive behavioural therapy have positive effects on internalizing symptoms (levels of anxiety and depression) (weak recommendation).
  · In patients with depression and co-occurring alcohol abuse disorder, both pharmacotherapy and cognitive behavioural therapy have positive effects for reducing alcohol consumption (weak recommendation).

*PICO question 8. Is psychological treatment effective to reduce depressive symptoms or to reduce substance use in patients with depression and substance use disorder?*

Hesse et al. (2009) carried out a systematic review and meta-analysis to assess integrated treatment of substance use disorders and co-morbid depression as compared with a treatment program solely focusing on the substance use disorder (control). For the outcome of improvement of depressive symptoms assessed with the Hamilton Rating Scale for Depression (HRSD), combined effect was $d = -4.6$ points on the HRSD for experimental condition compared with control (95% CI -7.4 to 1.7), with a significant moderately high heterogeneity in the outcome ($I^2 = 0.61$, $p = 0.05$) (low quality of evidence). For studies that reported

self-report questionnaire outcomes for depression, the combined effect was d = -0.58 (95% CI -1.10 to -0.06). Heterogeneity was not significant and low to moderate ($I^2 = 0.46$, $p = 0.14$) (low quality of evidence). Regarding percent days abstinent outcome, comparison favoured treatment with a mean difference of 13.75 (95% CI 0.51 to 22.99) ($I^2 = 0.17$, $p = 0.30$) (moderate quality of evidence).

- **Recommendations**
  · Psychological therapy for comorbid depression and SUD is a promising approach but it is not sufficiently empirically supported as an option to improve depressive symptoms (moderate recommendation).

## Conclusions

This review evidences that a small number of double-blind, placebo-controlled trials have been conducted in patients with depression and SUD aimed to evaluate the impact of pharmacotherapy on both depressive symptoms and the reduction in substance use. Several clinical trials have demonstrated a beneficial effect of antidepressants on mood symptoms in patients with comorbid SUD but yet failed to establish their effectiveness on substance use outcomes due to inconsistent results.

Our results suggest that 1) In patients with depression and alcohol use disorder, the administration of non-SSRI antidepressants instead of SSRI is recommended for improvement of depressive symptoms (strong recommendation). Neither SSRI (strong recommendation) nor non-SSRI (weak recommendation) antidepressants are recommended for reduction in alcohol consumption. 2) In patients with depression and cannabis use disorder, the use of venlafaxine is not recommended (weak recommendation). 3) In patients with depression and cocaine use disorder, the use of SSRI antidepressants for improving depressive symptoms (weak recommendation) or to reduce cocaine use is not recommended (strong recommendation). The use of non-SSRI antidepressants is only recommended for improving depressive symptoms (strong recommendation). 4) The administration of bupropion to reduce nicotine consumption is not recommended (strong recommendation). 5) Regarding psychological treatment, in patients with depression and co-occurring alcohol disorder, both pharmacotherapy and cognitive behavioural therapy have positive effects on internalizing symptoms and in reducing alcohol consumption (weak recommendation).

Very few of the randomized trials performed so far have provided consistent evidence for the management of both depression and substance use. In patients with depression and cannabis use, only venlafaxine has been assayed. Therefore, the need for more research in this area and for larger, multisite studies with generalizable samples to provide more definite evidence is mandatory.

## Conflict of interests

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

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