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

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

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Abstract

Substantial evidence has confirmed the high comorbidity between Attention-Deficit/Hyperactivity Disorder (ADHD) and a substance use disorder (SUD). This review synthesizes the pharmacological and psychosocial interventions conducted in ADHD and SUDs, and provides clinical recommendations using the GRADE approach. Our results suggest: 1) In patients with ADHD and alcohol use, atomoxetine is recommended to reduce ADHD symptoms (weak recommendation) and alcohol craving (weak recommendation). 2) In patients with ADHD and cannabis use disorder, atomoxetine is recommended to improve ADHD symptoms (weak recommendation), not to reduce cannabis use (weak recommendation). 3) In patients with ADHD and cocaine use disorder, methylphenidate is not recommended to improve ADHD symptoms or to reduce cocaine use (weak recommendation). 4) In patients with ADHD and comorbid nicotine use disorder, methylphenidate is recommended to improve ADHD symptoms (weak recommendation). Psychoestimulants,

Resumen

La evidencia actual confirma la alta comorbilidad entre el trastorno por déficit de atención con hiperactividad (TDAH) y trastorno por uso de sustancias (TUS). Esta revisión resume las intervenciones farmacológicas y psicosociales que se han evaluado en pacientes con TDAH y TUS, y ofrece recomendaciones mediante el enfoque GRADE. Nuestros resultados sugieren: 1) En pacientes con TDAH y trastorno por uso de alcohol, la atomoxetina es recomendable para reducir los síntomas de TDAH (recomendación débil) y el *craving* de alcohol (recomendación débil). 2) En pacientes con TDAH y trastorno por uso de cannabis, la atomoxetina es recomendable para mejorar los síntomas de TDAH (recomendación débil), no para reducir el uso de cannabis (recomendación débil). 3) En pacientes con TDAH y trastorno por uso de cocaína, el metilfenidato no es recomendable para mejorar los síntomas de TDAH o para reducir el uso de cocaína (recomendación débil). 4) En pacientes con TDAH y trastorno por uso de nicotina, es recomendable el metilfenidato para mejorar los

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such as methylphenidate or lisdexamfetamine dimesylate, are not recommended to reduce nicotine use (weak recommendation). 5) Regarding patients with ADHD and any SUD, the use of psychostimulants is recommended to improve ADHD symptoms (weak recommendation), not to reduce substance use (weak recommendation) or to improve retention to treatment (strong recommendation). In these patients, the use of atomoxetine is recommended to improve ADHD symptoms (weak recommendation), not to decrease substance use (weak recommendation) or to improve retention to treatment (strong recommendation). Atomoxetine and psychostimulants appear to be safe in patients with any SUD (strong recommendation). Our review suggests the need for more research in this area and for larger, multisite, randomized studies to provide more definite and conclusive evidence.

Keywords: Attention-Deficit/Hyperactivity Disorder, ADHD, substance use, cannabis, cocaine, alcohol, nicotine, psychostimulants, methylphenidate, lisdexamfetamine dimesylate, atomoxetine.

síntomas de TDAH (recomendación débil). Los psicoestimulantes, como metilfenidato o lisdexanfetamina, no son recomendables para reducir el uso de nicotina (recomendación débil). 5) Respecto de los pacientes con TDAH y cualquier TUS, el uso de los psicoestimulantes es recomendable para mejorar los síntomas de TDAH (recomendación débil), no para reducir el uso de sustancias (recomendación débil) o para mejorar la retención del tratamiento (recomendación fuerte). En estos pacientes, el uso de atomexetina es recomendable para mejorar los síntomas de TDAH (recomendación débil), no para reducir el uso de sustancias (recomendación débil) o para mejorar la retención del tratamiento (recomendación fuerte). La atomoxetina y los psicoestimulantes parecen ser seguros en pacientes con cualquier TUS (recomendación fuerte). Nuestra revisión sugiere la necesidad de realizar más investigaciones en esta área y de estudios aleatorizados, multicéntricos y de mayor tamaño muestral para proporcionar más evidencia definitiva y concluyente.

Palabras clave: Trastorno por déficit de atención con hiperactividad, TDAH, uso de sustancias, cannabis, cocaína, alcohol, nicotina, psicoestimulantes, metilfenidato, lisdexanfetamina, atomoxetina.

Substantial evidence has confirmed the high comorbidity between Attention-Deficit/Hyperactivity Disorder (ADHD) and a substance use disorder (SUD), with the estimation that ADHD is present in almost one out of every four patients with SUD (van Emmerik-van Oortmerssen et al., 2012). In addition, up to 50% of adult patients with ADHD may suffer from comorbid cannabis disorder (Torgersen, Gjervan & Rasmussen, 2006), 45% from alcohol use disorder (Biederman, Wilens, Mick, Faraone & Spencer, 1998), 40% from nicotine dependence (Pomerleau, Downey, Stelson & Pomerleau, 1995), 21% from cocaine use disorder (Lambert & Hartsough, 1998), and 30% from dependence to other drugs of abuse (Wilens, 2004).

The mechanism of the association between TUS and ADHD is not fully understood. Impulsivity has been postulated to be the factor linking both disorders, as the impairment in impulse control characteristic of ADHD patients would lead to an increased substance use and, consequently, to an increased risk of developing a SUD (Urcelay & Dalley, 2012). ADHD patients could also self-medicate to improve ADHD symptoms (Khantzian, 1985; Wilens et al., 2007).

The presence of ADHD has a negative influence on SUD. Patients with ADHD are more prone to begin using drugs at an early age (Wilens, Biederman, Mick, Faraone & Spencer, 1997) and the severity of SUD is higher among ADHD patients (Pérez de Los Cobos et al., 2011), with increased risk for relapse and drop-out from treatment (Humfleet et al., 2005). Also, drug consumption in ADHD patients increases criminal behaviour (Mannuzza et al., 2010) and the risk for fatal accidents (Dalsgaard, Ostergaard, Leckman, Mortensen & Pedersen, 2015).

Although effective drugs for treating ADHD are available in the therapeutic armamentarium, patients with dual ADHD and a SUD diagnosis are rarely treated with ADHD medications in clinical practice (Castells, Ramos-Quiroga, Bosch, Nogueira & Casas, 2011a; Castells et al., 2011b; Cunill & Castells, 2016a; Cunill, Castells, Tobias & Capellà, 2016b). Reason include scarce and inconclusive evidence of the efficacy of pharmacological treatment of ADHD in patients with comorbid SUD (Perez De Los Cobos, Siñol, Perez & Trujols, 2014), caution of treating physicians because of concerns about euphoric effects of psychostimulants, potential risk of abuse (Wilens et al., 2008a) or safety of stimulants especially methylphenidate which may enhance cardiovascular side effects of cocaine (Collins, Levin, Foltin, Kleber & Evans, 2006). Thus, considering the high prevalence of concurrent ADHD and SUD, in particular nicotine, cannabis, alcohol and cocaine, and the negative effects of this dual pathology, evidence-based recommendations for the management of these patients are needed.

Methods

Formulation of clinical questions

In accordance with evidence-based medicine principles, we used the 'PICO' structure (Patient-Intervention-Comparison-Outcomes [Oxman, Schünemann & Fretheim, 2006; Guyatt 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 an Attention-Deficit Hiperactivity Disorder (ADHD) and a SUD?*". Patients older than 18 years diagnosed with an ADHD and a SUD (including cannabis, cocaine, alcohol and/or nicotine) were the target population of this clinical

guideline. Opioid use disorder was not included because no systematic reviews with or without meta-analysis or randomized clinical trials were found.

Bibliographic search

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

- Pubmed (psycological intervention)

((metaanalysis OR "meta analysis" OR "systematic review")) 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))) AND (((((("Attention Deficit Disorder with Hyperactivity"[Mesh] OR ADHD)) 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" OR "substance abuse"))))

- Limits: Young Adult: 19-44 years; Middle Aged: 45-64 years
- Pubmed (exhaustive with systematic review and meta-analysis)

(((((("Attention Deficit Disorder with Hyperactivity"[Mesh] OR ADHD)) 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" OR "substance abuse") AND ((adult[MeSH:noexp] OR middle age[MeSH])))) 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 ((metaanalysis OR "meta analysis" OR "systematic review" OR systematic[sb]))

- Limits: Young Adult: 19-44 years; Middle Aged: 45-64 years

(((((("Attention Deficit Disorder with Hyperactivity"[Mesh] OR ADHD)) 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" OR "substance abuse") AND ((adult[MeSH:noexp] OR middle age[MeSH])))) 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 ((metaanalysis OR "meta analysis" OR "systematic review" OR systematic[sb]))

- Limits: +19 years
- Pubmed (exhaustive with Randomized Controlled Trial)

((("Attention Deficit Disorder with Hyperactivity"[Mesh] OR ADHD)) 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

- Cochrane

"attention deficit hyperactivity disorder" OR ADHD in Title, Abstract, Keywords and "alcohol abuse" OR "alcohol use" in Title, Abstract, Keywords

"attention deficit hyperactivity disorder" OR ADHD in Title, Abstract, Keywords and "nicotine dependence" OR "nicotine" in Title, Abstract, Keywords

"attention deficit hyperactivity disorder" OR ADHD in Title, Abstract, Keywords and "cannabis" OR "marijuana" in Title, Abstract, Keywords

"attention deficit hyperactivity disorder" OR ADHD in Title, Abstract, Keywords and "cocaine" in Title, Abstract, Keywords

- Tripdatabase

(ADHD* OR attention deficit hyperactivity disorder OR attention deficit hyperactivity*) AND (addiction* OR abuse substance OR substance abuse OR misuse OR substance dependence OR co-ocurr* OR concurren* OR dual diagnosis OR dual patholog* OR comorbidit*) AND (alcohol OR nicotine OR marijuana OR drinking OR cannabis OR cocaine OR smok*)

- PsycInfo

Index Terms: {Attention Deficit Disorder with Hyperactivity} AND **Index Terms**: {Nicotine} OR {Smokeless Tobacco} OR {Tobacco Smoking} OR {Cannabis} OR {Nicotine} OR {Smokeless Tobacco} OR {Tobacco Smoking} OR {Alcohol Abuse} OR {Alcohol Drinking Attitudes} OR {Alcoholism} OR {Ethanol} OR {Cocaine}

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 (Arranz et al., 2021) (San & Arranz, 2016).

Results

Figure 1 outlines PRISMA flowchart leading to the study selection. The search yielded 715 studies. 64 studies were deemed eligible for further assessment. The final selection included 8 studies (one metaanalysis). 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

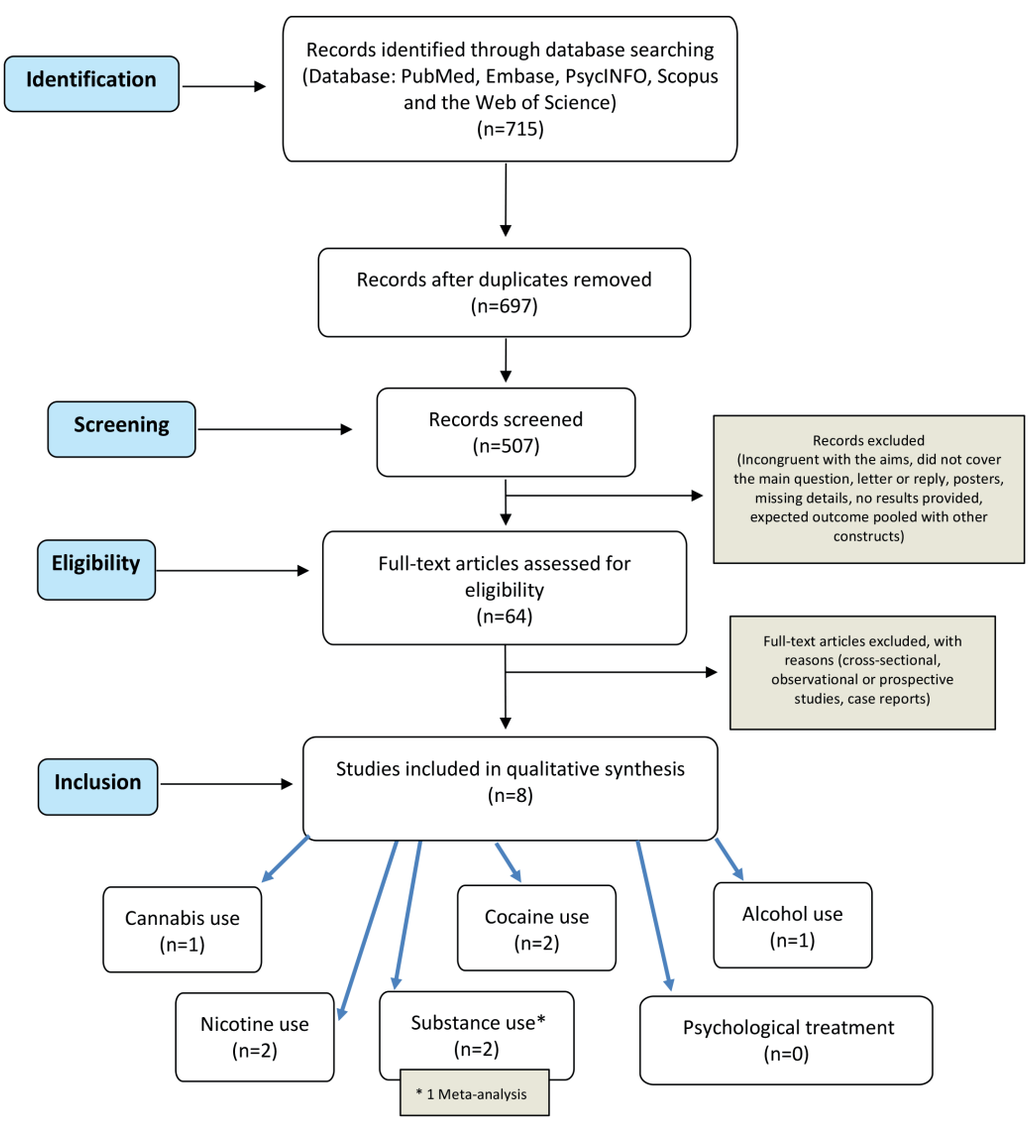

Figure 1. Flow chart of study selection process.

each study was assessed using standard criteria. A summarized report of these studies can be found in Table 1.

Patients with ADHD and alcohol use disorder

Details about included studies are shown in Table 1.

PICO question 1. *Are non-stimulant medications effective to improve symptoms of ADHD and/or reduce alcohol craving and drop-out from treatment in patients with ADHD and alcohol use disorder? and Are non-stimulant medications safe in patients with ADHD and comorbid alcohol use disorder?*

One randomized controlled trial (RCT) evaluated the effect of atomoxetine *vs* placebo in 147 Adults with diagnoses of ADHD and alcohol abuse and/or dependence that were abstinent from alcohol at least 4 days (maximum 30 days) before study randomization (Wilens et al., 2008b). Participants received atomoxetine (25-100mg daily) or placebo for 12 weeks. Changes in ADHD symptoms assessed using ADHD Investigator Symptom Rating Scale (AISRS) and Adult ADHD Self-Report Scale (ASRS) were significantly higher in the atomoxetine group as compared to placebo (AISRS, MD -5.30, 95% CI -9.51 to -1.09, $p = 0.01$; ASRS, MD -4.60, 95% CI -8.76 to -0.44, $p = 0.03$). Differences in GCI-I were also significant (MD 0.50, 95% CI -0.87 to -0.13, $p = 0.008$) (very low quality of evidence). No significant differences between treatment groups occurred in improvement of alcohol consumption (MD 0.10, 95% CI 0.00 to 0.20), number of drinks per day of alcohol use (MD -0.50, 95% CI -1.45 to 0.45), and percentage of patients with self-reported abstinence at the end of the study (OR 1.44, 95% CI 0.31 to 6.67) assessed by means of the Timeline Followback Method (TLFB) (very low quality of evidence). However, reduction in alcohol craving assessed using the Obsessive-Compulsive Drinking Scale OCDS e) was significantly higher in the atomoxetine group (MD -2.60, 95% CI -4.64 to -0.56, $p = 0.01$) (very low quality of evidence). Drop-outs were higher with atomoxetine than with placebo (OR 2.22, 95% CI 1.15 to 4.31; $p = 0.02$). In terms of safety, differences in drop-outs of treatment because of adverse events (OR 3.93, 95% CI 0.79 to 19.60) or number of patients with at least one adverse event (OR 1.82, 95% CI 0.77 to 4.29) were not observed (low/very low quality of evidence).

- Recommendations
  - · In adult patients with ADHD and co-occurring alcohol use disorder, the use of atomoxetine is recommended to improve severity of ADHD symptoms (weak recommendation) and alcohol craving (weak recommendation) but not to reduce alcohol consumption (weak recommendation).
  - · Atomoxetine should not be used to improve treatment retention (weak recommendation).
  - · The use of atomoxetine should not be discouraged for safety reasons (weak recommendation).

Patients with ADHD and cannabis use disorder

Details about included studies are shown in Table 1.

PICO question 2. *Are non-stimulant medications effective to improve symptoms of ADHD and/or reduce cannabis craving and drop-out from treatment in patients with ADHD and cannabis use disorder? and Are non-stimulant medications safe in patients with ADHD and comorbid cannabis use disorder?*

Only one RCT evaluated the effects of atomoxetine on the symptoms ADHD and cannabis use in patients with concurrent ADHD and cannabis abuse disorder (McRae-Clark et al., 2010). Participants received either atomoxetine (n = 19) or matching placebo (n = 19) for 12 weeks. Patients randomized to atomoxetine had greater improvement in ADHD on the CGI-I scale than participants treated with placebo (n = 38, MD -0.63, 95% CI -1.15 to -0.11, $p = 0.02$) but no changes in the severity of ADHD along the study assessed using the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADS) completed by the investigator (MD -2.49, 95% CI -7.36 to 2.38) and the Conners' Adult ADHD Rating Scale-Self (CAARS-SELF) completed by the participant (MD -4.00, 95% CI -9.99 to 1.99) were found (very low quality of evidence). For the outcome of cannabis use, there were no significant differences between atomoxetine and placebo in the number of negative urine drug tests during the study (MD 2.0, 95% CI -19.74 to 15.74), improvement of self-report use assessed by means of the TLFB (MD 8.0, 95% CI -11.97 to 27.97), and marijuana craving assessed by means of the Marijuana Craving Questionnaire (MCQ) (MD 3.66, 95% CI -5.68 to 13.0) (very low quality of evidence). No differences in drop-outs were found between groups (OR 0.73, 95% CI 0.24 to 2.20). Differences in safety variables (drop-outs from treatment due to adverse effects and number of patients with at least one adverse effect) were not found (OR 3.08, 95% CI 0.12 to 77.91; and OR 8.27 CI95% 0.40 to 172.05; respectively).

- Recommendations
  - · In adult patients with ADHD and cannabis use, the use of atomoxetine is recommended to improve ADHD symptoms (weak recommendation) but not to reduce cannabis use (weak recommendation). Atomoxetine should not be discouraged for safety reasons in patients with ADHD and cannabis use (weak recommendation).

Patients with ADHD and cocaine use disorder

Details about included studies are shown in Table 1.

PICO question 3. *Are psychostimulants effective to improve symptoms of ADHD and/or reduce cocaine craving and drop-out from treatment in patients with ADHD and cocaine use disorder? and Are psychostimulants safe in patients with ADHD and comorbid cocaine use disorder?*

Two RCTs assessed efficacy and safety of treatment with psychostimulants (methylphenidate) *vs* placebo in 154 adult patients with ADHD and cocaine dependence over 12 and 14 weeks, respectively (Schubiner et al., 2002) (Levin, Evans, Brooks & Garawi, 2007). Clinical improvement at the end of the study was greater in patients treated with methylphenidate compared to those treated with placebo (MD -0.80, 95% CI -1.30 to -0.30; $p = 0.002$). Nevertheless, no differences between groups were found for the proportion of patients that at the end of the study achieved 1) an improvement of ADHD symptoms whether the rater was the investigator (defined as 30% decrease in the Targeted Adult Attention Deficit Disorder Scale [TAADS] score) (OR 1.66, 95% CI 0.74 to 3.75) or the patient (defined as 30% decrease in the Adult ADHD Self-Report Scale (AARS) score) (OR 0.74, 95% CI 0.34 to 1.59); 2) an improvement of clinical impression (defined as CGI-I score < 3) (OR 1.19, 95% CI 0.53 to 2.69); and 3) an improvement of both ADHD symptoms and clinical impression (defined as decrease of 30% of AARS score and CGI score < 3) (OR 1.10, 95% CI 0.47 a 2.53) (very low quality of evidence). Also, no significant differences in self-reported cocaine use (MD -0.84, 95% CI -2.60 to 0.92), urinalysis results (MD 0.08, 95% CI -0.16 to 0.32), or clinical improvement of cocaine dependence (CGI-I score < 3) (OR 1.58, 95% CI 0.73 to 3.42) between patients assigned to treatment with methylphenidate or placebo were found (very low quality of evidence). Overall treatment drop-outs (OR 1.23, 95% CI 0.65 to 2.33) and drop-outs associated with adverse effects (OR 0.62, 95% CI 0.07 to 5.13) were similar in both study groups (very low quality of evidence).

- Recommendations
  - · In adult patients with ADHD and comorbid cocaine use, methylphenidate is not recommended to improve ADHD symptoms or to reduce cocaine consumption weak recommendation).
  - · The use of methylphenidate should not be discouraged for safety reasons (weak recommendation).

Patients with ADHD and nicotine use disorder

Details about included studies are shown in Table 1.

PICO question 4. *Are psychostimulants effective to improve symptoms of ADHD and/or reduce nicotine craving and drop-out from treatment in patients with ADHD and nicotine dependence? and Are psychostimulants safe in patients with ADHD and comorbid nicotine dependence?*

Two RCTs reported the efficacy and safety of methylphenidate *vs* placebo (Winhusen et al., 2010) and lisdexamfetamine dimesylate *vs* placebo (Kollins et al., 2014) in adult patients with ADHD and concurrent nicotine dependence. In 255 patients with ADHD and nicotine dependence treated for 11 weeks (Winhusen et al., 2010), the proportion of patients who achieved an improvement of ADHD (defined as 30% decrease of ADHD Rating Scale [ADHD-RS-IV] score and decrease of 1 point in the CGI-S) at the end of the study was higher in those treated with methylphenidate than in those treated with placebo (low quality of evidence) (OR 2.48, 95% CI 1.50 to 4.11, $p = 0.004$). On the contrary, no differences in ADHD symptom severity assessed also by means of ADHD-RS were found (MD -7.8; 95% CI -15.76 a 0.16) (low quality of evidence).

For the comparison of lisdexamfetamine dimesylate and placebo in 32 patients treated for 4 weeks (Kollins et al., 2014), differences in severity of ADHD symptoms (assessed using CAARS) at the end of the study were not found whether the rater was the investigator (MD -7.42; 95% CI -16.73 to 1.89) or the patient (MD -7.55; 95% CI -15.83 to 0.73) (low quality of evidence).

In both RCTs there were no significant differences between active treatment and placebo groups in objective (assessed by means of Carbon Monoxide [CO] levels) (OR 1.67, 95% CI 0.32 to 8.59) and self-reported (assessed using the TLFB) (OR 0.15, 95% CI 0.01 to 3.49) measures of smoking cessation or in the proportion of patients that achieved abstinence at the end of the study (OR 1.05, 95% CI 0.63 to 1.73) (low quality of evidence). Drop-outs from treatment at 11 and 4 weeks were also similar for the comparisons of methylphenidate *vs* placebo (OR 1.01, 95% CI 0.51 to 1.98) and lisdexamfetamine dimesylate *vs* placebo (OR 3.00, 95% CI 0.28 to 32.46) (low quality of evidence). The proportion of patients with drop-outs from treatment due to adverse events was significantly higher in patients treated with methylphenidate than in those treated with placebo (n = 255, OR 3.49, 95% CI 1.24 to 9.83, $p = 0.02$), but differences between and lisdexamfetamine dimesylate and placebo (OR 2.82, 95% CI 0.11 to 74.51) were not found (low quality of evidence).

- Recommendations
  - · In adult patients with ADHD and comorbid nicotine use, the use of methylphenidate is recommended to improve ADHD symptoms (weak recommendation) but not to reduce nicotine consumption (weak recommendation).
  - · Lisdexamfetamine dimesylate is not recommended to improve ADHD symptoms (weak recommendation) or to reduce nicotine consumption (weak recommendation)
  - · The use of methylphenidate or lisdexamfetamine dimesylate should not be discouraged for safety reasons (weak recommendation).

Patients with ADHD and substance use disorder

Details about included studies are shown in Table 1.

PICO question 4. *Are psychostimulants effective to improve symptoms of ADHD, reduce use and/or craving of substances and*

Table 1. *Attention Deficit Hyperactivity Disorder and Substance Use Disorder.*

AUTHOR	DESIGN	INTERVENTION	DIAGNOSIS	SUBSTANCE	EXP(N)/ COMP(N)	FOLLOW -UP	OUTCOME VARIABLES (CLINICAL, CONSUMPTION, PRAGMATIC AND SAFETY)	LIMITATIONS/ BIAS
Carpentier 2005	RCT, double-blind, crossover design	Group 1: Methylphenidate IR 15-45 mg/d Group 2: Placebo	ADHD (DSM-IV)	Any SUD (DSM-IV)	25/25	4 weeks	ADHD-RS-IV, COS and GAS	Small sample size. Very short follow-up. No wash-out period. Risk of other biases due to study design.
Cunill 2015	RCT SMRA	Group 1: any drug for ADHD Group 2: Placebo	ADHD (DSM criteria)	Any SUD	337/339	4 to 12 weeks	-Any ADHD scale -self-reported and objective abstinence -Treatment drop-out -Drop-out for AE	Attrition and other biases in some of the included studies.
Kollins 2012	RCT, double-blind, parallel design	Group 1: Lisdexamfetamine 30-70 mg/d Group 2: Placebo	ADHD (DSM-IV)	Nicotine dependence (diagnostic criteria NS)	17/15	4 weeks	-Self-administered CAARS, investigator-administered CAARS -Diary of consumption and CO levels in exhaled air -Treatment drop-out -Treatment drop-out for AE, number of patients with AE	Small sample size. Very short follow-up period.
Winhusen 2010	RCT, double-blind, parallel design	Group 1: methylphenidate OROS 18-72 mg/d Group 2: Placebo	ADHD (DSM-IV) and minimum score of 22 on ADHD-RS-IV	Nicotine dependence (DSM-IV)	127/128	11 weeks	-ADHD-RS-IV and CGI-S -CO levels in exhaled air -Treatment drop-out for AE, number of patients with AE	Short follow-up period.
Schubiner 2002	RCT, double-blind, parallel design	Group 1: methylphenidate IR 30-90 mg/d Group 2: Placebo	ADHD (DSM-IV)	Cocaine dependence (DSM-IV)	24/24	12 weeks	-CGI-I -ASI and urine analysis -Treatment drop-out -Treatment drop-out for AE	Small sample size. Short follow-up period. Risk of other biases due to baseline differences between the two groups and to the elimination of a third line of treatment with pemoline due to recruitment issues.
Levin 2007	RCT, double-blind, parallel design	Group 1: methylphenidate SR 10-60 mg/d Group 2: Placebo	ADHD (DSM-IV-TR) and minimum score of 23 on AARS	Cocaine dependence (DSM-IV TR)	53/53	13 weeks	-AARS, TAADDS and CGI-I -Consumption questionnaire and urine analysis -Treatment drop-out -Treatment drop-out for AE	Small sample size. Short follow-up period. Risk of attrition bias: 56% of patients dropped out.
McRae 2010	RCT, double-blind, parallel design	Group 1: Atomoxetine 25-100 mg/d Group 2: Placebo	ADHD (DSM-IV)	Cannabis dependence (DSM-IV)	19/19	12 weeks	-self-administered CAARS, investigator-administered CAARS, WRAADDS, CGI-I and CGI-S -TLFB, urine analysis and MCQ -Treatment drop-out -Treatment drop-out for AE, number of patients with AE	Small sample size. Short tracking period. Risk of attrition bias: 70% of patients dropped out.
Wilens 2008	RCT, double-blind, parallel design	Group 1: Atomoxetine 25-100 mg/d Group 2: Placebo	ADHD (DSM-IV TR) and minimum score of 20 on AISRS	Alcohol dependence or abuse (DSM-IV TR)	72/75	12 weeks	-ASRS, AISRS, CGI-S and CGI-I -TLFB y OCDS -Treatment drop-out -Treatment drop-out for AE, number of patients with AE	Small sample size. Short follow-up period. Risk of attrition bias: 46% of the patients dropped out and there were differences in reasons for drop-out between the two groups.

Note. AARS: Adult ADHD Self-report Scale; ADHD-RS-IV: ADHD Rating Scale; AE: adverse effects; AISRS: Adult ADHD Investigator Symptom Rating Scale; ARS: Adult ADHD Rating Scale; ASI: Addiction Severity Index Interview; ASRS: Adult Self Report Scale; CAARS: Conners' Adult ADHD Rating Scale; CGI-I: Clinical Global Impression-Improvement; CGI-S: Clinical Global Impression-Severity; CO: carbon monoxide; COS: Clinical Observation Scale; DSM-IV TR: Diagnostic and Statistical Manual of Mental Disorders, version IV, revised text; GAS: Global Assessment Scale; IR: immediate release; MCQ: marijuana craving questionnaire; NS: not specified; OCDS: Obsessive-Compulsive Drinking Scale; RCT: randomized clinical trial; SMRA: systematic review with meta-analysis; SR: sustained release; TAADDS: Targeted Adult Attention Deficit Disorder Scale; TLFB: Time-line Follow-Back self-reported interview; SUD: substance use disorder; WRAADDS: Wender-Reimherr Adult Attention Deficit Disorder scale.

drop-out from treatment in patients with ADHD and SUD? and Are psychostimulants safe in patients with ADHD and SUD?

The efficacy and safety of treatment with psychostimulants in patients with ADHD and SUD have been evaluated in one RCT (Carpentier, De Jong, Dijkstra, Verbrugge & Krabbe, 2005) and in one meta-analysis (Cunill et al., 2015). Data from the meta-analysis were extracted after excluding adolescents and patients with opioid and amphetamine dependence since these SUD were out of the scope of the guideline.

In the RCT, 25 patients with ADHD and SUD received methylphenidate or placebo for 4 weeks. The proportion of patients who achieved a 30% decrease in the Clinical Observation Scale (COS) and in the Global Assessment Scale (GAS) adapted for ADHD was significantly higher in the methylphenidate group (OR 9.04, 95% CI 1.74 to 46.89, $p = 0.009$) (very low quality of evidence). Differences in other measures, such as 30% decrease of ADHD-RS-IV score (OR 2.25, 95% CI 0.63 to 8.06), 30% decrease of combined ADHD-RS-IV, COS and GAS scores (OR 2.25,

95% CI 0.63 to 8.06), and severity of symptoms assessed at the end of the study using the ADHD-RS-IV, COS and GAS scores (MD -4.20, 95% CI -13.14 a 4.74;MD -3.80, 95% CI -9.31 a 1.71; and MD -1.80, 95% CI -4.41 a 0.81; respectively) were not found (very low quality of evidence).

In the meta-analysis of 5 studies of ADHD and SUD involving 466 patients, improvement of severity of ADHD symptoms (assessed using any ADHD rating scale) was significantly higher in patients treated with psychostimulants than in those given placebo (OR 2.30, 95% CI 1.61 to 3.30, $P < 0.00001$) (low quality of evidence). In this meta-analysis, measures of objective and self-reported drug use did not show reduction of drug consumption between active treatment with psychostimulants and placebo (OR 0.92, 95% CI 0.53 to 1.58) (low quality of evidence). Furthermore, differences between treatment with psychostimulants and placebo regarding drop-outs from treatment for any reason (OR 1.16, 95% CI 0.74 to 1.84) or for adverse events (RD 0.00, IC 95% -0.01 a 0.01) were not observed (high quality of evidence).

- Recommendations
  - In adult patients with ADHD and SUD, the use of psychostimulants (methylphenidate or lisdexamfetamine dimesylate) is recommended to improve ADHD symptoms (weak recommendation) but not to reduce substance use (weak recommendation).
  - The use of psychostimulants (methylphenidate or lisdexamfetamine dimesylate) should not be discouraged for safety reasons (strong recommendation).

PICO question 5. *Are non-stimulant medications effective to improve symptoms of ADHD, reduce use and/or craving of substances and drop-out from treatment in patients with ADHD and SUD? and Are non-stimulant medications safe in patients with ADHD and SUD?*

Data from one meta-analysis (Cunill, Castells, Tobias & Capellà, 2015) were extracted to assess the use of non-stimulants in adult patients with SUD. Studies in adolescents and in patients with opioid and amphetamine dependence were excluded as were studies assessing psychostimulant medications. Two RCTs including 225 patients that examined treatment with atomoxetine were analyzed. Active treatment was significantly better than placebo for improving severity of ADHD symptoms (assessed by means of any ADHD rating scale) (OR 2.03, 95% CI 1.20 to 3.44, $p = 0.008$) (very low quality of evidence). Significant differences between atomoxetine and placebo groups for other outcomes, including decrease of objective or self-reported substance use (OR 1.47, 95% CI 0.68 a 3.18) (very low quality of evidence) and drop-outs from treatment for any reason (OR 1.66, 95% CI 0.94 a 2.92) and for adverse effects (RD 0.03, 95% CI -0.01 a 0.06) (moderate quality of evidence) were not found.

- Recommendations
  - In adult patients with ADHD and SUD, the use of non-stimulant medications (atomoxetine) is recommended to improve ADHD symptoms (weak recommendation) but not to not decrease substance use (weak recommendation).
  - The use of non-stimulant medications (atomoxetine) should not be discouraged for safety reasons (strong recommendation).

Psychological treatment

PICO question 6. *Is psychological treatment effective to reduce symptoms of ADHD or to reduce use of drugs of abuse in patients with ADHD and SUD?*

No RCTs or meta-analysis addressing this objective was retrieved from the literature.

Discussion

This study has allowed for the first time the formulation of treatment recommendations for patients with ADHD and SUD. However, the scarce number of randomized studies in individuals with co-occurring ADHD and SUD remains a concern. Only two RCTs have studied the efficacy of non-stimulant medications (atomoxetine) in patients with ADHD and alcohol or cannabis use disorder and four have studied the efficacy of psychostimulants (methylphenidate and lisdexamphetamine dimesylate) in patients with nicotine and cocaine use disorder.

Our results suggest that 1) In patients with ADHD and alcohol use, atomoxetine is recommended to reduce ADHD symptoms and alcohol craving (weak recommendation) but it should not be used to improve treatment retention (weak recommendation). 2) In patients with ADHD and cannabis use disorder, atomoxetine is recommended to improve ADHD symptoms (weak recommendation), not to reduce cannabis use or to improve treatment retention (weak recommendation). 3) In patients with ADHD and cocaine use disorder, methylphenidate is not recommended to improve ADHD symptoms, to reduce cocaine use or to improve treatment retention (weak recommendation). 4) In patients with ADHD and comorbid nicotine use disorder, methylphenidate is recommended to improve ADHD symptoms (weak recommendation). Methylphenidate or lisdexamfetamine dimesylate are not recommended to reduce nicotine use or to improve treatment retention (weak recommendation). 5) Regarding patients with ADHD and any SUD, the use of psychostimulants (methylphenidate or lisdexamfetamine dimesylate) is recommended to improve ADHD symptoms (weak recommendation), not to reduce substance use (weak recommendation) or to improve retention to treatment (strong recommendation). In these patients, the use of non-stimulant medications (atomoxe-

tine) is recommended to improve ADHD symptoms (weak recommendation), not to decrease substance use (weak recommendation) or to improve retention to treatment (strong recommendation). Atomoxetine and psychostimulants appear to be safe in patients with any SUD (strong recommendation).

Mixed results on the efficacy of pharmacological treatment for patients with ADHD and comorbid substance use are reported in this review. Treatment of ADHD among dual patients results in modest improvements in ADHD symptoms, albeit with a smaller effect size than that observed in patients without SUD (Cunill & Castells, 2016a). Therefore, although pharmacological treatment can be recommended in these patients, this recommendation is weakened by the low quality of the studies available. Conversely, we cannot recommend pharmacological ADHD treatment to improve substance use or drop-out rates. We can neither make any recommendation with regard to the psychological treatment of ADHD nor the treatment of SUD in patients with dual ADHD, given that there are no RCTs focusing on the efficacy of such treatments in dual patients.

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Conflict of interest

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

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