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Clinical management of adult patients with serious mental disorder and comorbid diagnosis of substance use disorder

Manejo clínico de los pacientes adultos con un trastorno mental grave y un diagnóstico comórbido de trastorno por uso de sustancias

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****** The names of the components of the group of experts of the dual pathology clinical practice guideline are listed in alphabetical order in the appendix.

In 2016 we published two editorials (San, Arranz & Grupo de expertos de la guía de práctica clínica de salud mental, 2016; San, Arranz, Bernardo, Arrojo & Grupo de expertos de la guía de práctica clínica de salud mental, 2016) which described the progress being made in developing a clinical practice guide for the treatment of dual pathology. These papers highlighted the significant increase in the prevalence of the pathology and the need to provide professionals with a series of recommendations following proper clinical practice guide methodology. The idea was mooted in 2013 by the then president of the Spanish Society of Biological Psychiatry and has since been supported until today despite a lack of evidence-based scientific literature on how to define and approach this pathology in clinical settings.

People with a serious mental illness and a substance-related disorder have what is known as dual pathology. They have a differentiated profile since their cases are more severe than patients diagnosed with only a serious mental illness or a substance use disorder. In the field of psychiatry and mental health, dual disorders are more the rule than the exception. It is estimated that over 25% of patients undergoing treatment in mental health services present a lifetime substance use disorder (SUD), and that almost 70% of patients treated in specialised addiction units have a lifetime mental disorder.

For this reason, the identification of substance misuse at the earliest opportunity offers a better chance of early diagnosis and treatment, resulting in a better prognosis for these patients, and the procedure can thus be integrated into personalized medicine. To this end, it is important to investigate substance use in all patients attending care services for addiction, mental health, emergencies, general medicine and in the prison system.

The most recent consensus documents covering therapeutic recommendations for dual pathology are unanimous in advocating the integration of SUD treatment with management strategies for mental disorders not related to substance use. It is incorrect to assume that treating only the psychiatric disorder not related to substance use will be sufficient to control the SUD, and vice versa. Integrated or combined treatment requires incorporating and, on occasions, modifying some aspects of the treatments applied when both pathologies do not coexist. It is desirable that the treatment combines pharmacological and psychotherapeutic interventions (in individual and/or group format), as well as family or social interventions where necessary. The most

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common psychosocial treatments include motivational approaches, cognitive-behavioural therapy, contingency management, relapse prevention, case management and skills training. To be effective, these treatments should be well coordinated, involve teamwork and a multidisciplinary approach, educated and trained staff, provide 24-hour care and different program types, and include long-term follow-up.

The current issue of the journal features the five articles (Arranz et al., 2022; Cunill et at., 2022; González-Pinto et al., 2022; Sáiz et al., 2022; Torrens et al., 2022) summarizing the initial publication, first in digital and later in paper format, of the complete clinical practice guide. The papers incorporate the most important information. All follow a similar structure that includes Introduction, Methods (formulation of clinical questions, literature search strategy, assessment of evidence quality and formulation of recommendations, review and external assessment), Results (formulation of PICO questions: patient, intervention, comparison, outcome/result), Discussion/Conclusions, Acknowledgments, Conflict of interests and References.

The papers are particularly aimed at those health professionals (psychiatrists, psychologists, professionals in the field of dual disorders, primary care doctors and nurses) who make decisions about the pharmacological and/or psychological treatment of patients with a severe mental disorder and a comorbid substance use disorder.

The studies included in each of the articles cover the following and provide information on:

a. Design: randomized, double-blind, placebo-controlled clinical trial of any pharmacological or psychological treatment.
b. Patients over 18 years of age diagnosed with major depressive disorder, schizophrenic spectrum disorder, anxiety disorder, bipolar disorder or ADHD, together with a substance use disorder (alcohol, cannabis, cocaine or nicotine).
c. Outcome variables assessed in the studies are substance use (decrease or abstinence) and/or the psychiatric disorder symptoms.

The main aim is to collect concrete recommendations based on the results of the scientific literature in order to treat patients with a serious mental disorder and a substance use disorder attending inpatient and outpatient treatment centres. The recommendations mentioned in the five articles are proposals for therapeutic interventions in the pharmacological and/or psychological field that address PICO questions and are classified as:

- Strong recommendations: Most patients should receive the recommended intervention.
- Weak recommendations: Different options are appropriate for different patients. The psychiatrist/psychologist has to help each patient reach a decision that is most consistent with their values and preferences.

Considering the objectives of the dual pathology clinical practice guide and its subsequent scientific implementation, the active participation of scientific societies such as the Spanish Society of Biological Psychiatry (guide promoter), the Spanish Society of Psychiatry (currently merged as the Spanish Society of Psychiatry and Mental Health), the Spanish Society of Drug Addiction, the Spanish Society of Dual Pathology, Socidrogalcohol, and the Health Service of Galicia (SERGAS), the latter in its capacity as funding entity for the guide, as was the Spanish Society of Biological Psychiatry. Other organizations that have provided support for this project are CIBERSAM and RTA.

Conflict of interests

Luis San has received research funding and has acted as consultant or speaker for the following companies and entities: Adamed, Eli Lilly, Ferrer, Janssen-Cilag, Lundbeck, Otsuka, Rovi and Servier.

Belén Arranz has acted as consultant/speaker for the following companies and entities: Adamed, Esteve, Janssen-Cilag, Lundbeck, Otsuka, Rovi and Servier.

Miquel Bernardo has received research funding and has acted as consultant or speaker for the following companies and entities: ABBiotics, Adamed, Angelini, Casen Recordati, Janssen-Cilag, Menarini, Rovi and Takeda.

Manuel Arrojo declares no conflict of interests.

Ana González-Pinto has received research funding and has acted as consultant or speaker for the following companies and entities: Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Sanofi-Aventis, Alter, Angelini, Exeltis, Novartis, Takeda, Ministerio de Sanidad (CIBERSAM), Instituto Carlos III, Gobierno Vasco and the European Research Framework Program.

Appendix

B. Arranz, M. Arrojo, E. Becoña, M. Bernardo, L. Caballero, X. Castells, R. Cunill, G. Flórez, M. D. Franco, M. Garriga, J.M. Goikolea, A. González-Pinto, M. Landabaso, A. López, J. Martinez-Raga, A. Merino, M. Paramo, G. Rubio, G. Safont, P.A. Sáiz, L. San, I. Solà, J. Tirado, M. Torrens and I. Zorrilla.

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The relationship between the socio-economic gradient and cigarette consumption in Spain

La relación entre el gradiente socioeconómico y el consumo de cigarrillos en España

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Abstract

The objective of the study was to analyze the relationship between individual socioeconomic characteristics and cigarette consumption in Spain. The sample consisted of 19,931 individuals aged 15 or older who completed the *European Health Interview Survey for Spain* (EHSS-2014). Variables: prevalence and intensity of cigarette consumption. Multivariate ordered logistic regression analysis was performed with the following socioeconomic variables: social classes, educational attainment, main activity, economic situation and, for the working population, the activity sector. Other control variables were sociodemographic variables and healthy lifestyle habits (physical exercise, diet and alcohol consumption). The factors that relate to greater prevalence are: lower social class, not having university studies, being unemployed, having worse economic situation and working in hospitality industry. On the other hand, the variables related to higher intensity of cigarette consumption of the smoking population are: lower social class, not having university studies, and being neither a student nor on a permanent contract. Regarding control variables, those regressors associated with a higher prevalence and intensity of cigarette consumption are: being male, being aged between 36 and 65, being divorced, having fewer children at home and having worse lifestyle habits.

Keywords: Smoking; cigarettes; socio-economic gradient; lifestyle habits; health; European Health Interview Survey.

Resumen

El objetivo del estudio fue analizar la relación entre las características socioeconómicas individuales y el consumo de cigarrillos en España. La muestra estaba formada por 19.931 individuos de 15 o más años de edad de la *Encuesta Europea de Salud en España* (EESE) de 2014. Variables: prevalencia y nivel de consumo. Se realizó análisis de regresión multivariante logística ordinal con las variables socioeconómicas clase social, nivel educativo, actividad principal, situación económica y sector de actividad (solo para población trabajadora). Otras variables de control incluidas fueron las características sociodemográficas y los hábitos de vida saludables (ejercicio físico, alimentación y consumo de alcohol). Los factores que se relacionan con mayor prevalencia en el consumo de cigarrillos son: inferior clase social, no tener estudios universitarios, ser desempleado, tener peor situación económica y trabajar en hostelería. Por su parte, las variables relacionadas con el nivel de consumo de la población fumadora son: inferior clase social, no tener estudios universitarios, y no ser estudiante ni trabajador indefinido. En cuanto a las variables de control, aquellos regresores asociados a mayor prevalencia y nivel de consumo son: sexo masculino, edad entre 36 y 65 años, ser divorciado, menor número de niños en el hogar y peores hábitos de vida.

Palabras clave: Tabaquismo; cigarrillos; gradiente socioeconómico; hábitos de vida saludables; salud; Encuesta Europea de Salud.

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Data from the latest *Spanish National Health Survey* (*Encuesta Nacional de Salud de España 2017*, ENSE-2017) show that the prevalence of daily tobacco use in the population aged 15 and above is 22.1%, a decrease in the smoking habit of over 4 percentage points over the last decade. In the previous surveys of 2011-12 and 2006 the figure stood at 23.9% and 26.4%, respectively.

Regarding the international context, Figure 1 shows the prevalence of smokers for all EU-28 countries based on data from the last two available Eurobarometers (numbers 429 and 458) on *Attitudes of Europeans towards tobacco and electronic cigarettes* for the periods 2014 and 2017 (European Commission, 2014, 2017).

As can be seen, smoking prevalence in the EU-28 has remained stable at around 26% for both periods, 2014 and 2017, although there are significant differences between countries. While important decreases in smoking prevalence are observed in countries such as Belgium (-6.2%), Denmark (-4.4%) or Sweden (-4.3%), there have been marked increases in countries such as Slovakia (+5.6%), Czech Republic (+4.5%) or France (+4.1%).

While Spain saw a decrease in smoking prevalence of around 2% between 2014 (29.5%) and 2017 (27.4%), this decline was preceded by an earlier fall of 3.5 points between 2012 (33%) and 2014 (29.5%), which took Spain from 4th place in the EU-27 ranking in 2012 in terms of smoking prevalence to 13th in the EU-28 in 2017 (European Commission, 2012, 2014, 2017).

The high cost of smoking in health and social terms, together with the fact that it is a risk factor susceptible to prevention, has made *reducing smoking prevalence* one of the priority objectives in the health policies of all socioeconomically similar countries. In the case of Spain, information and awareness campaigns on the effects of tobacco exist alongside (i) the prohibition of smoking in public places, collective means of transport and workplaces; (ii) regulation regarding not only the manufacture, presentation and sale of tobacco products but also advertising and sponsorship; and (iii) heavy taxes on tobacco production and use.

These interventions, together with the influence of the economic crisis on smoking (Martín-Álvarez, Golpe, Iglesias & Ingelmo, 2020), likely explain not only the decrease in the prevalence of cigarette smoking but also the changes in smoking behaviours towards the use of other (sometimes more affordable) tobacco products such as hand rolled cigarettes, cigars, cigarillos or pipe tobacco (López-Nicolás, Cobacho & Fernández, 2013). It is no less true, however, that such interventions rarely take into account that smoking, despite its presence in all social groups, does not affect the entire population equally (Almeida, Golpe, Iglesias & Martín-Álvarez, 2021).

Thus, according to the López, Collishaw and Piha (1994) model of the spread of the epidemic in developed countries, Spain is in *phase IV*, characterized by a smoking prevalence with a higher concentration among the most disadvantaged socioeconomic groups. This influence of the *socioeconomic gradient* on smoking has been sufficiently documented in the international academic literature, showing an association between smoking and factors such as unemployment, level of education, type of occupation and socioeconomic situation (Schaap, Van Agt & Kunst, 2008; White, Redner, Bunn & Higgins, 2016). The higher prevalence of unhealthy lifestyle habits in groups of lower socioeconomic level is one of the mechanisms linking this unfavourable socioeconomic situation with worse health (Macintyre, 1997). More specifically, smoking in groups with lower socioeconomic status is the most important cause of socioeconomic differences in mortality (Stringhini et al., 2010).

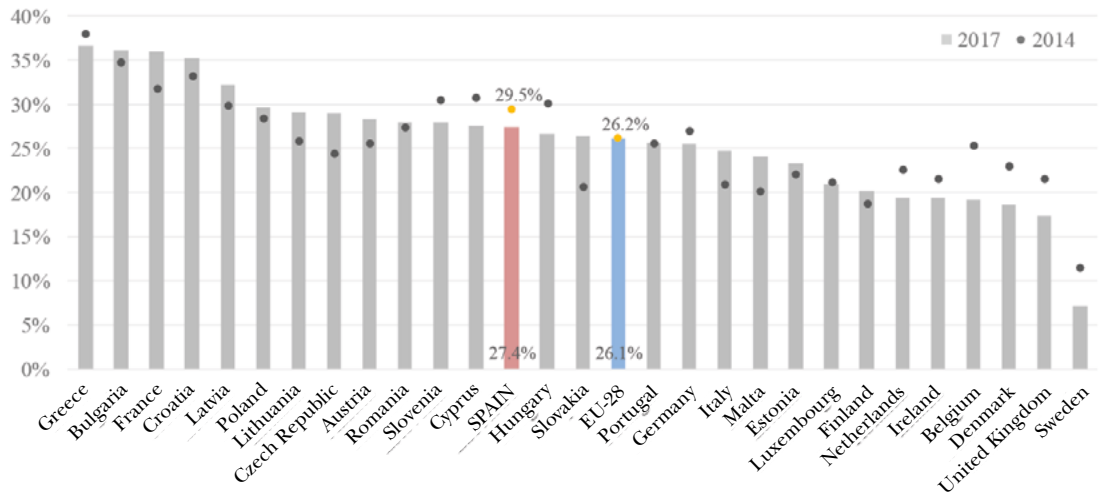

Figure 1. Prevalence of smokers (cigarettes, cigars, cigarillos or pipes) in the EU-28.
Source: Special Eurobarometers 429 (2014) and 458 (2017). European Commission

However, the generalizability of the effects of this gradient to different economies is not so clear and needs data-based support (Sarkar et al., 2017). Unfortunately, the studies analysing these associations at a national level are practically anecdotal and their results are sometimes not supported by multivariate regression models but only by bivariate descriptive analyses (the studies by Agudo et al., 2004 and Pinilla & Abásolo, 2017 are notable exceptions).

Therefore, correcting this gap in the literature by characterizing the smoking population in Spain from a socioeconomic perspective, thereby identifying the groups at highest risk of prevalence and use, becomes a priority objective from the perspective of health authorities aiming for a more effective design of smoking control policies, with more specific, focused and more easily evaluable goals.

With this objective in mind, using microdata from the 2014 *European Health Survey in Spain* (EHSS-2014), the present study analyses the *prevalence* and *intensity* of cigarette smoking using bivariate and multivariate analysis techniques. Using the EHSS-2014 made it possible to generate comparable information at a European level based on the most recent data available. It was decided to focus on cigarettes (including hand rolled) as a tobacco product, reflecting its still leading role in terms of total consumption, despite changes detected recently.

Methods

Study instrument

This study uses the records of participants in the 2014 European Health Survey in Spain (EHSS) (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2015). The general aim of the EHSS, designed and coordinated by EUROSTAT, is to provide information on the health of the Spanish population in a harmonized and comparable way at the European level in order to plan and assess actions in health matters. It is a cross-sectional survey, carried out every five years by the Spanish National Statistics Institute (Instituto Nacional de Estadística, INE), in collaboration with the Spanish Ministry of Health, Social Services and Equality (Ministerio de Sanidad, Servicios Sociales e Igualdad). A three-stage sampling design is used, stratified by census tracts, households and people. The data are freely accessible to any researcher on the INE website in the form of an anonymized microdata file.

The EHSS-2014 is structured in two questionnaires: households and adults. The household questionnaire has only a *sociodemographic* module, while the adult questionnaire consists of four different modules: (i) *sociodemographic*, (ii) *health status*, (iii) *health care*, and (iv) *health determinants*. This study included the variables of both questionnaires and all modules.

The *health determinants* module provided information on the smoking (section V), diet (section U), physical activity (section T) and physical characteristics (section S) of participants. In particular, this module allows the construction of the following variables used in the analysis: *prevalence* of cigarette smoking, *intensity* of cigarette smoking, type of diet, leisure-time physical exercise, alcohol use and Body Mass Index (BMI).

The *health care* module offered information on participants' health insurance (section O), which was used to generate the health insurance modality variable.

The *health status* module provided information on the mental health of participants (section G), enabling the variable of mental health in the last 12 months to be generated.

Finally, the *sociodemographic* modules, both in the household and adult questionnaires, revealed the household composition (section A), demographic (section E) and economic activity characteristics (section F) of each participant. Specifically, the construction of the variables sex, age, marital status, number of children in the household, social class, educational level, main activity and activity sector (only for participants with paid work) is based on these modules.

Design and participants

The study was observational, epidemiological and descriptive. The object of study was the totality of the records of participants aged 15 years or older participating in the EHSS-2014, comprising a total of 22,842 records. Those participants who regularly smoke products other than cigarettes were excluded from the final sample. While hand-rolled cigarettes were therefore not excluded, cigars, pipe tobacco and other products were (barely 1% of the total records). Likewise, participants with missing values for variables relevant for performing this analysis were also excluded. The final sample thus comprised a total of 19,931 records.

Procedure

From the information available in the EHSS-2014, the *prevalence* and *level* of cigarette smoking were selected as the *dependent* variables of the study. To assess prevalence, three situations were considered: (1) never smoker, (2) ex-smoker and (3) smoker. To assess intensity, four levels were considered: (1) occasional smoker, (2) daily smoker of up to 10 cigarettes, (3) daily smoker of 11 to 20 cigarettes and (4) daily smoker of over 20 cigarettes.

The *main independent* variables selected for analysis were those related to the *socioeconomic gradient*, that is, social class (based on the occupation of the individual or the reference person), level of educational attainment, and economic/work-related variables such as main occupation, health insurance (only public health cover, excluding state mu-

tuals vs. private insurance or mutuals) and activity sector, according to the National Classification of Economic Activities (NACE Rev.2) (only for participants with paid work).

Independent *control* variables were (i) *sociodemographic*: sex, age, marital status and number of children in the household; (ii) *health status*: BMI and mental health in the last 12 months; and (iii) *healthy lifestyle habits*: leisure-time physical exercise, type of diet and alcohol use.

Statistical analysis

Statistical analysis of the data was performed with the Stata/MP-16 program and consisted of a descriptive analysis by calculating number (n) and proportion (%) for qualitative variables and calculating means and standard deviations for quantitative variables. The proportions of categorical variables were also compared using chi-square tests for contingency tables. In order to measure prevalence and intensity of cigarette smoking, six ordinal multivariate logistic regression models were performed, for which the probability ratios or "odds ratio" (OR) were obtained with 95% CI. Selecting the *main independent* variables was done on the basis of previous knowledge of the relationship between the *socioeconomic gradient* and smoking. The inclusion of independent *control* variables also linked to smoking (as argued in the Discussion section) was based on a forward selection procedure, without this process significantly altering the coefficients associated with the *main independent* variables. All hypothesis tests were two-tailed and statistical significance was set at $p < 0.05$ (two tails).

Results

Bivariate analysis

Figure 2 shows the information regarding prevalence and intensity of cigarette smoking of the participants in the final sample.

Table 1 shows how these patterns of prevalence and intensity of consumption vary for different specific population subgroups based on the independent variables.

The most prevalent subgroups within the population of never smokers (48% of the final sample) were people with primary education (57%), people who mainly study (78%) or do housework (66.3%), retirees or early retirees (54.6%), workers in the education sector (52.6%), women (59.1%), people over 65 (61.1%), and widows/widowers (70.5%).

The population of *ex-smokers* (28% of the final sample) is dominated by people of social class I (31.3%), those with work disability (37.4%), retirees or early retirees (36.3%), business owners or professionals with employees (32.5%), civil servants (32.4%), men (36.6%), people between 51 and 65 years (36.3%), and married (33.8%).

Regarding *smokers* (24% of the final sample), the most prevalent groups are people from social class VI (27.3%), people with secondary education (31.5%) and vocational training (31.1%), unemployed (38.5%), workers with a temporary contract (33.7%), business owners without employees or the solo self-employed (32.9%), those with work disability (32.8%), workers in the hospitality sector (38.2%), manufacturing (35.6%) and construction industries (33.5%) among others, men (27.9%), people aged between 15 and 35 years (33.8%) and between 36 and 50 years (32.2%), divorced (37.7%), separated (35.5%), and single (33.8%).

Within the population of smokers, the group of *occasional smokers* (8.4% of the final sample of smokers) includes people from social class I (12.1%), people with a university education (11.4%), students (17.2%), business owners or professionals with employees (12.2%), workers in artistic, recreational and entertainment sectors (17.9%) and in professional, scientific and technical activities (17.5%), and people aged 15 to 35 years (12.1%).

Among *daily smokers of more than 20 cigarettes* (6.8% of the final sample of smokers), the largest groups are people with work disabilities (12.4%), business owners without salaried employees or the solo self-employed (9.9%), business owners or professionals with salaried employees (9.4%), workers in the construction (13.9%) and transport and storage sectors (10.5%), men (9.2%), people between 51 and 65 years (10.1%), separated (12.2%), and divorced (9.6%).

In relation to the *quantitative variables*, daily smokers of over 20 cigarettes (compared to daily smokers of 10 or fewer cigarettes and occasional smokers) present higher BMI, higher daily alcohol use, fewer weekly hours of physical ex-

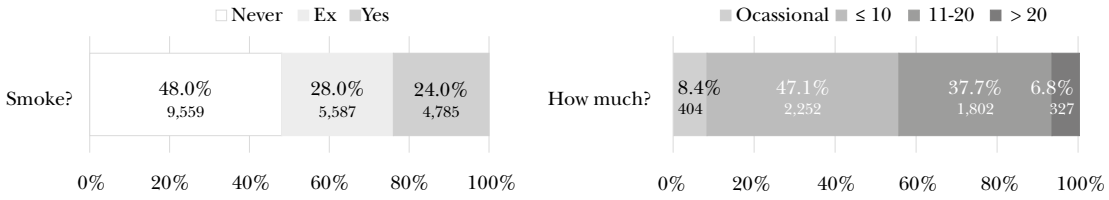

Figure 2. Prevalence (left panel) and intensity of cigarette smoking (right panel) in Spain in 2014.
Source: Own research with data from the EHSS-2014.

Table 1. *Prevalence and intensity of cigarette smoking in Spain in 2014 by different characteristics.*

	n (%)	Prevalence (%)			P	Intensity of smoking (%)				p
		Never	Ex	Smoker		Ocas-sional	Daily smoker			
							≤ 10	11-20	› 20	
Total	19,931 (100%)	48.0%	28.0%	24.0%		8.4%	47.1%	37.7%	6.8%	
Mean cigarettes smoked (1-80) [a, b]							6.93 (2.87)	17.5 (3.04)	33.0 (8.31)	
Main Independent Variables –Socioeconomic Gradient–										
Social class [c]					‹ 0.001					‹ 0.001
Class I (0-1)	2,316 (11.6%)	47.6%	31.3%	21.1%		12.1%	51.1%	30.5%	6.3%	
Class II (0-1)	1,173 (8.6%)	48.9%	29.4%	21.7%		9.2%	51.7%	33.7%	5.4%	
Class III (0-1)	3,882 (19.5%)	47.6%	28.7%	23.7%		8.9%	48.9%	36.5%	5.7%	
Class IV (0-1)	2,946 (14.8%)	47.0%	29.9%	23.1%		7.8%	45.4%	39.9%	6.9%	
Class V (0-1)	6,387 (32.0%)	47.6%	27.5%	24.9%		7.1%	46.9%	38.8%	7.2%	
Class VI (0-1)	2,687 (13.5%)	50.2%	22.5%	27.3%		8.6%	41.6%	41.2%	8.6%	
Educational attainment					‹ 0.001					‹ 0.001
Primary education (0-1)	6,436 (32.3%)	57.0%	27.6%	15.4%		6.4%	41.5%	43.2%	8.9%	
Secondary education (0-1)	6,598 (33.1%)	41.0%	27.5%	31.5%		8.2%	45.6%	39.1%	7.1%	
Vocational training (0-1)	2,934 (14.7%)	41.1%	27.8%	31.1%		8.7%	49.2%	36.7%	5.4%	
University education (0-1)	3,963 (19.9%)	49.9%	29.8%	20.3%		11.4%	55.2%	28.1%	5.3%	
Economic/work-related variables										
Main activity					‹ 0.001					‹ 0.001
Business owner or professional with employees (0-1)	532 (2.7%)	39.7%	32.5%	27.8%		12.2%	35.8%	42.6%	9.4%	
Business owner without employees or solo self-employed (0-1)	1,138 (5.7%)	37.7%	29.4%	32.9%		7.7%	39.6%	42.8%	9.9%	
Civil servant (0-1)	1,129 (5.6%)	46.0%	32.4%	21.6%		9.0%	46.7%	39.0%	5.3%	
Worker with permanent contract (0-1)	4,704 (23.6%)	41.0%	28.4%	30.6%		9.0%	48.6%	36.9%	5.5%	
Worker with temporary contract (0-1)	1,313 (6.6%)	43.8%	22.5%	33.7%		9.5%	47.2%	37.4%	5.9%	
Other work situation (0-1) [d]	179 (0.9%)	41.3%	27.4%	31.3%		3.6%	44.6%	41.1%	10.7%	
Unemployed (0-1)	2,717 (13.6%)	36.7%	24.8%	38.5%		8.4%	46.0%	37.8%	7.8%	
Student (0-1)	1,077 (5.4%)	78.0%	5.8%	16.2%		17.2%	69.5%	12.1%	1.2%	
Retiree or early retiree (0-1)	5,115 (25.7%)	54.6%	36.3%	9.1%		3.9%	47.0%	41.4%	7.7%	
Work disability (0-1)	369 (1.8%)	29.8%	37.4%	32.8%		7.4%	39.7%	40.5%	12.4%	
Housework (0-1)	1,604 (8.0%)	66.3%	17.8%	15.9%		6.3%	51.4%	37.6%	4.7%	
Other jobless situation (0-1)	54 (0.3%)	37.0%	31.5%	31.5%		5.9%	17.6%	47.1%	29.4%	
Health insurance					‹ 0.001					0.285
Only public health -no state mutuals- (0-1)	15,850 (79.5%)	48.1%	27.4%	24.5%		8.1%	46.9%	38.0%	7.0%	
State mutuals or private insurance (0-1)	4,081 (20.5%)	47.5%	30.5%	22.0%		9.8%	47.7%	36.4%	6.1%	
Only workers										
Total	8,995 (45.1%)	41.6%	28.4%	30.0%		8.9%	46.2%	38.4%	6.5%	
Sector (NACE Rev.2)					‹ 0.001					‹ 0.001
A Agriculture, forestry and fishing (0-1)	415 (4.6%)	40.7%	27.0%	32.3%		10.4%	33.6%	47.8%	8.2%	
B Mining industry (0-1)	28 (0.3%)	17.9%	46.4%	35.7%		20.0%	20.0%	60.0%	0.0%	
C Manufacturing industry (0-1)	1,155 (12.8%)	34.1%	30.3%	35.6%		9.0%	43.1%	41.3%	6.6%	
D Electric power, gas, steam and air conditioning (0-1)	63 (0.7%)	39.7%	33.3%	27.0%		5.9%	64.7%	29.4%	0.0%	
E Water supply, sanitation, waste and decontamination (0-1)	74 (0.8%)	29.7%	32.4%	37.9%		10.7%	46.4%	32.2%	10.7%	
F Construction (0-1)	493 (5.5%)	35.9%	30.6%	33.5%		4.3%	40.6%	41.2%	13.9%	
G Car sales and repairs (0-1)	1,366 (15.2%)	41.4%	26.2%	32.4%		10.4%	53.2%	30.8%	5.6%	
H Transport and storage (0-1)	403 (4.5%)	35.7%	31.3%	33.0%		3.8%	41.3%	44.4%	10.5%	
I Hospitality (0-1)	647 (7.2%)	36.9%	24.9%	38.2%		8.1%	39.7%	44.5%	7.7%	
J Information and communications (0-1)	251 (2.8%)	48.6%	22.3%	29.1%		8.2%	43.8%	41.1%	6.9%	
K Finance and insurance (0-1)	244 (2.7%)	49.2%	25.8%	25.0%		13.1%	45.9%	37.7%	3.3%	
L Real estate (0-1)	63 (0.7%)	33.3%	34.9%	31.8%		5.0%	50.0%	40.0%	5.0%	

M	Professional, scientific and technical activities (0-1)	435 (4.8%)	47.8%	28.5%	23.7%		17.5%	48.5%	27.2%	6.8%	
N	Administrative and auxiliary services (0-1)	424 (4.7%)	39.4%	27.6%	33.0%		7.1%	53.6%	35.7%	3.6%	
O	Public administration and defence; Obligatory social security (0-1)	776 (8.6%)	42.4%	32.2%	25.4%		9.6%	42.7%	41.6%	6.1%	
P	Education (0-1)	707 (7.9%)	52.6%	26.9%	20.5%		5.5%	55.2%	34.5%	4.8%	
Q	Health and social services (0-1)	827 (9.2%)	43.3%	30.7%	26.0%		7.9%	48.4%	39.5%	4.2%	
R	Artistic, recreational and entertainment activities (0-1)	160 (1.8%)	48.1%	27.5%	24.4%		17.9%	46.2%	30.8%	5.1%	
S	Other services (0-1)	193 (2.1%)	39.9%	31.1%	29.0%		10.7%	53.6%	33.9%	1.8%	
T	Household activities (0-1)	266 (3.0%)	54.5%	20.7%	24.8%		10.6%	51.5%	34.9%	3.0%	
U	Working for extraterritorial organisations (0-1)	5 (0.1%)	40.0%	40.0%	20.0%		0.0%	0.0%	100.0%	0.0%	
Independent Control Variables											
Sociodemographic variables											
Sex						‹ 0.001					‹ 0.001
	Women (0-1)	9,399 (47.2%)	59.1%	20.4%	20.5%		8.8%	53.2%	34.0%	4.0%	
	Men (0-1)	10,532 (52.8%)	35.5%	36.6%	27.9%		8.2%	42.0%	40.6%	9.2%	
	Age (15-99) [a]		52.0 (20.3)	55.3 (15.6)	44.9 (13.4)		40.4 (13.1)	43.8 (14.1)	46.4 (12.5)	49.0 (11.0)	
Age						‹ 0.001					‹ 0.001
	15-35 years (0-1)	4,006 (20.1%)	48.0%	18.2%	33.8%		12.1%	53.5%	31.9%	2.5%	
	36-50 years (0-1)	6,204 (31.1%)	40.6%	27.2%	32.2%		7.9%	45.1%	40.2%	6.9%	
	51-65 years (0-1)	4,906 (24.6%)	38.0%	36.3%	25.7%		5.9%	41.8%	42.2%	10.1%	
	Over 65 years (0-1)	4,815 (24.2%)	61.1%	32.1%	6.8%		4.5%	50.3%	37.9%	7.3%	
Marital status						‹ 0.001					‹ 0.001
	Single (0-1)	5,209 (26.1%)	49.8%	18.7%	31.5%		9.9%	50.5%	34.1%	5.6%	
	Married (0-1)	11,096 (55.7%)	44.4%	33.8%	21.8%		8.7%	46.1%	38.4%	6.8%	
	Separated (0-1)	507 (2.5%)	36.1%	28.4%	35.5%		7.2%	42.8%	37.8%	12.2%	
	Divorced (0-1)	937 (4.7%)	33.8%	28.5%	37.7%		4.0%	39.4%	47.0%	9.6%	
	Widow/Widower (0-1)	2,182 (11.0%)	70.5%	20.4%	9.1%		3.0%	47.3%	42.2%	7.5%	
	Number of children in the household (0-6) [a]		0.39 (0.74)	0.39 (0.74)	0.45 (0.75)		0.55 (0.83)	0.46 (0.76)	0.43 (0.73)	0.33 (0.66)	
Healthy lifestyle habits											
	Weekly hours of physical exercise in leisure time (0-50)		2.20 (3.66)	2.45 (4.04)	1.99 (3.68)		2.72 (4.35)	2.27 (3.87)	1.67 (3.36)	0.93 (2.53)	
	Healthy diet index (-13 to 25) [g]		11.2 (5.05)	11.4 (4.92)	8.87 (5.76)		9.42 (5.19)	9.31 (5.70)	8.39 (5.87)	7.74 (5.80)	
	Average daily consumption of pure alcohol in grams (0-185.71) [h]		3.03 (7.14)	6.95 (10.8)	7.42 (12.5)		6.57 (9.96)	6.11 (10.5)	8.22 (13.1)	13.0 (20.6)	
State of Health											
	Body Mass Index (1-4) [a, e]		2.67 (0.77)	2.80 (0.75)	2.58 (0.76)		2.55 (0.76)	2.50 (0.72)	2.62 (0.76)	2.90 (0.83)	
Mental health (last 12 months)						‹ 0.001					‹ 0.001
	Mental health disease/problem (0-1) [f]	2,402 (12.1%)	50.4%	24.0%	25.6%		6.5%	40.6%	38.9%	14.0%	
	Mentally healthy (ref.) (0-1)	17,529 (87.9%)	47.6%	28.6%	23.8%		8.7%	48.0%	37.5%	5.8%	

Note. a) Quantitative variable. Information reported is mean and standard deviation; b) Information only available for daily smokers; c) Derived variable based on the occupation of the reference person: I – Directors and managers of businesses with 10 or more salaried employees and professionals traditionally associated with university degrees, II – Directors and managers of businesses with fewer than 10 salaried employees and professionals traditionally associated with university degrees and other technical support professionals. Athletes and artists, III – Intermediate occupations and self-employed, IV – Supervisors and workers in qualified technical occupations, V – Qualified workers in the primary sector and other semi-skilled workers, VI – Unskilled workers; d) Includes workers with a verbal contract or with no contract, family help, members of a cooperative and other situations; e) This discrete ordered variable has values between 1 and 4 and captures whether the individual's weight-height ratio, measured as their BMI value within the International Obesity Task Force (IOFT) scale is classified as underweight (BMI ‹ 18.5; BMI variable value = 1), normal weight (18.5 ≤ BMI ‹ 25; BMI variable value = 2), overweight (25 ≤ BMI ‹ 30; BMI variable value = 3) or obese (BMI ≥ 30; BMI variable value = 4); f) Depression, chronic anxiety or other mental problems; g) This index is calculated by adding frequencies of eating fresh fruit (excluding juices), natural fruit or vegetable juices, vegetables, salads and vegetables, legumes and dairy products, and in turn subtracting the frequencies of eating sweets, sugared soft drinks, fast food, and salty snacks. The frequency of each of these food groups is measured on the following scale: 0 - Never, 1 - Less than once a week, 2 - Once or twice a week, 3 - Three times a week, 4 - Four to six times a week, 5 - Once or more per day; h) Equivalent used in grams of pure alcohol: beer with alcohol: 10g per drink unit, wine or cava: 10g per drink unit, aperitifs with alcohol (vermouth, sherry): 20g per drink unit, liqueurs, anise, pacharán: 20g per drink unit, whisky, cognac, mixed: 20g per drink unit, local drinks (cider, carajillo ...): 10g per drink unit; p: significance level of the chi-square test. *Source*. Own research with data from the EHSS-2014.

ercise, lower healthy eating index and fewer children in the household.

Multivariate analysis

The results of the multivariate analysis of cigarette smoking prevalence are presented in four regression models, 1A, 1B, 2A and 2B, in Table 2. To assess prevalence, three situations were considered: (1) never smoker, (2) ex-smoker and (3) smoker. The ordered nature of the model used generates two outputs in each regression: (i) situations 3-2 versus 1, smoker and ex-smoker (versus never smoker), and (ii) situation 3 versus 2-1, smoker (versus ex-smoker and never smoker). It is precisely the orderly nature of the model which means that, in each of the two regression outputs, the alternative situation or situations (situation 1 or situations 2-1) are better, from a health perspective, than the main situations or situation (situations 3-2 or situation 3).

Models 1A and 1B include the entire final sample (19,931) while models 2A and 2B only comprise the working population (8,995). Type A models capture the information on the socioeconomic gradient through social class. Type B models, meanwhile, replace the compact information on the socioeconomic gradient captured by social class with those variables directly related to this gradient: educational level and economic/work-related variables as the main activity, health insurance (as a proxy of the economic situation) and sector of activity (only model 2B).

First, the results associated with the *probability of belonging to the smoker and ex-smoker population (versus never smokers)* are analysed, as shown in the left panel of Table 2. In relation to the variables associated with the *socioeconomic gradient*, model 1A shows how this probability in the *total sample* increases in social classes IV (OR = 1.13), V (OR = 1.20) and VI (OR = 1.19) versus social class I. In model 1B, this probability increases in the population with secondary education (OR = 1.52) and vocational training (OR = 1.35) compared to the population with university education. Regarding the main employment activity (model 1B), and compared to the situation of a business owners without employees or the solo self-employed, this probability increases in people with work disabilities (OR = 1.49), the unemployed (OR = 1.30), retirees or early retirees (OR = 1.28) and decreased for students (OR = 0.24) and people doing housework (OR = 0.66). On the other hand, having only public healthcare (model 1B) increases this probability (OR = 1.10).

When analysing this probability for the *sample of workers*, models 2A and 2B show greater effects of social class and educational level, respectively, than that observed for the *total sample* in models 1A and 1B. Regarding activity sector, and compared to hospitality workers, model 2B shows how this probability decreases, in particular for people doing household activities (OR = 0.52), working in artistic, recreational and entertainment sectors (OR = 0.59), or in information and communications (OR = 0.61) and education (OR = 0.68) sectors.

Regarding the *independent control variables*, models 1A and 1B show how this probability decreases for the *total sample* in women, increases in people aged 36-65 years (compared to people aged 15-35 years), increases in separated and divorced and decreases for widow/widowers (compared to singles), increases for the population with worse habits (less physical exercise, less healthy eating, greater alcohol use), decreases for people with lower BMI, and increases for those with some disease or mental health problem. Models 2A and 2B, meanwhile, show similar results for the *working population*.

Results regarding the *probability of belonging to the smoking population (compared to ex-smokers and never smokers)* are shown in the right panel of Table 2. In relation to the variables associated with the *socioeconomic gradient*, model 1A shows how this probability for the *total sample* increases significantly in social classes III (OR = 1.16), IV (OR = 1.23), V (OR = 1.32) and VI (OR = 1.47) compared to social class I. In model 1B, this probability increases for the population with primary (OR = 1.53) or secondary education (OR = 1.87) and vocational training (OR = 1.53), compared to the population with university education. Regarding the main activity (model 1B), and compared to the situation of business owners without employees or the solo self-employed, this probability increases for the unemployed (OR = 1.20), while it decreases for students (OR = 0.26), retirees or early retirees (OR = 0.60), people doing housework (OR = 0.75) and civil servants (OR = 0.76). On the other hand, having only public health cover (model 1B) increases this probability (OR = 1.15).

When analysing this probability for the *sample of workers*, models 2A and 2B show greater effects of social class and similar effects of educational level, respectively, than that observed for the *total sample* in models 1A and 1B. Regarding the main employment activity (model 2B), and compared to the situation of business owners without employees or the solo self-employed, this probability decreases for business owners or professionals with employees (OR = 0.78). Regarding activity sectors (model 2B), and compared to hospitality workers, this probability decreases significantly for workers in artistic, recreational and entertainment sectors (OR = 0.63), household activities (OR = 0.65), other services (OR = 0.66), agriculture, livestock, forestry and fishing (OR = 0.70), education (OR = 0.72), and professional, scientific and technical activities (OR = 0.74).

As for the *independent control variables*, models 1A and 1B show for the *total sample* how this probability decreases in women, increases in people aged between 36 and 50 years and decreases in people over 65 years (compared to people aged 15-35), increases for the divorced and separated, and decreases for married and widows/widowers (compared

Table 2. *Results of the multivariate analysis of the association between cigarette smoking prevalence in Spain in 2014 and different characteristics.*

	Smoker and Ex-smoker (vs Never smoker)								Smoker (vs Ex-smoker and Never smoker)							
Model	**1A**		**1B**		**2A**		**2B**		**1A**		**1B**		**2A**		**2B**	
Sample	**All (n = 19,931)**		**All (n = 19,931)**		**Only workers (n = 8,995)**		**Only workers (n = 8,995)**		**All (n = 19,931)**		**All (n = 19,931)**		**Only workers (n = 8,995)**		**Only workers (n = 8,995)**	
Variables capturing social class	**Yes**		**No**		**Yes**		**No**		**Yes**		**No**		**Yes**		**No**	
Variables linked to social class	**No**		**Yes**		**No**		**Yes**		**No**		**Yes**		**No**		**Yes**	
Main Independent Variables –Socioeconomic Gradient–	**OR**	**CI 95%**	**OR**	**CI 95%**	**OR**	**CI 95%**	**OR**	**CI 95%**	**OR**	**CI 95%**	**OR**	**CI 95%**	**OR**	**CI 95%**	**OR**	**CI 95%**
Social class																
Class I (ref.) (0-1)	1				1				1				1			
Class II (0-1)	1.04	0.91 1.18			1.01	0.85 1.19			1.07	0.92 1.25			1.02	0.84 1.24		
Class III (0-1)	1.10	0.99 1.22			1.18 *	1.03 1.36			1.16 *	1.02 1.31			1.22 *	1.04 1.42		
Class IV (0-1)	1.13 *	1.00 1.27			1.40 ***	1.18 1.64			1.23 **	1.08 1.41			1.37 **	1.14 1.64		
Class V (0-1)	1.20 ***	1.08 1.33			1.44 ***	1.25 1.65			1.32 ***	1.17 1.49			1.48 ***	1.27 1.72		
Class VI (0-1)	1.19 **	1.05 1.34			1.55 ***	1.29 1.85			1.47 ***	1.28 1.69			1.77 ***	1.47 2.14		
Educational attainment																
Primary education (0-1)			0.96	0.86 1.07			1.19 **	1.06 1.35			1.53 ***	1.28 1.83			1.48 ***	1.22 1.79
Secondary education (0-1)			1.52 ***	1.39 1.66			1.66 ***	1.51 1.84			1.87 ***	1.65 2.12			1.77 ***	1.54 2.03
Vocational training (0-1)			1.35 ***	1.21 1.49			1.47 ***	1.31 1.65			1.53 ***	1.34 1.74			1.63 ***	1.41 1.89
University education (ref.) (0-1)			1				1				1				1	
Economic/work-related variables																
Main activity																
Business owner or professional with employees (0-1)			0.85	0.68 1.05			0.85	0.68 1.06			0.79	0.63 1.00			0.78 *	0.62 0.99
Business owner without employees or solo self-employed (ref.) (0-1)			1				1				1				1	
Civil servant (0-1)			0.93	0.78 1.11			0.93	0.75 1.16			0.76 **	0.63 0.93			0.80	0.63 1.03
Worker with permanent contract (0-1)			0.97	0.84 1.11			0.94	0.81 1.09			0.91	0.79 1.05			0.87	0.75 1.01
Worker with temporary contract (0-1)			1.02	0.86 1.21			0.95	0.80 1.13			1.00	0.83 1.19			0.92	0.76 1.10
Other work situation (0-1)			1.28	0.91 1.78			1.24	0.88 1.75			1.05	0.74 1.49			0.98	0.68 1.41
Unemployed (0-1)			1.30 **	1.12 1.51							1.20 *	1.03 1.40				
Student (0-1)			0.24 ***	0.20 0.30							0.26 ***	0.21 0.32				
Retiree or early retiree (0-1)			1.28 **	1.07 1.54							0.60 ***	0.49 0.74				
Work disability (0-1)			1.49 **	1.15 1.94							0.99	0.76 1.29				
Housework (0-1)			0.66 ***	0.55 0.79							0.75 **	0.62 0.92				
Other jobless situation (0-1)			0.96	0.54 1.72							0.89	0.48 1.63				
Health insurance																
Only public health -no state mutuals- (0-1)			1.10 *	1.01 1.19			1.05	0.95 1.17			1.15 **	1.05 1.26			1.10	0.98 1.23
State mutuals or private insurance (ref.) (0-1)			1				1				1				1	
Only workers																
Sector (NACE Rev.2)																
A Agriculture, forestry and fishing (0-1)							0.71 *	0.54 0.93							0.70 *	0.53 0,92
B Mining industry (0-1)							2.24	0.82 6.08							0.93	0.41 2,13
C Manufacturing industry (0-1)							0.94	0.76 1.16							0.95	0.77 1,18
D Electric power, gas, steam and air conditioning (0-1)							0.79	0.45 1.37							0.75	0.41 1,35
E Water supply, sanitation, waste and decontamination (0-1)							0.96	0.56 1.66							1.13	0.67 1,91
F Construction (0-1)							0.77 *	0.59 0.99							0.82	0.63 1,07
G Car sales and repairs (0-1)							0.73 **	0.60 0.89							0.79 *	0.65 0,97
H Transport and storage (0-1)							0.80	0.61 1.05							0.86	0.65 1,13

Table 2. *Results of the multivariate analysis of the association between cigarette smoking prevalence in Spain in 2014 and different characteristics* (cont.).

I	Hospitality (ref.) (0-1)										1													1					
J	Information and communications (0-1)										0.61	**	0.45	0.83										0.79		0.57	1,10		
K	Finance and insurance (0-1)										0.67	*	0.49	0.92										0.75		0.53	1,07		
L	Real estate (0-1)										1.27		0.72	2.22										1.01		0.57	1,78		
M	Professional, scientific and technical activities (0-1)										0.72	*	0.55	0.93										0.74	*	0.55	0,98		
N	Administrative and auxiliary services (0-1)										0.82		0.64	1.07										0.88		0.68	1,15		
O	Public administration and defence; Obligatory social security (0-1)										0.78		0.61	1.01										0.76	*	0.58	1,00		
P	Education (0-1)										0.68	**	0.53	0.88										0.72	*	0.55	0,94		
Q	Health and social services (0-1)										0.90		0.72	1.14										0.82		0.64	1,04		
R	Artistic, recreational and entertainment activities (0-1)										0.59	**	0.41	0.85										0.63	*	0.42	0,95		
S	Other services (0-1)										0.86		0.61	1.20										0.66	*	0.46	0,95		
T	Household activities (0-1)										0.52	***	0.38	0.71										0.65	*	0.46	0,91		
U	Working for extraterritorial organisations (0-1)										0.60		0.08	4.41										0.26		0.03	2,67		
Independent Control Variables																														
Sociodemographic variables																														
Sex																														
Women (0-1)		0.48	***	0.45	0.51	0.52	***	0.48	0.56	0.89	*	0.81	0.98	0.94		0.85	1.04	0.62	***	0.57	0.67	0.65	***	0.60	0.70	0.89	*	0.80	0.98	0.96		0.85	1.07
Men (ref.) (0-1)		1				1				1				1				1				1				1				1			
Age																														
15-35 years (ref.) (0-1)		1				1				1				1				1				1				1				1			
36-50 years (0-1)		1.74	***	1.59	1.91	1.39	***	1.26	1.53	1.28	***	1.14	1.44	1.28	***	1.14	1.45	1.38	***	1.25	1.52	1.16	**	1.04	1.28	1.09		0.96	1.23	1.11		0.98	1.26
51-65 years (0-1)		1.92	***	1.72	2.14	1.64	***	1.45	1.85	1.72	***	1.49	1.99	1.69	***	1.46	1.97	0.95		0.84	1.07	0.91		0.80	1.03	0.91		0.78	1.06	0.94		0.80	1.11
Over 65 years (0-1)		0.91		0.81	1.02	0.78	**	0.65	0.93									0.23	***	0.19	0.27	0.34	***	0.27	0.43								
Marital status																														
Single (ref.) (0-1)		1								1								1								1							
Married (0-1)		1.13	**	1.04	1.22	1.03		0.95	1.13	1.04		0.92	1.16	1.00		0.89	1.12	0.81	***	0.74	0.88	0.72	***	0.66	0.79	0.75	***	0.67	0.85	0.71	***	0.63	0.80
Separated (0-1)		1.58	***	1.29	1.93	1.35	**	1.11	1.65	0.98		0.75	1.28	0.93		0.71	1.23	1.45	***	1.18	1.78	1.27	*	1.03	1.55	0.97		0.73	1.29	0.94		0.70	1.25
Divorced (0-1)		1.75	***	1.50	2.04	1.51	***	1.29	1.77	1.37	**	1.11	1.68	1.32	**	1.07	1.62	1.53	***	1.31	1.79	1.32	***	1.13	1.55	1.31	*	1.07	1.60	1.25	*	1.02	1.54
Widow/widower (0-1)		0.64	***	0.56	0.74	0.54	***	0.47	0.62	0.68	*	0.49	0.94	0.65	*	0.47	0.90	0.78	**	0.65	0.93	0.74	**	0.62	0.88	1.00		0.71	1.42	0.95		0.67	1.35
Number of children in the household (0-6)		0.97		0.92	1.02	0.97		0.93	1.02	0.98		0.92	1.04	0.99		0.93	1.05	0.86	***	0.82	0.91	0.87	***	0.83	0.92	0.88	***	0.83	0.94	0.89	**	0.83	0.95
Healthy lifestyle habits																														
Weekly hours of physical exercise in leisure time (0-50)		0.98	***	0.97	0.99	0.98	***	0.97	0.99	0.99		0.98	1.00	0.99		0.98	1.00	0.96	***	0.95	0.97	0.96	***	0.95	0.97	0.96	***	0.95	0.98	0.96	***	0.95	0.98
Healthy diet index (-13 to 25)		0.97	***	0.97	0.98	0.97	***	0.97	0.98	0.97	***	0.96	0.98	0.97	***	0.97	0.98	0.96	***	0.95	0.97	0.96	***	0.95	0.97	0.95	***	0.94	0.96	0.95	***	0.94	0.96
Average daily consumption of pure alcohol in grams (0-185.71)		1.04	***	1.03	1.04	1.04	***	1.03	1.04	1.04	***	1.03	1.05	1.04	***	1.04	1.05	1.03	***	1.02	1.03	1.02	***	1.02	1.03	1.03	***	1.02	1.03	1.03	***	1.02	1.03
State of Health																														
Body Mass Index (1-4)		0.94	**	0.90	0.97	0.92	***	0.88	0.96	0.98		0.92	1.05	0.97		0.91	1.03	0.82	***	0.78	0.86	0.80	***	0.76	0.84	0.81	***	0.76	0.87	0.80	***	0.75	0.86
Mental health (last 12 months)																														
Mental health disease/problem (0-1)		1.16	**	1.06	1.27	1.11	*	1.01	1.22	1.20	*	1.00	1.43	1.18		0.99	1.41	1.27	***	1.15	1.40	1.24	***	1.12	1.38	1.31	**	1.10	1.57	1.31	**	1.09	1.57
Mentally healthy (ref.) (0-1)		1				1				1				1				1				1				1				1			

Note. * p ‹ 0.05; ** p ‹ 0.01; *** p ‹ 0.001; All models also include the following geographic variables as control variables: place of birth (categorical variable indicating whether participant was born in or outside Spain), size of the municipality (7 categorical variables from smallest to largest population: ‹ 10 thousand inhabitants, 10-20 thousand inhabitants, 20-50 thousand inhabitants, 50-100 thousand inhabitants, 100-500 thousand inhabitants not provincial capital, provincial capital ‹ 500 thousand inhabitants, › 500 thousand inhabitants), autonomous community (or city) (19 categorical variables corresponding to the 17 autonomous communities and the 2 autonomous cities in Spain); a In models 2A and 2B only for workers, age ranges from 18 to 65 years.

Source. Own research with data from EHSS-2014.

to singles), increases for the population with less healthy habits, decreases for people with lower BMI, and increases for people with some disease or health problem For their part, models 2A and 2B show similar results for the *working population*.

The results of the multivariate analysis of cigarette smoking levels in the *total sample of smokers* are presented in models 3A and 3B of Table 3 (4,785 records). To measure the level of smoking, four levels were considered: (1) occasional smoker, (2) daily smoker of up to 10 cigarettes, (3) daily smoker of 11 to 20 cigarettes and (4) daily smoker of over 20 cigarettes. The ordered nature of the model generates three outputs in each regression: (i) levels 4-3-2 vs. 1, daily smoker (vs. occasional smoker), (ii) levels 4-3 vs. 2-1, daily smoker of more than 10 cigarettes (vs. daily smokers of up to 10 cigarettes and occasional smokers) - and (iii) level 4 vs. 3-2-1, daily smoker of over 20 cigarettes (vs. daily smokers of up to 20 cigarettes and occasional smokers). In this case, the ordered nature of the model again means that, in each of the three outputs in the regression, the alternative level or levels (level 1, levels 2-1 or levels 3-2-1) are better in health terms than the levels or the main level (levels 4-3-2, levels 4-3 or level 4).

Analogously to Table 2, model 3A captures the information on the socioeconomic gradient through social class, while 3B includes those variables directly related to this gradient: educational attainment and economic/work-related variables such as the main work activity and health insurance.

First, the results related to the *probability of belonging to the daily smoker population (versus occasional smoker)*, presented in the left panel of Table 3, are analysed. Regarding the variables associated with the *socioeconomic gradient,* model 3A shows how this probability increases for social classes III (OR = 1.48), IV (OR = 1.64), V (OR = 1.99) and VI (OR = 1.68) compared to social class I. Model 3B shows how, compared to the population with a university education, this probability increases for the population with basic (OR = 1.49) and secondary education (OR = 1.48). Regarding main work activity, and compared to the situation of business people without employees or the solo self-employed, it is observed how this probability decreases for those people whose main activity is studying (OR = 0.51).

With respect to the *independent control variables*, models 3A and 3B show how this probability increases in people aged between 36 and 65 years (compared to those aged 15-35 years) and in divorcees (compared to singles), as well as for the population doing less physical exercise and eating a less healthy diet.

Next, the results related to the *probability of belonging to the population that smokes over 10 cigarettes daily (versus daily smokers of under 10 cigarettes and occasional smokers)* are analysed; these are presented in the central panel of Table 3. Regarding the variables associated with the socioeconomic gradient, model 3A shows how this probability increases significantly in social classes IV (OR = 1.36), V (OR = 1.34) and VI (OR = 1.50) as against social class I. In model 3B, compared to the population with a university education, this probability increases for the population with primary (OR = 1.84) or secondary education (OR = 1.66) and vocational training (OR = 1.55). Regarding the main activity (model 3B), and compared to the situation of business owners without employees or the solo self-employed, this probability decreases for students (OR = 0.20), workers on permanent contracts (OR = 0.72) and the unemployed (OR = 0.73).

In relation to the *independent control variables*, models 3A and 3B show how this probability is reduced in women and in households with a greater number of children, while increasing in people between 36 and 65 years of age (compared to those aged 15-35 years), in divorcees (compared to singles), in the population with less healthy behaviours, and among those with higher BMI or with some disease or mental health problem.

Finally, the results related to the *probability of belonging to the daily population of smokers of over 20 cigarettes* are analysed (versus *daily smokers of under 20 cigarettes* and *occasional smokers*), as shown in the right panel of Table 3. In relation to the variables associated with the *socioeconomic gradient* and, contrary to findings regarding the rest of the probabilities analysed in this study, models 3A and 3B do not show any significant effect of social class, education or health insurance. Regarding the main work activity (model 3B), however, compared to the situation of business owner without employees or the solo self-employed, this probability decreases for retirees or early retirees (OR = 0.44) and workers with a permanent contract (OR = 0.57).

Regarding the *independent control variables*, models 3A and 3B show how this probability decreases in women and increases in people aged 36 to 65 years (compared to those aged 15-35 years), in the population with the worst habits, and in people with higher BMI or with some disease or mental health problem.

Discussion

To tackle inequalities in smoking prevalence, interventions and socio-health policies should target groups with a higher risk of prevalence, so the main aim of this study was to identify such risk groups.

The findings confirm the relationship between the *socioeconomic gradient* and both the prevalence and the intensity of smoking in Spain, which is consistent with the predictions of the epidemiological model by López et al. (1994) for the spread of the epidemic in the most disadvantaged groups and with the international academic literature documenting this association (Schaap et al., 2008; White et al., 2016). These results are robust in their identification either

Table 3. Results of the multivariate analysis of the association between the intensity of cigarette smoking in Spain in 2014 and different characteristics.

	Daily smoker (vs Occasional smoker)						Daily smoker › 10 cigarettes (vs Daily smoker ≤ 10 and Occasional smoker)						Daily smoker › 20 cigarettes (vs Daily smoker ≤ 20 and Occasional smoker)					
Model	**3A**			**3B**			**3A**			**3B**			**3A**			**3B**		
Sample	**Only smokers (n = 4,785)**			**Only smokers (n = 4,785)**			**Only smokers (n = 4,785)**			**Only smokers (n = 4,785)**			**Only smokers (n = 4,785)**			**Only smokers (n = 4,785)**		
Variables capturing social class	**Yes**			**No**			**Yes**			**No**			**Yes**			**No**		
Variables linked to social class	**No**			**Yes**			**No**			**Yes**			**No**			**Yes**		
Main Independent Variables –Socioeconomic Gradient–	**OR**	**CI 95%**		**OR**	**CI 95%**		**OR**	**CI 95%**		**OR**	**CI 95%**		**OR**	**CI 95%**		**OR**	**CI 95%**	
Social class																		
Class I (ref.) (0-1)	1						1						1					
Class II (0-1)	1.37	0.87	2.17				1.13	0.85	1.51				0.93	0.51	1.69			
Class III (0-1)	1.48 *	1.02	2.13				1.24	0.98	1.57				0.87	0.54	1.39			
Class IV (0-1)	1.64 *	1.09	2.46				1.36 *	1.06	1.75				0.83	0.51	1.36			
Class V (0-1)	1.99 ***	1.40	2.84				1.34 *	1.07	1.67				1.02	0.66	1.57			
Class VI (0-1)	1.68 *	1.13	2.51				1.50 **	1.17	1.93				1.12	0.70	1.79			
Educational attainment																		
Primary education (0-1)				1.49 *	1.01	2.20				1.84 ***	1.47	2.32				1.07	0.69	1.67
Secondary education (0-1)				1.48 *	1.10	1.99				1.66 ***	1.37	2.01				1.06	0.71	1.57
Vocational training (0-1)				1.38	0.98	1.94				1.55 ***	1.25	1.92				0.92	0.58	1.44
University education (ref.) (0-1)				1						1						1		
Economic/work-related variables																		
Main activity																		
Business owner or professional with employees (0-1)				0.61	0.32	1.15				0.91	0.61	1.35				0.74	0.38	1.47
Business owner without employees or solo self-employed (ref.) (0-1)				1						1						1		
Civil servant (0-1)				1.06	0.58	1.95				0.89	0.63	1.27				0.53	0.26	1.08
Worker with permanent contract (0-1)				0.90	0.58	1.38				0.72 **	0.56	0.91				0.57 *	0.38	0.88
Worker with temporary contract (0-1)				1.02	0.61	1.71				0.80	0.59	1.07				0.75	0.43	1.29
Other work situation (0-1)				2.33	0.53	10.27				1.16	0.64	2.11				1.59	0.61	4.15
Unemployed (0-1)				0.97	0.61	1.53				0.73 *	0.57	0.94				0.74	0.47	1.15
Student (0-1)				0.51 *	0.28	0.94				0.20 ***	0.12	0.33				0.27	0.06	1.18
Retiree or early retiree (0-1)				1.82	0.79	4.21				0.78	0.54	1.14				0.44 *	0.23	0.86
Work disability (0-1)				0.77	0.35	1.73				0.79	0.51	1.23				0.64	0.32	1.28
Housework (0-1)				1.27	0.65	2.50				0.81	0.57	1.15				0.65	0.31	1.36
Other jobless situation (0-1)				0.91	0.11	7.77				1.84	0.56	6.05				1.96	0.59	6.48
Health insurance																		
Only public health -no state mutuals- (0-1)				1.16	0.87	1.53				0.90	0.76	1.07				0.94	0.66	1.32
State mutuals or private insurance (ref.) (0-1)				1						1						1		
Independent Control Variables																		
Sociodemographic variables																		
Sex																		
Women (0-1)	0.91	0.73	1.15	0.92	0.72	1.16	0.66 ***	0.57	0.75	0.69 ***	0.60	0.79	0.45 ***	0.34	0.60	0.46 ***	0.34	0.62
Men (ref.) (0-1)	1			1			1			1			1			1		
Age																		
15-35 years (ref.) (0-1)	1			1			1			1			1			1		
36-50 years (0-1)	1.94 ***	1.49	2.53	1.83 ***	1.39	2.40	1.98 ***	1.67	2.34	1.75 ***	1.47	2.08	1.92 **	1.30	2.84	1.83 **	1.23	2.73
51-65 years (0-1)	2.54 ***	1.77	3.64	2.15 ***	1.47	3.14	2.29 ***	1.86	2.81	1.92 ***	1.54	2.39	2.55 ***	1.65	3.93	2.47 ***	1.58	3.87
Over 65 years (0-1)	3.15 ***	1.71	5.78	1.54	0.64	3.72	1.65 **	1.22	2.21	1.33	0.88	2.00	1.79	0.98	3.26	2.37 *	1.07	5.25
Marital status																		
Single (ref.) (0-1)	1			1			1			1			1			1		
Married (0-1)	0.97	0.75	1.27	0.92	0.70	1.21	1.12	0.96	1.30	1.03	0.88	1.20	1.12	0.83	1.52	1.11	0.81	1.51
Separated (0-1)	1.06	0.57	1.97	1.05	0.56	1.97	1.18	0.84	1.64	1.10	0.79	1.53	1.56	0.92	2.65	1.56	0.92	2.65
Divorced (0-1)	2.01 *	1.12	3.62	1.94 *	1.07	3.50	1.79 ***	1.39	2.31	1.72 ***	1.33	2.22	1.51	0.96	2.36	1.46	0.93	2.28
Widow/widower (0-1)	2.46 *	1.02	5.89	2.22	0.92	5.37	1.41 *	1.01	1.97	1.29	0.92	1.81	1.35	0.72	2.54	1.49	0.78	2.83
Number of children in the household (0-6)	0.86	0.74	1.00	0.86	0.74	1.00	0.89 *	0.81	0.97	0.88 **	0.80	0.97	0.88	0.72	1.07	0.86	0.70	1.04
Healthy lifestyle habits																		
Weekly hours of physical exercise in leisure time (0-50)	0.96 **	0.94	0.99	0.96 **	0.94	0.99	0.95 ***	0.93	0.96	0.95 ***	0.93	0.96	0.90 ***	0.85	0.94	0.90 ***	0.85	0.94
Healthy diet index (-13 to 25)	0.96 ***	0.94	0.98	0.96 ***	0.94	0.98	0.96 ***	0.94	0.97	0.96 ***	0.94	0.97	0.95 ***	0.93	0.97	0.95 ***	0.93	0.98
Average daily consumption of pure alcohol in grams (0-185.71)	1.00	0.99	1.01	1.00	0.99	1.01	1.01 ***	1.01	1.02	1.01 ***	1.01	1.02	1.02 ***	1.01	1.03	1.02 ***	1.01	1.03
State of Health																		
Body Mass Index (1-4)	0.93	0.80	1.08	0.92	0.79	1.06	1.15 **	1.06	1.25	1.13 **	1.04	1.23	1.58 ***	1.36	1.83	1.55 ***	1.34	1.81
Mental health (last 12 months)																		
Mental health disease/problem (0-1)	1.08	0.76	1.54	1.08	0.76	1.55	1.35 **	1.13	1.62	1.33 **	1.11	1.61	2.79 ***	2.09	3.71	2.79 ***	2.07	3.77
Mentally healthy (ref.) (0-1)	1			1			1			1			1			1		

Note. * p ‹ 0.05; ** p ‹ 0.01; *** p ‹ 0.001; All models also include the following geographic variables as control variables: place of birth (categorical variable indicating whether participant was born in or outside Spain), size of the municipality (7 categorical variables from smallest to largest population: ‹ 10 thousand inhabitants, 10-20 thousand inhabitants, 20-50 thousand inhabitants, 50-100 thousand inhabitants, 100-500 thousand inhabitants not provincial capital, provincial capital ‹ 500 thousand inhabitants, › 500 thousand inhabitants), autonomous community (or city) (19 categorical variables corresponding to the 17 autonomous communities and the 2 autonomous cities in Spain). *Source*. Own research with data from EHSS-2014.

through the variables capturing social class, or through level of education and economic/work-related variables.

More specifically, regarding social class, both prevalence and intensity of cigarette smoking is seen to increase in groups of lower social class. Class (based on occupation) can point to differences between workers in the workplace and social relationships at work, which can generate important differences in relation to smoking given the heterogeneity within each group in terms of attitudes, social norms and social support (Sorensen, Barbeau, Hunt & Emmons, 2004).

Regarding educational attainment, it is observed in particular how university study is associated not only with lower smoking prevalence but also, within the population of smokers, lower intensity. Regarding this result, it is also observed how studying as the main activity is associated with lower prevalence and intensity, suggesting the importance of formal educational processes in the fight against this epidemic. Not surprisingly, educational level is the most used factor of the socioeconomic gradient in the set of studies analysing the association between socioeconomic status and smoking (Schaap et al., 2008). In practice, those with more education perform better in almost all dimensions of health, adopt healthier behaviours and live longer (Maralani, 2014).

Also interesting is the result regarding unemployed participants, with high smoking prevalence but lower levels of intensity. This duality seems indicative of a double effect. On the one hand, redundancy could not only be considered a stress-inducing event, associated with relapse into smoking (McKee, Maciejewski, Falba & Mazure, 2003), but also places the individual in a more disadvantaged and vulnerable collective where smoking is more frequent (Falba, Teng, Sindelar & Gallo, 2005; Okechukwu, Bacic, Cheng & Catalano, 2012). This higher prevalence observed among the unemployed is consistent with that observed in those participants whose only form of health insurance is the public health system (and, therefore, a worse economic situation), whose prevalence is also higher. There is, therefore, evidence associating lower levels of work income with the population of smokers (Levine, Gustafson & Velenchik, 1997). On the other hand, the lower purchasing power of these groups may cause people to simply reduce their levels of smoking (Falba et al., 2005). In the case of the unemployed in Spain, in particular, the financial difficulties associated with the lack of employment coexist with the effects of the 2008 crisis and high cigarette prices.

This situation allows some interesting arguments to be posited. In the first place, the need to incorporate the unemployed into specific prevention and smoking cessation plans seems urgent. Second, the employment policies developed by the different public services not only have a direct effect in terms of reducing unemployment, but could also have a significant indirect effect in the fight against smoking. Third, tax increases on tobacco products appear to trigger greater decreases in the smoking levels of lower-income groups, that is, those showing a higher prevalence, which suggests the suitability of these measures. In other words, a higher price elasticity of demand for cigarettes is observed among the most vulnerable socioeconomic groups, which is consistent with the existing evidence for other countries (Colman & Remler, 2008; Nargis, Fong, Chaloupka & Li, 2014). The latest tax increases, however, have turned Spain from being a transit country for illicit tobacco into a destination market, precisely in regions such as Andalusia and Extremadura where the level of unemployment is higher (Calderoni, Angelini, Mancuso & Rotondi, 2014). Such tax increases must therefore be accompanied by greater pressure against tax evasion and smuggling to prevent a substitution effect from occurring in the change from legal towards illicit product use.

In terms of the working population, various sectors are seen to have lower prevalence, some of which are associated with higher educational levels, such as the education sector, professional, scientific and technical activities, in public administration and defence, or in artistic, recreational and entertainment sectors. The opposite is observed, however, in other sectors such as hospitality, construction or transport and storage. These results are consistent with the evidence available in the international literature on higher prevalence and intensity of smoking in manual (or blue-collar) workers compared to office (or white-collar) workers (Okechukwu et al., 2012). Thus, the need for greater watchfulness regarding workers in specific sectors is urgent, and more systematic programs to control smoking should be designed for them. In this sense, the working environment itself has been revealed as an effective context for habit control interventions in manual workers (Cahill & Lancaster, 2014). However, the very nature of many manual jobs causes workers to change employers frequently, making it difficult to reach them through these programs (Okechukwu et al., 2012). Furthermore, it is precisely these sectors that are most sensitive to economic fluctuation, leading workers to repeatedly alternate between employment and jobless situations (as can be seen in the current COVID-19 crisis, especially in the hospitality sector). This state of flux doubles the vulnerability of these workers regarding their smoking habit: higher smoking prevalence and intensity in situations of job loss (Montgomery, Cook, Bartley & Wadsworth, 1998) on the one hand and, on the other, higher smoking intensity in recessive economic situations (Okechukwu et al., 2012).

These results as a whole make it possible not only to identify more precisely the at-risk groups in the fight against smoking in Spain, but also to highlight the need for more evidence to be collected to improve treatment of dependence in special populations, such as are the groups with the lowest socioeconomic levels (Fagan et al., 2004).

This study also includes in its analysis other control variables related to smoking, such as *sociodemographic characteristics, healthy lifestyle habits*, and *health status*. The analysis of the results obtained in relation to these variables gives rise to some further interesting arguments.

In the first place, this study reveals some demographic factors characterising cigarette users in Spain. In particular, men, people aged between 36 and 50 years, divorcees, and people whose children do not live at home show both higher prevalence and intensity in their smoking. In this sense, although the results associated with the sex and age of the smoker are very common in epidemiological studies (Pinilla & Abásolo, 2017; Leal-López, Sánchez-Queija & Moreno, 2019; Rodríguez-Muñoz, Carmona-Torres, Hidalgo -Lopezosa, Cobo-Cuenca & Rodríguez-Borrego, 2019), the evidence obtained as regards marital status and number of children in the household is more novel and could be of interest in designing better tobacco control programs for specific groups. In particular, these results suggest a relationship with the set of studies which identify a positive association between smoking and factors such as loneliness and negative affect (see Dyal & Valente, 2015, for a review).

Second, a robust association is observed between healthy lifestyle habits and reduced smoking prevalence and intensity, consistent with the existing academic literature; although within the latter, studies focused on specific population subgroups predominate, such as adolescents (Rodríguez-García, López Villalba, López-Miñarro & García-Cantó, 2013), marginalized groups (Watanabe et al., 2013) or pregnant women (Ino, Shibuya, Saito & Inaba, 2011). The results presented here therefore contribute to this literature in showing the existence of this virtuous association between healthy lifestyle habits and less smoking for the total population, which is less frequent in academic research (the work of Agudo et al., 2004 is an exception). In brief, regular physical exercise, good diet and nutrition and the responsible use of alcohol are not only highly recommended behaviours given their enormous physical and psychological benefits (Woodcock, Franco, Orsini & Roberts, 2011), but promoting them is shown to be an indispensable ally in the design of plans by the health authorities against the smoking epidemic.

Thirdly, this analysis presents other valuable evidence in terms of its contribution to the design of tobacco control programs targeting specific groups, such as those linking smoking and health status, as captured through BMI and mental health. Regarding BMI, this study shows how smokers present lower values than non-smokers. However, the results also show how BMI values increase with rising levels of smoking, yet both associations are consistent with the available evidence (Chiolero, Faeh, Paccaud & Cornuz, 2008). Specifically, the reduction in appetite and the higher energy expenditure associated with nicotine seem to explain the negative association between smoking prevalence BMI values. Higher levels of smoking, however, seems to be associated with a set of coexisting risk factors (sedentary lifestyle, irregular eating and excess alcohol use) which could explain the weight gain. As regards mental health, this study presents evidence showing a positive relationship between cigarette smoking and having a disease or mental health problem, which is consistent with the existing results in the epidemiological literature linking tobacco use to problems such as depression or anxiety (Mykletun, Overland, Aarø, Liabø & Stewart, 2008).

This work is not without limitations, of which the cross-section data available in the EHSS-2014 is probably the most important. Thus, the fact that the information available refers to a single period does not allow cause-effect relationships to be established, only statistical associations. In other words, it is not possible in light of this evidence to make statements of such as people are smokers because of their work, economic or family situation, or simply because of their lifestyle. Furthermore, the data from this study do not allow us to distinguish normal cigarettes from hand-rolled ones, which would be interesting in itself, or to incorporate other tobacco products such as cigars or pipes, given the small number of observations in the sample, or water pipes or e-cigarettes due to the exclusion of these products from the questionnaire. The exploration of possible joint effects between the different variables associated with the socio-economic gradient has also been outside the limits of this study for reasons of brevity and focus. Other natural extensions of this study would be the use of EHSS-2019 data (not yet available at the time of writing), which would allow us to know how the smoking habit has changed in Spain in the last five years, or the expansion of the reference frame to other countries also participating in the European Health Survey, which would enable a comparative perspective with countries of our socio-economic environment.

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Conflicts of interests

The authors declare no conflicts of interest.

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Clinical practice guideline on pharmacological and psychological management of adult patients with schizophrenia spectrum disorders and a comorbid substance use

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

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Abstract

Although correct diagnosis and management of patients with schizophrenia and a comorbid substance use disorder (SUD) would determine a decrease in morbidity and mortality in these patients, development of efficient therapeutic strategies is still pending. We present recommendations on the pharmacological and psychological management of these patients following the 'PICO' structure (Patient-Intervention-Comparison-Outcomes). 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. Our results suggest: 1) In patients with schizophrenia and cannabis use disorder, it is not possible to recommend one antipsychotic drug over another (between olanzapine, risperidone or haloperidol) for improving psychotic symptoms, reducing cannabis use, or improving pragmatic variables (weak recommendation). Clozapine cannot be recommended to reduce cannabis use (weak

Resumen

Aunque el correcto diagnóstico y manejo de los pacientes con esquizofrenia y un diagnóstico comórbido de trastorno por uso de sustancias (TUS) determinaría una disminución de la morbilidad y mortalidad en estos pacientes, el desarrollo de estrategias terapéuticas eficientes es todavía una asignatura pendiente. Presentamos recomendaciones sobre el manejo farmacológico y psicológico de estos pacientes siguiendo la estructura PICO (Paciente-Intervención-Comparación-Outcome/resultados). Realizamos una evaluación de la calidad de los estudios y un resumen de la evidencia para cada pregunta siguiendo las recomendaciones del grupo de trabajo GRADE («Grading of Recommendations, Assessment, Development and Evaluation»). Nuestros resultados sugieren: 1) En pacientes con esquizofrenia y trastorno por consumo de cannabis, no es posible recomendar un fármaco antipsicótico sobre otro (entre olanzapina, risperidona o haloperidol) para mejorar los síntomas psicóticos, reducir el consumo de cannabis o mejorar las variables pragmáticas

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recommendation). 2) In patients with schizophrenia and cocaine use disorder we recommend haloperidol over olanzapine to reduce craving (moderate recommendation), and olanzapine over haloperidol to improve motor side effects in these patients (moderate recommendation). 3) In patients with schizophrenia and alcohol use disorder while naltrexone is recommended to reduce alcohol use (in terms of reducing alcohol craving) (weak recommendation), there is insufficient evidence to make any recommendation on the use of adjuvant acamprosate (weak recommendation). 4) In patients with schizophrenia and nicotine use disorder, adjuvant bupropion and varenicline are recommended for reducing nicotine use and nicotine abstinence (strong/moderate recommendation). 5) In patients with schizophrenia and polydrug use disorder, second-generation over first-generation antipsychotic drugs and olanzapine over other second-generation antipsychotics are recommended to improve psychotic symptoms (moderate/weak recommendation).

Keywords: Schizophrenia; substance use; comorbid; dual pathology; antipsychotic; cannabis; cocaine; alcohol; nicotine.

(recomendación débil). No se puede recomendar la clozapina para reducir el consumo de cannabis (recomendación débil). 2) En pacientes con esquizofrenia y trastorno por consumo de cocaína, recomendamos haloperidol sobre olanzapina para reducir el craving (recomendación moderada) y olanzapina sobre haloperidol para mejorar los efectos secundarios motores en estos pacientes (recomendación moderada). 3) En pacientes con esquizofrenia y trastorno por consumo de alcohol, mientras que se recomienda naltrexona para reducir el consumo de alcohol (en términos de reducción del craving de alcohol) (recomendación débil), no hay evidencia suficiente para hacer ninguna recomendación sobre el uso de acamprosato como adyuvante (recomendación débil). 4) En pacientes con esquizofrenia y trastorno por consumo de nicotina, se recomiendan bupropión y vareniclina adyuvantes para reducir el consumo y la abstinencia de nicotina (recomendación fuerte/moderada). 5) En pacientes con esquizofrenia y trastorno por policonsumo, se recomiendan antipsicóticos de segunda generación sobre los de primera generación y olanzapina sobre otros antipsicóticos de segunda generación para mejorar los síntomas psicóticos (recomendación moderada/débil).

Palabras clave: Esquizofrenia; consumo de sustancias; comórbido; patología dual; antipsicótico; cannabis; cocaína; alcohol; nicotina.

Diagnosis and treatment of dual disorders, co-occurrence of a substance use disorder (SUD) in patients with mental illness, poses several challenges for mental health professionals and healthcare services (Nielsen, Toftdahl, Nordentoft & Hjorthøj, 2017). Overall, more than 25% of patients on treatment in mental healthcare services experience a SUD and almost 70% of patients on treatment in addiction centres experience a mental illness at some point of their lives (Hunt, Large, Cleary, Lai & Saunders, 2018).

A large number of studies have shown that SUD is more frequent in patients with schizophrenia than in the general population (Addy, Radhakrishnan, Cortes & D'Souza, 2012; Fonseca-Pedrero, Lucas-Molina, Pérez-Albéniz, Inchausti & Ortuño-Sierra, 2020; Matali et al., 2016). The overall prevalence of SUD in people with schizophrenia is approximately 50% (Regier et al., 1990; Thornton et al., 2012). Nicotine, alcohol and cannabis are the most commonly consumed drugs by patients with schizophrenia, followed by amphetamines in Australia and cocaine in USA (García, Gomar, García-Portilla & Bobes, 2019; Green, Noordsy, Brunette & O'Keefe, 2008). In a subanalysis of the CATIE study (Clinical Antipsychotics Trials of Intervention Effectiveness Project Schizophrenia Trial), the percentages of substance use for patients with schizophrenia a comorbid SUD were 87% for alcohol, 44% for cannabis and 36% for cocaine (nicotine consumption was not counted) (Swartz et al., 2008). Multidrug use is very common; for example, cannabis consumers also consume nicotine and/or alcohol (Kavanagh, Mcgrath, Saunders, Dore & Clark, 2002) and it has been demonstrated that alcohol and cannabis increase the effects of nicotine (Mueser & Gingerich, 2013). The use of drugs of abuse in patients with schizophrenia is associated with a higher risk of accidents, violent behaviour, self-harm, poorer prognosis of psychosis, higher rates of hospitalization and use of emergency psychiatric services, increase of depressive symptoms, suicidal behaviour, impulsivity, criminality and unemployment (Large, Mullin, Gupta, Harris & Nielssen, 2014; Heiberg et al., 2018). Also, drugs of abuse can interact with antipsychotic drugs affecting the side effects profile and adherence to medication (Margolese, Malchy, Negrete, Tempier & Gill, 2004).

Patients with schizophrenia and co-occurring SUD are not typically included in traditional treatment algorithms, although differential therapeutic decision trees are available for consumption of drugs of abuse and schizophrenia (Hasan et al., 2012, 2015). Moreover, patients with schizophrenia and comorbid SUD are usually excluded from clinical trials assessing the efficacy of different psychoactive drugs, due to fear of possible interactions between substances of abuse and the experimental drug, as well as because of the high rate of nonadherence and treatment drop-outs of this population (Wobrock & Soyka, 2008).

Although correct diagnosis and management of schizophrenia patients with comorbid SUD would

determine a decrease in morbidity and mortality in these patients, development of efficient therapeutic strategies is still pending (Addy et al., 2012). With the development in the last two decades of integrated management approaches and individualized treatment plans (Crockford & Addington, 2017), the demand for multidisciplinary treatment regimens is increasing, where pharmacological and psychological interventions for substance use and schizophrenia are simultaneously integrated (Murthy, Mahadevan & Chand, 2019). Also, an early combined treatment of both SUD and schizophrenia is recommended in patients with moderate or severe symptoms affecting functionality (Hasan et al., 2012). Regarding the duration of treatment, there is no evidence suggesting the need to modify temporal schedules proposed in the different therapeutic algorithms for each condition separately (Hasan et al., 2015). Cautious selection of pharmacological treatment assessing effectiveness, safety, potential drug interactions and adherence-related problems is crucial in patients with a dual diagnosis.

So far, systematic reviews and meta-analysis have reported outcomes of interventions in patients with co-occurring SUD and schizophrenia spectrum disorders (Baker, Thornton, Hiles, Hides & Lubman, 2012; Crockford & Addington, 2017; Hunt, Siegfried, Morley, Sitharthan & Cleary, 2013; Kishi & Iwata, 2015; Krause et al., 2019; Pearsall, Smith & Geddes, 2019; Temmingh, Williams, Siegfried & Stein, 2018; Wilson & Bhattacharyya, 2016). However, to our knowledge, a clinical practice guideline with clear-cut recommendations on the pharmacological and psychological management of these patients is lacking. Therefore, the aim of the present *Clinical Practice Guideline* is to provide healthcare professionals (psychiatrists, professionals in the field of dual pathology, psychologists and primary care physicians) involved in the care of patients with dual diagnosis with practical recommendations based on scientific evidence to assist in the decision-making process in their clinical practice. The guideline can also be directed to other professionals in the field of SUD and to patients and their families.

Methods

Creation of the working group

The multidisciplinary guideline development working group included specialists in psychiatry, psychology and pharmacology, with large experience in the management of patients with dual diagnosis. Bi-monthly meetings were held between May 2017 and May 2019 so as to independently handling and analysing the evidence collected from the literature.

Formulation of clinical questions

In accordance with evidence-based medicine principles, we used the 'PICO' structure (Patient-Intervention-Comparison-Outcomes) (Guyatt et al., 2011) 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 severe mental illness and a SUD?*". Patients older than 18 years diagnosed with a schizophrenia spectrum disorder and a SUD (including cannabis, cocaine, alcohol and/or nicotine) were the target population of this clinical practice guideline. Opioid use disorder was not included because no systematic reviews with or without meta-analysis or randomized clinical trials were found.

Written study protocol was registered in the PROSPERO database (CRD 42014013996).

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:

((((“Schizophrenia”[Mesh] OR schizophrenia OR “Schizophrenia and Disorders with Psychotic Features”[Mesh])) AND (“Trifluoperazine”[Mesh] OR “Haloperidol”[Mesh] OR “Flupenthixol”[Mesh] OR “Perphenazine”[Mesh] OR “Chlorpromazine”[Mesh] OR “Methotrimeprazine”[Mesh] OR “levomepromazine maleate”[Supplementary Concept] OR first generation antipsychotic*)) 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”).

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

((((“Schizophrenia”[Mesh] OR “Schizophrenia and Disorders with Psychotic Features”[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 (“Alcohol Drinking”[Mesh] OR “Drinking Behavior”[Mesh] OR “alcohol use” OR “alcohol abuse” OR “nicotine use” OR “Marijuana Abuse”[Mesh] OR “Marijuana Smoking”[Mesh] OR “cannabis use” OR “Cocaine-Related Disorders”[Mesh] OR “cocaine use” OR “cocaine abuse”)) AND (“Risperidone”[Mesh] OR risperidone OR “olanzapine” [Supplementary Concept] OR “olanzapine fluoxetine combination” [Supplementary Concept] OR olanzapine OR

"ziprasidone" [Supplementary Concept] OR ziprasidone OR "quetiapine" [Supplementary Concept] OR quetiapine OR "paliperidone palmitate" [Supplementary Concept] OR paliperidone OR "aripiprazole" [Supplementary Concept] OR aripiprazole OR "Asenapine" [Supplementary Concept] OR asenapine OR "zotepine" [Supplementary Concept] OR zotepine OR "sultopride" [Supplementary Concept] OR "sertindole" [Supplementary Concept] OR sertindole OR second generation antipsychotic*).

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

((((("Schizophrenia"[Mesh] OR schizophrenia OR "Schizophrenia and Disorders with Psychotic

Features"[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 ("Alcohol Drinking"[Mesh] OR "Drinking Behavior"[Mesh] OR "alcohol use" OR "alcohol abuse" OR "nicotine use" OR "Marijuana Abuse"[Mesh] OR "Marijuana Smoking"[Mesh] OR "cannabis use" OR "Cocaine-Related Disorders"[Mesh] OR "cocaine use" OR "cocaine abuse")) AND ("Lithium"[Mesh] OR "Lithium Chloride"[Mesh] OR "Lithium Carbonate"[Mesh] OR lithium OR "Valproic Acid"[Mesh] OR valproate OR "lamotrigine 2-Nglucuronide"[Supplementary Concept] OR lamotrigine OR carbamazepine OR oxcarbazepine OR mood stabilizer*).

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

((((("Schizophrenia"[Mesh] OR schizophrenia OR "Schizophrenia and Disorders with Psychotic Features"[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 ("Alcohol Drinking"[Mesh] OR "Drinking Behavior"[Mesh] OR "alcohol use" OR "alcohol abuse" OR "nicotine use" OR "Marijuana Abuse"[Mesh] OR "Marijuana Smoking"[Mesh] OR "cannabis use" OR "Cocaine-Related Disorders"[Mesh] OR "cocaine use" OR "cocaine abuse")) AND (("Disulfiram"[Mesh] OR disulfiram OR "Naltrexone"[Mesh] OR naltrexone OR "acamprosate" [Supplementary Concept] OR acamprosate OR "topiramate" [Supplementary Concept]

OR topiramate OR "Bupropion"[Mesh] OR bupropion OR nicotine replacement therapy OR "varenicline" [Supplementary Concept] OR varenicline OR "varenicline N-carbamoylglucuronide" [Supplementary Concept]) AND ((Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Review[ptyp] OR systematic[sb]) AND (adult[MeSH:noexp] OR aged[MeSH])))

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

Inclusion criteria for published studies followed the PICO structure (Guyatt et al., 2011): (a) study design: metanalyses, Cochrane review, systematic review, randomized double or single blind clinical trial; (b) population: subjects with a schizophrenia related disorder and a cannabis, cocaine, alcohol or nicotine use; (c) treated with first/second generation antipsychotics / atypical antipsychotics / naltrexone / disulfiram / acamprosate / bupropion / varenicline; (d) outcomes related to the improvement of the symptoms of schizophrenia, and/or outcomes related to the substance use (decreased use/abstinence), and/or pragmatic variables, such as side effects.

Evaluation of the quality of the evidence and formulation of recommendations

Due to a paucity of pharmacological guidelines for this treatment group, no consistent comparator or 'gold standard' was available. 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) (Schünemann et al., 2008).

The GRADE system assigns separate grades for the quality of evidence and for the strength of recommendations (Mustafa et al., 2013). The quality of the evidence is defined as the extent to which 'one can be confident that an estimate of effect or association can be correct'. This is based on the likelihood that further targeted research would not change confidence in the estimate. The strength of recommendation indicates 'the extent of the grader's confidence that adherence to the recommendation will do more good than harm' (Gopalakrishna, Langendam, Scholten, Bossuyt & Leeflang, 2013). Controversial recommendations or those lacking evidence were resolved by consensus of the working group.

Given the wide variation in the methodology of studies, outcomes reported and the limited numbers of original research reports that focused on each antipsychotic, we decided against a quantitative analysis of the data in the form of a metaanalysis and instead limited this report to a qualitative synthesis of all available evidence. 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. For clarity purposes, recommendations are here divided according to substance.

External review and evaluation

The guideline was reviewed externally by a multidisciplinary and independent group of experts selected for their knowledge of the methodology of preparing clinical practice guidelines, the pathology

covered and the scope of application. The final version was revised and approved by the working group. The evidence was evaluated using the AGREE II (Appraisal of Guidelines for Research and Evaluation) instrument (Makarski & Brouwers, 2014) (www.agreecollaboration.org), which contains 23 items grouped into 6 domains: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability and editorial independence. The items are rated from 1 (strongly disagree) to 7 (strongly agree).

Results

Study selection

Figure 1 outlines PRISMA flowchart leading to the study selection. The search yielded 650 studies. 36 studies were deemed eligible for further assessment. The final selection included 24 studies. Open-label, cohort or case-control studies, cross-sectional and observational studies, case reports, letters, posters and abstracts of presentations to specialist meetings and conferences were not included in the Guideline. Only articles published in English were included. Data were extracted from the included studies using a predefined template and the quality of each study was assessed using standard criteria. A summarized report of these studies can be found in Tables 1 to 5.

Patients with schizophrenia and cannabis use disorder

Details about included studies are shown in Table 1.

PICO question 1. *Is the administration of antipsychotics effective to improve schizophrenia symptoms, to reduce cannabis use or to improve pragmatic and functionality variables in patients with schizophrenia and cannabis use?*

Three randomized controlled trials (RCTs) assessed the effect of antipsychotics for improving schizophrenia

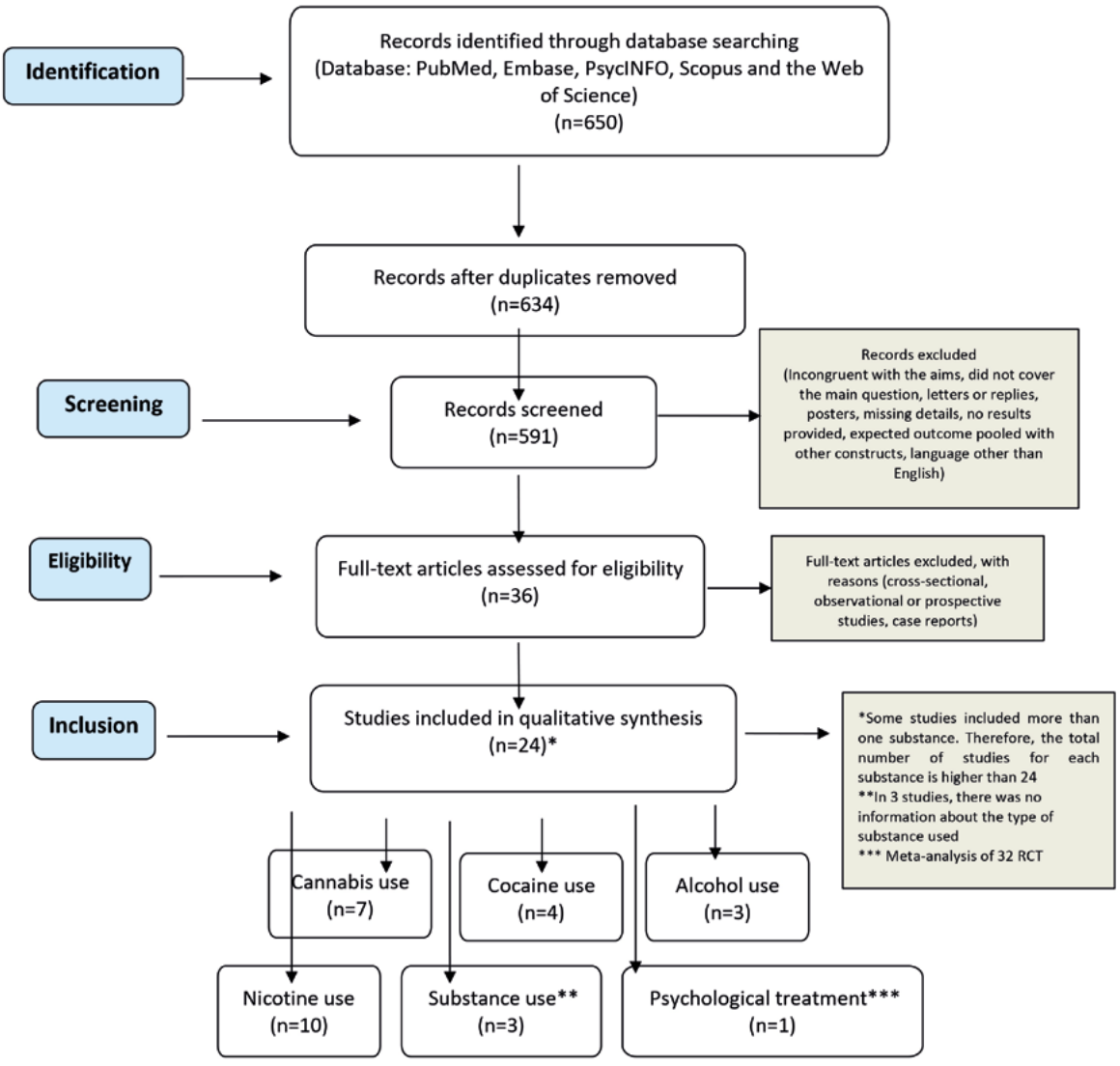

Figure 1. Flow chart of study selection process.

Table 1. *Studies on schizophrenia and cannabis use disorder.*

Author	Design	Intervention	Patients	Exp(n)/ Comp(n)	Follow-up	Outcome variables (clinical, use & pragmatics)	Limitations/ Biases
Akerele 2007	RCT, Double-Blind, Outpatient	1. OLZ 5-20mg/d 2. RIS 3-9mg/d	Schizophrenia or SAD + SUD (cocaine, cannabis). SCID.	10/13	14 weeks	- HAM-D. PANSS positive, PANSS negative. - Urine test, Craving. - Side effects: AIMS, SAS.	Small sample. Mostly men (89%). Short follow-up. Possible selective publication bias. Funded by Lilly. Follow-up dropouts: 57.1% completed study (OLZ n=6; RIS n=10).
Berk 1999	RCT, Double-Blind, Inpatient	1. OLZ 10mg/d 2. HAL 10mg/d	Psychosis + SUD (cannabis) MINI.	15/15	4 weeks	- BPRS, CGI-S, CGI-I. - Functioning: GAF. - Side effects: SAS, BARS.	Small sample. Mostly men (93.3%). Short follow-up. 1-day wash period. Diagnosis of cannabis-induced psychosis is controversial.
Brunette 2011	RCT, Double-Blind, Bi-centre, Outpatient	1. Change to CLZ 400-550 mg/d 2. Usual antipsychotic treatment	Schizophrenia or SAD + SUD (cannabis). DSM-IV.	15/16	12 weeks	- BPRS, CGI, SANS. - Urine test, units/week consumed, Substance abuse scale. - SAS, BARS, AIMS, adherence to treatment.	Small sample. Short follow-up. 1-day wash period. Flexible dose of CLZ in the first 4 weeks along with initial antipsychotic switch. Possible selective publication bias.
Green 2004	RCT, Double-Blind	1. OLZ 5-20mg/d 2. HAL 2-20mg/d	First schizophrenic episode (Schizophrenia, SAD, Schizophreniform) + SUD (cannabis, alcohol). DSM-IV, SCID.	131/131	12 weeks	- PANSS, CGI.	Exclusion criteria: substance dependence in previous month. *Lilly Research Laboratories* participated indirectly/ directly in the study.
Nimwegen 2008	RCT, Double-Blind, Multicentre, Inpatient + outpatient	1. OLZ 5-20mg/d 2. RIS 1.25-5mg/d	Schizophrenia, SAD, Schizophreniform + SUD (cannabis). DSM-IV-TR, SCID.	63/65	6 weeks	- OCDUS, DDQ, Cannabis self-report (meetings/ week). - SWN.	Small sample. Short follow-up period. Only 41/128 patients were using cannabis at start of study. 70% of the patients completed study. *Eli-Lilly* participated indirectly/ directly in the study.
Sevy 2011	ERCT, Double-Blind, Inpatient	1. OLZ 2.5-20mg/d 2. RIS 1- 6 mg/d	First schizophrenic episode, SAD, Schizophreniform + SUD (cannabis).	28/21	16 weeks	- Treatment response, positive symptoms, CGI. - Urine Test, Substance Use Questionnaire. - Weight gain, SAS, BARS.	Small sample. 75% of the patients in the OLZ group and 76% of the RIS group completed the study. Possible selective publication bias.
Siris 1992	RCT, Double-Blind. Inpatient + outpatient	1. IMI 50-200mg/d + usual treatment 2. Placebo + usual treatment	Schizophrenia or SAD + SUD (cannabis) RDC.	14/7	9 weeks	- CGI-I, CGI-S, SADS.	Small sample. Short follow-up. The most usual treatment was fluphenazine decanoate weekly.

Note. AIMS: Abnormal Involuntary Movement Scale; BARS: Barnes Akathisia Rating Scale; BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression; CLZ: Clozapine; DDQ: Drug Desire Questionnaire; GAF: Global Assessment Functioning; HAL: Haloperidol; HAM-D: Hamilton Depression Rating Scale; IMI: Imipramine; MINI: Mini International Neuropsychiatric Interview; OCDUS: Obsessive Compulsive Drug Use Scale; OLZ: Olanzapine; PANSS: Positive and Negative Syndrome Scale; RCT: Randomized clinical trial; RIS: Risperidone; SADS: Schedule for Affective Disorders and Schizophrenia; SANS: Scale for the Assessment of Negative Symptoms; SAS: Simpson Angus Scale; SCID: Structured Clinical Interview for DSM-IV; SAD: Schizoaffective Disorder; SWN: Subjective Well-being under Neuroleptics Scale. SUD: Substance Use Disorder.

symptoms, olanzapine *vs* risperidone in one (Sevy et al., 2011) and olanzapine *vs* haloperidol in two RCTs (Berk, Brook & Trandafir, 1999; Green et al., 2004). In the comparison of olanzapine and risperidone in hospitalized patients with schizophrenia or schizoaffective disorder, neither differences in improvement of positive symptoms measured with the SADS-C scale nor in the percentage of patients with clinical response were found (very low quality of evidence) (Sevy et al., 2011). In the two RCTs that compared olanzapine and haloperidol in hospitalized patients with a first psychotic episode, schizophrenia or schizoaffective disorder, differences in the mean change of PANSS at week 12 or in the percentage of patients with clinical response were not found (very low quality

of evidence) (Green et al., 2004). Similar findings in the mean change of BPRS, CGI-S scores or CGI-I scores were observed (low quality of evidence) (Berk et al., 1999).

In RCTs performed in patients with schizophrenia or schizoaffective disorder in the ambulatory and in-patient settings, the comparison of olanzapine and risperidone to reduce cannabis use did not show significant differences using different measures. These included cannabis urine test (very low quality of evidence) (Akerele & Levin, 2007); three craving questionnaire (moderate quality of evidence) (Van Nimwegen et al., 2008); marijuana craving questionnaire (very low quality of evidence) (Akerele & Levin, 2007); self-reports (moderate quality of evidence) (Van Nimwegen et al., 2008); and substance use questionnaire (very low quality of evidence) (Sevy et al., 2011).

Regarding pragmatic variables, olanzapine and risperidone did not show significant differences in the SAS scale of motor side effects (very low quality of evidence) (Sevy et al., 2011); body mass index (BMI) (quality of evidence very low) (Sevy et al., 2011); and SWN scale (moderate quality of evidence) (Van Nimwegen et al., 2008).

Recommendations

- It is not possible to recommend one antipsychotic drug over another for improving psychotic symptoms, reduction of cannabis use, or improvement of pragmatic variables (weak recommendation).

PICO question 2. *Is the administration of adjunctive antidepressants effective to improve schizophrenia symptoms, to reduce cannabis use or to improve pragmatic and functionality variables in patients with schizophrenia and cannabis use?*

One RCT evaluated adjunctive imipramine *vs* placebo during 9 weeks in patients with schizophrenia or schizoaffective disorder treated with fluphenazine (Siris, Bermanzohn, Mason, Rifkin & Alvir, 1992). Treatment with adjunctive imipramine was associated with a mean decrease of 0.54 and 0.93 points in the CGI-S and CGI-I scales, respectively (very low quality of evidence). In the SADS scale, imipramine-treated patients showed mean decreases of 2.4, 6.9 and 7.1 points in the items of "mood", "other associated symptoms" and "endogenous symptoms", respectively, and a mean increase of 0.26 points in the "hallucinations" item as compared with placebo, whereas differences in "delirious ideation" were not observed (very low quality of evidence). Also, patients treated with imipramine showed a significant decrease of the mean score in the HDRS scale (very low quality of evidence).

Recommendations

- In patients with schizophrenia and co-occurring cannabis use disorder, adjunctive imipramine to current antipsychotic treatment for improving affective symptoms is recommended (weak recommendation).

PICO question 3. *Is the administration of clozapine effective to improve schizophrenia symptoms, to reduce cannabis use or to improve pragmatic and functionality variables in patients with schizophrenia and cannabis use?*

Despite the evidence on the efficacy of clozapine in patients with schizophrenia and substance use (Arranz, Garriga, García-Rizo & San, 2018; Drake, Xie, McHugo & Green, 2000; Green, Zimmet, Strous & Schildkraut, 1999), only one RCT has assessed the impact of clozapine compared with treatment as usual on cannabis use in outpatients with schizophrenia and co-occurring cannabis use disorder (Brunette et al., 2011). In this study with a weekly follow-up for 12 weeks using self-report measures, clozapine was not associated with a significant decrease of cannabis consumption (very low quality of evidence).

Recommendations

- In patients with schizophrenia and co-occurring cannabis use disorder, the use of clozapine to reduce cannabis use cannot be recommended (weak recommendation).

Patients with schizophrenia and cocaine use disorder

Details about included studies are shown in Table 2.

PICO question 4. *Is the administration of antipsychotics effective to improve schizophrenia symptoms, to reduce cocaine use or to improve pragmatic and functionality variables in patients with schizophrenia and cocaine use?*

Two RCTs compared olanzapine *vs* haloperidol for improving psychotic symptoms in ambulatory schizophrenia or schizoaffective disorder patients (Sayers et al., 2005; Smelson et al., 2006). Significant differences at 26 weeks of treatment using a 30% improvement in the BPRS as well as SAPS or SANS scales were not found. Differences were not found either in PANSS positive symptoms, PANSS negative symptoms and PANSS general symptoms subscale (low quality of evidence). One RCT compared olanzapine *vs* risperidone (Akerele & Levin, 2007) and between-group differences in positive and negative PANSS subscales were not observed .

For the outcome of cocaine use, olanzapine *vs.* haloperidol showed similar results in two RCTs (Sayers et al., 2005; Smelson et al., 2006) assessing cocaine use by drug positive urine testing (low quality of evidence). Differences between the two drugs using self-administered craving scales were not found in the items of VCCQ "sick after cue", "mood after cue" and "craving intensity after cue" (Smelson et al., 2006). However, olanzapine was associated with greater craving for cocaine in the "energy after cue" item of VCCQ (Smelson et al., 2006) and craving VAS score (Sayers et al., 2005) (low quality of evidence). In a RCT that compared olanzapine *vs* risperidone, differences between

Table 2. *Studies on schizophrenia and cocaine use disorder.*

Author	Design	Intervention	Patients	Exp(n)/ Comp(n)	Follow-up	Outcome variables (clinical, use & pragmatics)	Limitations/ Biases
Akerele 2007	RCT, Double-Blind, Outpatient	1. OLZ 5-20mg/d 2. RIS 3-9mg/d	Schizophrenia or SAD + SUD (cocaine, cannabis). SCID.	12/123	14 weeks	- HAM-D. PANSS positive, PANSS negative. - Urine test, Craving. - Side effects: AIMS, SAS.	Small sample. Short follow-up. Mostly men (89%). Possible selective publication bias. No data collected on use of other substances. Funded by *Eli Lilly*. Follow-up dropouts: 57.1% completed the study (OLZ n=6; RIS n=10).
Perry 2004	RCT, Double-Blind, Inpatient	1. Mazindol add-on + usual antipsychotic 2. Placebo + usual antipsychotic	Schizophrenia or SAD + SUD (cocaine). SCID.	11/13	6 weeks	- PANSS positive, PANSS negative. - Urine Test, Visual Analogue Craving Scale, Quantitative Cocaine Inventory. - Side effects: AIMS, modified Webster scale.	Small sample. Short follow-up. Possible selective publication bias. Common antipsychotics used: 9 patients received HAL, 5 fluphenazine, 4 PRZ decanoate, 1 HAL decanoate, 1 trifluoperazine,1 CLZ y 1 RIS.
Sayers 2005	RCT, Double-Blind, Outpatient	1. OLZ 10mg/d 2. HAL 10mg/d	Schizophrenia or SAD + SUD (cannabis). DSM-IV.	12/12	36 weeks	- BPRS, SANS, SAPS. - Urine test. Visual analogue scale. - Side effects: AIMS, BARS, SAS.	Of the 170 patients initially identified, only 24 were included (small sample). High drop-out rate.
Smelson 2006	RCT, Double-Blind	1. OLZ 10mg/d 2. HAL 10mg/d Dosage from 5 to maximum 20mg/d	Schizophrenia or SAD + SUD (cannabis) RDC.	16/15	6 weeks	- General PANSS, positive PANSS, negative PANSS. - Urine test. VCCQ.	Schizophrenia + SUD (cocaine). DSM-IV.

Note. AIMS: Abnormal Involuntary Movement Scale; BARS: Barnes Akathisia Rating Scale; BPRS: Brief Psychiatric Rating Scale; CLZ: Clozapine; HAL: Haloperidol; HAM-D: Hamilton Depression Rating Scale; OLZ: Olanzapine; PANSS: Positive and Negative Syndrome Scale; RCT: Randomized clinical trial; RIS: Risperidone; SAD: Schizoaffective Disorder; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; SAS: Simpson Angus Scale; SCID: Structured Clinical Interview for DSM-IV; SUD: Substance Use Disorder; VCCQ: Voris Cocaine Craving Questionnaire.

these two drugs to reduce cocaine consumption were not observed (Akerele & Levin, 2007).

In relation to pragmatic variables, olanzapine showed significantly less motor side effects measured with the AIMS scale than haloperidol (Sayers et al., 2005) (low quality of evidence).

Recommendations

- The administration of haloperidol over olanzapine to reduce craving in patients with schizophrenia and comorbid cocaine use disorder is recommended (moderate recommendation).
- The administration of olanzapine over haloperidol is recommended to improve motor side effects in patients with schizophrenia and comorbid cocaine use disorder (moderate recommendation).

PICO question 5. *Is the administration of adjuvant dopamine agonists effective to improve schizophrenia symptoms, to reduce cocaine use or to improve pragmatic and functionality variables in patients with schizophrenia and cocaine use?*

One RCT evaluated the efficacy of adjuvant treatment with mazindol *vs* placebo during 6 weeks in 24 hospitalized patients with schizophrenia or schizoaffective disorder (Perry et al., 2005). For all outcomes, including positive and negative symptoms of PANSS, cocaine consumption and intensity of craving measured with self-administered QCI and VAS, respectively, and improvement of extrapyramidal symptoms measured with AIMS or the Modified Webster scale differences between the groups of mazindol and placebo were not observed (moderate quality of evidence).

Recommendations

- The use of dopamine agonists to improve psychotic symptoms, reduce cocaine use or cocaine craving or improve pragmatic variables in schizophrenia patients with comorbid cocaine use disorder cannot be recommended (weak recommendation).

Patients with schizophrenia and alcohol use disorder

Details about included studies are shown in Table 3

PICO question 6. *Is the administration of antipsychotics effective to improve schizophrenia symptoms, to reduce alcohol use or to improve pragmatic and functionality variables in patients with schizophrenia and alcohol use?*

Only one RCT with 262 patients with first-episode schizophrenia-related psychosis and co-occurring alcohol

use disorder was published to answer this question (Green et al., 2004). A comparison of olanzapine *vs* haloperidol showed no differences after 12 weeks of treatment in improvement of psychosis measured with changes of PANSS or response to treatment (PANSS and CGI) (very low quality of evidence).

Recommendations

- There is insufficient evidence to make any recommendation on the use of antipsychotics to improve psychotic symptoms, to reduce alcohol use and/or alcohol craving or to improve pragmatic variables in schizophrenia patients with comorbid alcohol use disorder (weak recommendation).

PICO question 7. *Is the administration of adjuvant opioid antagonists (naltrexone) effective to improve schizophrenia symptoms, to reduce alcohol use or to improve pragmatic and functionality variables in patients with schizophrenia and alcohol use?*

One RCT assessed the use of adjuvant naltrexone *vs* placebo in 31 outpatients with schizophrenia or schizoaffective disorder (Petrakis et al., 2004). At 12 weeks of treatment, no differences in any subscales of PANSS were found nor in alcohol use (reduction of number of days of alcohol consumption, heavy drinking days and number of drinks per day of alcohol use) (very low quality of evidence). Assessment of alcohol craving with the TCQ instrument, patients in the naltrexone group showed a mean reduction of 2.17 points (less craving) (very low quality of evidence).

Recommendations

- In patients with schizophrenia and co-occurring alcohol use disorder, naltrexone is recommended to reduce alcohol use (in terms of reducing alcohol craving) (weak recommendation).

PICO question 8. *Is the administration of adjuvant acamprosate effective to improve schizophrenia symptoms, to reduce alcohol use or to improve pragmatic and functionality variables in patients with schizophrenia and alcohol use?*

One RCT evaluated the use of acamprosate *vs* placebo in 23 outpatients with schizophrenia spectrum disorders and alcohol dependence (Ralevski et al., 2011). After 12 weeks of treatment, improvement in cognition function using a battery of neuropsychological tests was not found. In the Hopkins 30 min delay questionnaire, acamprosate scored significantly better than placebo but in the Gordon Box distractibility and in the Wisconsin % perseverative errors

Table 3. *Studies on schizophrenia and alcohol use disorder.*

Author	Design	Intervention	Patients	Exp(n)/ Comp(n)	Follow-up	Outcome variables (clinical, use & pragmatics)	Limitations/ Biases
Green 2004	ECA, Double-blind	1. OLZ 5-20mg/d 2. HAL 2-20mg/d	First pscychotic episode (Schizophrenia, SAD, Schizophreniform) + SUD (cannabis, alcohol). DSM-IV, SCID.	131/131	12 weeks	- PANSS, CGI. Treatment response.	Exclusion criteria: substance dependence in the previous month. *Lilly Research Laboratories* participated indirectly/directly in the study.
Petrakis 2004	ECA, Double-blind, Outpatient	1. NTX 50mg/d + usual treatment 2. Placebo + usual treatment	Schizophrenia/ SAD + SUD (alcohol). SCID.	16/15	12 weeks	- PANSS general, PANSS positive, PANSS negative. - Days of use. Drinks per day of use. Days of abusive drinking. TCQ. - Side effects: AIMS, HSCL. Adherence.	Small sample. Short follow-up. Exclusively men (100%). Participants also underwent cognitive behavioural treatment for relapse prevention. Patients financially rewarded ($160). Four patients were hospitalized during the study: two from the NTX group and one from the placebo for psychotic decompensation.
Ralevski 2011	ECA, Double-blind, Outpatient	1. ACAM 1998mg/d + usual treatment 2. Placebo + usual treatment	Schizophrenia, TEA, Schizophreniform + SUD (alcohol). DSM-IV, SCID.	12/11	12 weeks	- PANSS, Hopkins Verbal Learning Test, Gordon Diagnostic System, WCST. - Number of days of use. Binge drinking days. Drinks per day of drinking. Days of abstinence. OCDUS. - Adhesion.	Small sample. Short follow-up. Mostly men (82.6%). Possible selective publication bias.

Note. ACAM: Acamprosate; AIMS: Abnormal Involuntary Movement Scale; HAL: Haloperidol; HSCL: Hopkins Symptoms checklist; NTX: Naltrexone; OCDUS: Obsessive Compulsive Drug Use Scale; OLZ: Olanzapine; PANSS: Positive and Negative Syndrome Scale; RCT: Randomized clinical trial; SAD: Schizoaffective Disorder; SCID: Structured Clinical Interview for DSM-IV; SUD: Substance Use Disorder; TCQ: Tiffany Craving Questionnaire; WCST: Wisconsin Card Sorting Test.

tests, the group of acamprosate scored significantly worse as compared to placebo (very low quality of evidence). In the analysis of the outcome of alcohol consumption, adjuvant acamprosate was not superior to placebo in number of days of alcohol consumption, heavy drinking days, number of drinks per day of alcohol use, consecutive days of abstinence and alcohol craving (very low or low quality of evidence).

Recommendations

- There is insufficient evidence to make any recommendation of the use of adjuvant acamprosate to improve psychotic symptoms, to reduce alcohol use or to improve pragmatic variables in schizophrenia patients with comorbid alcohol use disorder (weak recommendation).

Patients with schizophrenia and nicotine use disorder

Details about included studies are shown in Table 4.

PICO question 9. *Is the administration of adjuvant bupropion effective to improve schizophrenia symptoms, to reduce nicotine use or to improve pragmatic and functionality variables in patients with schizophrenia and nicotine use?*

Three RCTs evaluated the effect of 12-week treatment with adjuvant bupropion *vs* placebo in outpatients with schizophrenia (Evins, Mays, Rigotti, Tisdale, Cather & Goff, 2001); Evins et al., 2007; George et al., 2002). Regarding improvement of schizophrenia symptoms assessed with PANSS positive and PANSS negative symptoms subscales and the Ham-D questionnaire, differences between bupropion and placebo were not found (low quality of evidence).

Five RCTs evaluated the outcome of nicotine abstinence at 6 months of follow-up for the comparisons of bupropion vs placebo and bupropion and transdermal nicotine patch *vs* placebo and transdermal nicotine patch (Evins et al., 2001, 2005, 2007; George et al., 2002, 2008). No differences were found in the individual studies, but analysis of data of the five RCTs showed almost three-fold higher abstinence rates in the bupropion groups. In six RCTs in which the outcome was nicotine abstinence at the end of the active treatment period (Evins et al., 2001, 2005, 2007; George et al., 2002, 2008; Weiner et al., 2012), bupropion was significantly more effective than placebo but this difference was not observed in the comparison of and bupropion and transdermal nicotine patch vs placebo and transdermal nicotine patch (very low quality of the evidence). Analysis of pooled data of the seven RCTs showed significant differences in favour of bupropion.

When smoking abstinence was determined by expired breath CO level at 6 months of follow-up (Evins et al., 2001, 2005, 2007) exhaled CO levels as compared with baseline decreased significantly in the bupropion group (moderate quality of evidence). When expired CO levels were determined at the end of the period of active treatment (Evins et al., 2001, 2005, 2007; Weiner et al., 2012), differences in favour of bupropion were also observed (moderate quality of evidence). In three RCTs that evaluated self-reported cigarette smoking abstinence at the end of a 12-week treatment period (Evins et al., 2001, 2005, 2007) significant differences in the bupropion group *vs* placebo were found (moderate quality of evidence). In relation to reduction in the number of cigarettes/day at the end of 8-week treatment in hospitalized patients (Akbarpour et al., 2010) or 14-week treatment in outpatients (Bloch et al., 2010), differences between bupropion and placebo were not found (low quality of evidence).

Recommendations

- Evidence is insufficient to make a recommendation on the use of bupropion to reduce psychotic symptoms (weak recommendation).
- Adjuvant bupropion is recommended for reducing nicotine use and nicotine abstinence in patients with schizophrenia and co-occurring nicotine dependence (strong/moderate recommendation).

PICO question 10. *Is the administration of adjuvant varenicline effective to improve schizophrenia symptoms, to reduce nicotine use or to improve pragmatic and functionality variables in patients with schizophrenia and nicotine use?*

Two RCTs evaluated the use of adjuvant varenicline *vs* placebo after 12 weeks of treatment in outpatients with schizophrenia using exhaled CO levels and self-reported cigarette smoking abstinence (Weiner et al., 2011; Williams et al., 2012). Varenicline was significantly more effective than placebo to achieve abstinence at 12 weeks (moderate quality of evidence) but at 6 months of follow-up differences disappeared.

Recommendations

- There is no evidence of the efficacy of varenicline to reduce psychotic symptoms.
- Adjuvant varenicline is recommended to achieve nicotine abstinence in patients with schizophrenia and co-occurring nicotine dependence (strong/moderate recommendation).

Patients with schizophrenia and poly substance use disorder

Details about included studies are shown in Table 5.

PICO question 11. *Is the administration of antipsychotics effective to improve schizophrenia symptoms, to reduce general drug use or to improve pragmatic and functionality variables in patients with schizophrenia and polysubstance use?*

Three RCTs compared olanzapine vs risperidone (Akerele & Levin, 2007; Green et al., 2004) and five arms of antipsychotic therapy (olanzapine *vs* perphenazine *vs* risperidone *vs* quetiapine *vs* ziprasidone) (Swartz et al., 2008) in hospitalized and outpatients with schizophrenia.

Table 4. *Studies on schizophrenia and nicotine use disorder.*

BUPROPION vs PLACEBO

Author	Design	Intervention	Patients	Follow-up	Concomitant treatments	Outcome variables (clinical, use & pragmatics)	Limitations/ Biases
Akbarpour 2010	RCT, Inpatient	Bupropion 300 mg/d Placebo	32 patients Men only	8 weeks	No other intervention carried out	-Abstinence: not determined. -Decrease in use: number of cigarettes. o biological confirmation. -Medical state: MMSE.	Only men included. No information provided on the pharmacological treatment of patients. No biological confirmation of reduction in use.
Bloch 2010	RCT, Outpatient	Bupropion 300 mg/d Placebo	61 patients 46 men	14 weeks	Both groups received 15 CBT sessions	-Abstinence: not determined. -Decrease in use: number of cigarettes, Fagerström test in weeks 7 and 14. -Medical state: PANSS and BPRS.	No information is provided on the pharmacological treatment of patients.
Evins 2001	RCT, Outpatient	Bupropion 150 mg/d Placebo	19 patients. Stable antipsychotic dose 8 patients with CLZ	12 weeks active treatment 6 months follow-up	Both groups received 9 1-hour CBT sessions	-Abstinence at week 12 and 24 (self-reports verified by CO levels expired air ‹9 ppm of serum cotinine ‹14 ng/ml). -Reduction in number of cigarettes, determined by serum cotinine, a 50% reduction in the number of cigarettes and a 30% decrease in expired CO. -Medical state: BPRS, SANS and HAM-D. -Extrapyramidal symptoms: SAS and AIMS.	One patient withdrew from the study before starting treatment.
Evins 2005	RCT, Outpatient	Bupropion 300 mg/d Placebo	57 patients 39 men 12 with CLZ	12 weeks active treatment 6 months follow-up	Both groups received 12 1-hour CBT sessions	-Abstinence at 7 days, and at 4.12 and 24 weeks (self-reports verified by CO levels expired air ‹9 ppm. -Reduction of number of cigarettes through expired CO and self-reports. -Medical state: PANSS, SANS, HAM-D and HAM-A. -Parkinsonism: SAS and AIMS.	More patients randomized with clozapine (11/28) In the placebo group than in the bupropion group (1/25).
Evins 2007	RCT, Outpatient	Bupropion 300 mg/d Placebo	51 pacientes 16 with CLZ	12 weeks active treatment 6 months follow-up	Both groups received: (1) 12 1-hour CBT sessions; (2) Transdermal patch at decreasing doses (3) nicotine gum if needed	-Abstinence at week 8, 12, 24 and 52 by self-report and verified by expired CO ‹8 ppm. -Reduction in number of cigarettes in weeks 12 and 24. -Medical state: PANSS, SANS, HAM-D and STAI. - Parkinsonism: SAS and AIMS.	5/25 in the bupropion group and 8/26 in the control group dropped out of the study. Unclear distribution by sex.
George 2002	RCT, Outpatient	Bupropion 300 mg/d Placebo	32 patients 18 men	10 weeks active treatment 6 months follow-up	Both groups received 10 sessions of motivational group therapy, psychoeducation and relapse prevention	-Abstinence in week 10 and in month 6 (expired CO ‹10ppm). - Decrease in ise (self-reports and expired CO). -Medical state: PANSS and BDI. -Parkinsonism: Webster Scale and AIMS.	None evident.
George 2008	RCT, Outpatient	Bupropion 300 mg/d Placebo	59 patients 35 men 9 with CLZ	10 weeks active treatment 6 months follow-up	Both groups received 10 sessions of group behavioural therapy and transdermal patch	-Abstinence between days 43 and 70 and at 6 m (self-reports and CO expired ‹10ppm). -The reduction in consumption was not an outcome variable. -Medical state: PANSS, BDI and HAM-D.	None evident.
Weiner 2012	RCT, Outpatient	Bupropion 300 mg/d Placebo	46 patients 37 men 13 with CLZ 28 with atypical AP	12 weeks	Both groups received 9 group therapy sessions	-Abstinence: expired CO ‹10 ppm in 4 visits. -Reduce used: expired CO, Fagerström test. and urine cotinine. -Medical state: BPRS and SANS. -Motor side effects: SAS. -Neuropsychological variables.	None evident.

VARENICLINA vs PLACEBO

Author	Design	Intervention	Patients	Follow-up	Concomitant treatments	Outcome variables (clinical, use & pragmatics)	Limitations/ Biases
Williams 2012	RCT, Outpatient	Varenicline 1 mg/d Placebo	128 patients 98 men 109 with atypical AP	12 weeks	Both groups received psychological support	-Abstinence at weeks 4, 12 and 24 (self-reports verified by CO levels expired air <10 ppm). -Decrease in use: 50% decrease in the number of cigarettes. -Medical state: PANSS, SAS, CSSRS, CGI. -Extrapyramidal symptoms: SAS and AIMS.	Ratio 2:1 (varenicline: placebo).
Weiner 2011	RCT, Outpatient	Varenicline 1 mg/d Placebo	9 patients All with atypical AP	12 weeks	Individual psychological therapy	-Abstinence: CO expired <10 ppm in week 12. -Reduced use: expired CO. -Medical state: BPRS and CDS.	Patient demographics not included.

Note. AIMS: Abnormal Involuntary Movement Scale; AP: Antipsychotics; BDI: Beck Depression Inventory; BPRS: Brief Psychiatric Rating Scale; CBT: Cognitive-behavioural therapy; CGI: Clinical Global Impression; CLZ: Clozapine; CO: Carbon monoxide; CDS: Calgary Depression Scale; CSSRS: Columbia Suicide Severity Rating Scale; GAF: Global Assessment Functioning; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; MMSE: Mini-Mental State Examination; PANSS: Positive and Negative Syndrome Scale; RCT: Randomized clinical trial; SANS: Scale for the Assessment of Negative Symptoms; SAS: Simpson Angus Scale; State Trait Anxiety Inventory (STAI).

Table 5. *Studies on schizophrenia and various substance use disorders.*

Author	Design	Intervention	Patients	Exp(n)/ Comp(n)	Follow-up	Outcome variables (clinical, use & pragmatics)	Limitations/ Biases
Akerele 2007	RCT, Double blind, Outpatient	1. OLZ 5-20mg/d 2. RIS 3-9mg/d	Schizophrenia o Tr Schizoaffective + SUD (cocaine, cannabis). SCID.	14/14	14 weeks	- HAM-D. PANSS positive, PANSS negative. - Urine Test, Craving. - Side effects: AIMS, SAS. Compliance.	Small sample. Short follow-up. Mostly men (89%). Possible selective publication bias. No data on use of other substances collected. Funded by *Eli Lilly*. Follow-up dropouts: 57.1% completed the study (OLZ n=6; RIS n=10).
Green 2004	RCT, Double blind	1. OLZ 5-20mg/d 2. HAL 2-20mg/d	Fist psychotic episode (Schizophrenia, SAD, Schizophreniform) + SUD (cannabis, alcohol). DSM-IV, SCID.	131/131	12 weeks	- PANSS, CGI. Treatment response.	Exclusion criteria: substance dependence in the last month. *Lilly Research Laboratories* participated indirectly/directly in the study.
Swartz 2008	RCT, Double blind, Multicentre Inpatient + outpatient	1. OLZ 7.5-30mg/d 2. PRZ 8-32mg/d 3. QUE 200-800mg/d 4. RIS 1.5-6mg/d 5. ZPR 40-160mg/d	Schizophrenia + SUD or non-SUD SCID.	(N= 1432). OLZ 142/ PRZ 124/ QUE 137/ RIS 157/ ZPS 83	18 months	- CGI-S, PANSS. - Drop-out rate. Inpatient.	Medication dosage was flexible and based on clinical judgment. Adherence was monitored by counting the number of pills. Possible selection bias: "patients with concurrent tardive dyskinesia (n = 231) entered a randomization scheme that prevented them from entering PER treatment."

Note. AIMS: Abnormal Involuntary Movement Scale; CGI: Clinical Global Impression; HAL: Haloperidol; HAM-D: Hamilton Depression Rating Scale; OLZ: Olanzapine; PANSS: Positive and Negative Syndrome Scale; PRZ: Perphenazine; QUE: Quetiapine; RCT: Randomized clinical trial; RIS: Risperidone; SAD: Schizoaffective Disorder; SAS: Simpson Angus Scale; SCID: Structured Clinical Interview for DSM-IV; SUD: Substance Use Disorder; ZPR: Ziprasidone.

In the outcome of improvement of psychotic symptoms, olanzapine was significantly more effective than risperidone at 18 months in all comparisons using CGI-S, PANSS total score, PANSS positive subscale, PANSS negative subscale and PANSS general (very low quality of evidence). In all these scales, olanzapine was more effective than first-generation antipsychotics (haloperidol, perphenazine), and second-generation antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone) more effective than first-generation antipsychotic drugs (haloperidol, perphenazine) (quality of evidence very low). In the evaluation of improvement of depressive symptoms with the Ham-D scale in 28 outpatients treated for 14 weeks, there were no differences between olanzapine and risperidone (low quality of evidence) (Akerele & Levin, 2007).

Regarding pragmatic variables for the outcomes of side effects, treatment adherence, drop-out from treatment and hospital re-admission, significant differences between

olanzapine and risperidone were not found. In the outcome of drop-out from treatment for any reason, similar results were obtained in the comparisons of olanzapine vs perphenazine and second-generation antipsychotics vs perphenazine (very low quality of evidence).

Recommendations

- In patients with schizophrenia and polydrug use, the use of second-generation over first-generation antipsychotic drugs and olanzapine over other second-generation antipsychotics is recommended to improve psychotic symptoms (moderate/weak recommendation).

Psychological treatment

PICO question 12. *Is psychological treatment effective to improve schizophrenia symptoms, to reduce drug use or to improve pragmatic and functionality variables in patients with schizophrenia and drug use?*

A meta-analysis of 32 RCTs with 3165 participants assessed the effects of psychosocial interventions for reduction of substance use in people with a serious mental illness compared with standard care (Hunt et al., 2013). No benefits were observed in improvement of psychotic symptoms measured with clinical scales for the comparisons of usual treatment with cognitive-behavioural therapy (CBT), CBT/ motivational interview (MI) and MI alone (very low quality of evidence). For the outcome of interest of decrease in drug consumption, including alcohol, cannabis and substance use at different time intervals (6, 12 and 36 months), differences between usual care and integral treatment, CBT, CBT/MI and MI were not documented (low or very low quality of evidence). In abstaining from alcohol during 6 months, one RCT showed significant differences favouring MI (very low quality of evidence). Differences of interventions *vs* usual treatment in other outcomes including reduction of hospitalizations or global functionality were not found.

Recommendations

- In patients with schizophrenia and co-occurring substance abuse disorder, no recommendation can be made regarding the most appropriate psychological intervention to improve psychotic symptoms, decrease substance use or improve functionality.

Conclusions

This review provides an overview of the efficacy of pharmacological and psychological treatment for patients with schizophrenia and comorbid SUD. Adults and young people with schizophrenia and coexisting substance use disorders commonly present for treatment in clinical practice. One of the major strengths of our review consists of the strict selection of RCTs. However, although useful insights in the efficacy of dual diagnosis outpatient treatment were revealed, the small number of included studies, the very low quality of evidence clearly and the very small sample sizes illustrates the need for additional high-quality research. Therefore, limited treatment data are available that demonstrate preferential treatment practices regarding the use of specific pharmacological or psychological interventions for people with schizophrenia and coexisting substance use disorders.

Our results suggest that

1. In patients with schizophrenia and cannabis use, it is not possible to recommend one antipsychotic drug over another (between olanzapine, risperidone or haloperidol) for improving psychotic symptoms, reducing cannabis use, or improving pragmatic variables (weak recommendation). Clozapine cannot be recommended to reduce cannabis use (weak recommendation). Adjunctive imipramine for improving affective symptoms is recommended (weak recommendation).
2. In patients with schizophrenia and cocaine use we recommend haloperidol over olanzapine to reduce craving (moderate recommendation), however olanzapine is recommended over haloperidol to improve motor side effects in these patients (moderate recommendation). The use of dopamine agonists (mazindol) to improve psychotic symptoms, reduce cocaine use or cocaine craving or improve pragmatic variables cannot be recommended (weak recommendation).
3. In patients with schizophrenia and alcohol use disorder there is insufficient evidence to make any recommendation on the use of antipsychotics to improve psychotic symptoms, to reduce alcohol use and/or alcohol craving or to improve pragmatic variables (weak recommendation). However, while naltrexone is recommended to reduce alcohol use (in terms of reducing alcohol craving) (weak recommendation), there is insufficient evidence to make any recommendation on the use of adjuvant acamprosate to improve psychotic symptoms, to reduce alcohol use or to improve pragmatic variables (weak recommendation).
4. In patients with schizophrenia and nicotine dependence, we cannot recommend the use of bupropion to reduce psychotic symptoms (weak recommendation). Adjuvant bupropion or varenicline are recommended for reducing nicotine use and nicotine abstinence (strong/moderate recommendation).
5. In patients with schizophrenia and polydrug use, the use of second-generation over first-generation antipsychotic drugs and olanzapine over other

second-generation antipsychotics is recommended to improve psychotic symptoms (moderate/weak recommendation).

6. In patients with schizophrenia and co-occurring substance abuse disorder, no recommendation can be made regarding the most appropriate psychological intervention to improve psychotic symptoms, decrease substance use or improve functionality.

Best practices involve integrated psychosis and substance use treatments, emphasizing inclusion in treatment, ongoing evaluation of substance use patterns, and coordinated care attempting to match treatment needs to severity of both disorders and stage of change (De Witte, Crunelle, Sabbe, Moggi & Dom, 2014). Although treatment of people with schizophrenia and coexisting substance use disorders can have its challenges, outcome data demonstrate that treatment is beneficial, and there being significant optimism for potentially greater improvements when substance use is stopped (Crockford & Addington, 2017).

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Conflict of interests

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

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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	Human, 18 years or older, RCT OR Review, Systematic Reviews, Meta-Analysis
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	
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	

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

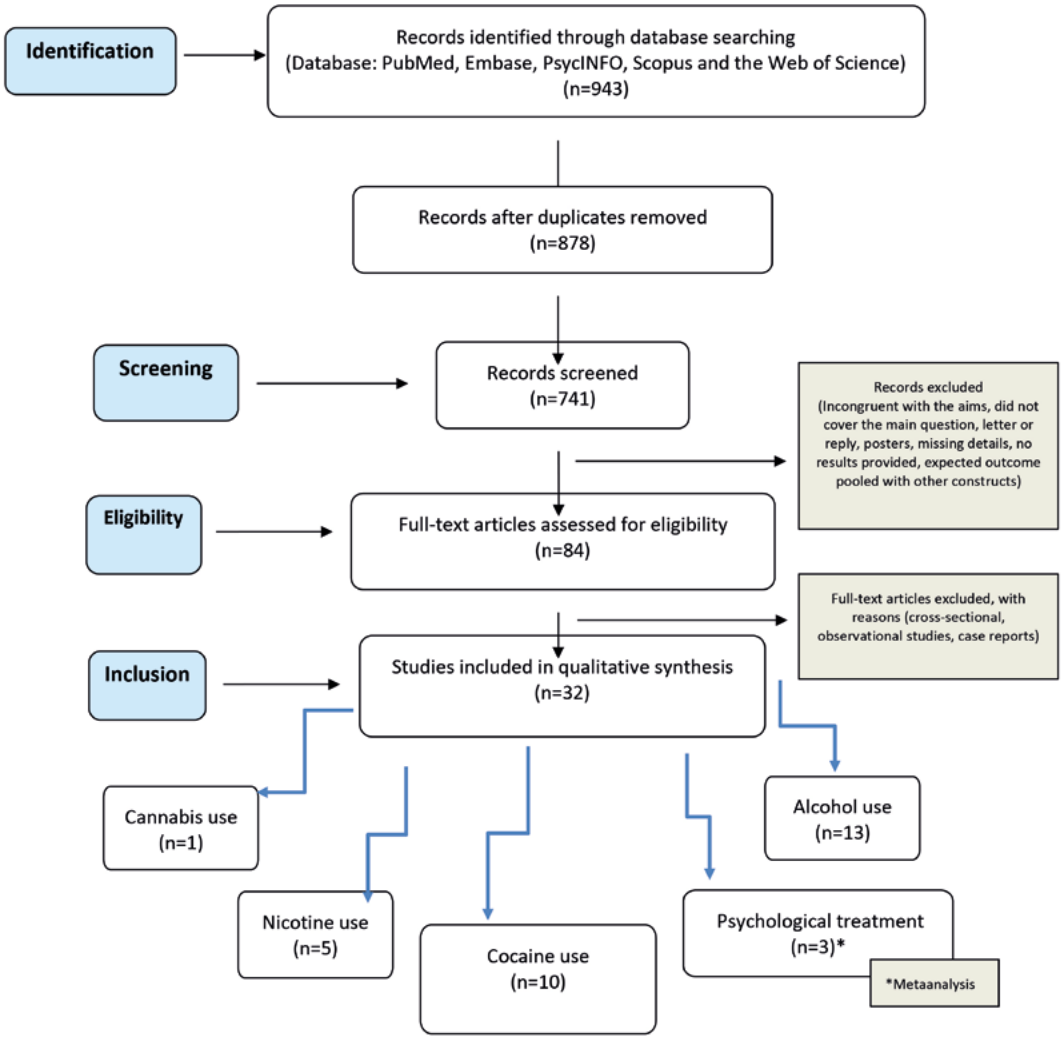

Figure 1. Flow chart of study selection process.

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).

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 Group B*: HDRS≤16	89/100 70/69	≥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.
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.

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

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.

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Conflict of interests

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

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

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

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Abstract

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

Resumen

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

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

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

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

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

Methods

Formulation of clinical questions

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

Bibliographic search

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

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

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

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

Evaluation of the quality of the evidence and formulation of recommendations

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

External review and evaluation

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

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

Results

Study selection

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

Patients with BD and alcohol use

Details about included studies are shown in Table 1.

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

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

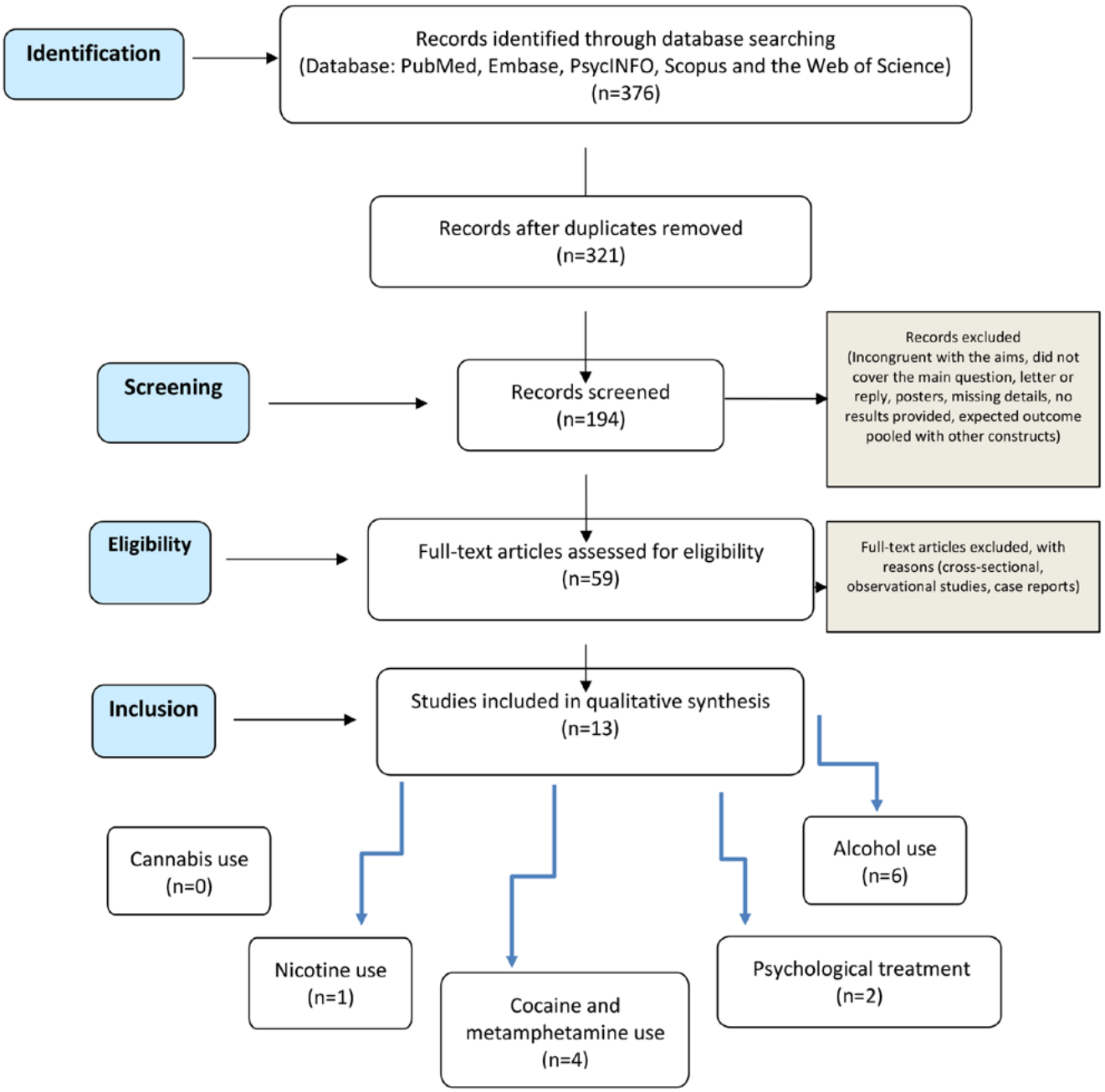

Figure 1. Flow chart of study selection process.

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

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

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

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

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

Table 1. *(cont.)*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Patients with BD and cocaine, methamphetamine or psychostimulant use

Details about included studies are shown in Table 2.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Patients with BD and nicotine use

Details about included studies are shown in Table 3.

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

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

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

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

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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Abstract

This review synthesizes the pharmacological and psychosocial interventions that have been conducted in comorbid anxiety disorders and SUDs while also providing clinical recommendations about which intervention elements are helpful for addressing substance use versus anxiety symptoms in patients with these co-occurring conditions. The best evidence from randomized controlled trials was used to evaluate treatment options. The strength of recommendations was described using the GRADE approach. Clinical trials are only available for posttraumatic stress disorder (PTSD) and for social anxiety. Concerning the comorbid substance use, all the studies have included patients with alcohol use, none of them have dealt with cocaine, cannabis or nicotine use. Although some treatments have shown benefit for anxiety symptoms without benefits for alcohol or other substance use, only limited pharmacological approaches have been

Resumen

Esta revisión resume las intervenciones farmacológicos y psicosociales que han sido llevadas a cabo en trastornos de ansiedad con un diagnóstico comórbido de trastorno por uso de sustancias y además proporciona recomendaciones clínicas respecto de cuáles elementos de intervención son útiles para hacer frente a los síntomas del uso de sustancias y los síntomas de ansiedad en pacientes con estas afecciones concurrentes. Se utilizó la mejor evidencia de ensayos controlados aleatorizados para evaluar las opciones de tratamiento. La fuerza de las recomendaciones se describió mediante el enfoque GRADE. Hay ensayos clínicos disponibles únicamente para el trastorno por estrés postraumático (TEPT) y para el trastorno de ansiedad. En cuanto al diagnóstico comórbido de trastorno por uso de sustancias, todos los estudios han incluido pacientes con consumo de alcohol, ninguno de ellos ha abordado el consumo de cocaína, cannabis o nicotina.

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assayed (sertraline, desipramine, paroxetine, buspirone, naltrexone and disulfiram). Our results suggest that 1) we can (weakly) recommend the use of desipramine over paroxetine to alleviate symptoms of anxiety in patients with a PTSD and alcohol use; 2) In these patients, the use of naltrexone to reduce symptoms of anxiety is also recommended (weak strength); and 3) SSRI antidepressants vs placebo can be recommended to reduce alcohol use (weak recommendation). Our review highlights the need for more research in this area and for larger, multisite studies with generalizable samples to provide more definite guidance for clinical practice.
Keywords: Anxiety; posttraumatic stress disorder; alcohol; selective serotonin reuptake inhibitors; desipramine; naltrexone; disulfiram.

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

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

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

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

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

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

Methods

Formulation of clinical questions

In accordance with evidence-based medicine principles, we used the 'PICO' structure (Patient-Intervention-Comparison-Outcomes (Guyatt et al., 2008; Oxman, Schünemann & Fretheim, 2006) to formulate the following review question: "*What is the effect of a pharmacological and/or psychological intervention for the treatment of adult patients with Anxiety Disorder and a SUD?",* being Patients: Adult patients with Anxiety Disorder and coexisting/co-occurring substance / alcohol / cannabis / cocaine /nicotine use disorder; Interventions: Any Pharmacological OR any Psychological Treatment; Comparator: Placebo OR any pharmacological treatment OR any psychological treatment and Outcomes: Reduction of clinical symptoms of anxiety disorder; Improved Substance Use Disorder and Improved pragmatic and functional measures. The target population of these clinical guidelines are patients older than 18 years diagnosed with an AD and a SUD (including cannabis, cocaine, alcohol and/or nicotine). Opioid use disorder was not included because no systematic reviews with or without meta-analysis or randomized clinical trials were found.

Bibliographic search

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

- Pubmed (pharmacological intervention)

((((“Stress Disorders, Post-Traumatic”[Mesh] OR “Obsessive-Compulsive Disorder”[Mesh] OR “Panic Disorder”[Mesh] OR “Anxiety Disorders”[Mesh] OR posttraumatic stress disorder* OR obsessive compulsive disorder* OR panic disorder* OR anxiety disorder*)) AND (substance abuse OR substance dependence OR substance use OR comorbidity OR misuse OR co-occurr* OR coexist* OR concurren* OR dual diagnosis OR dual disorder OR dual pathology OR “Diagnosis, Dual (Psychiatry)”[Mesh])) AND (“Alcohol Drinking”[Mesh] OR “Drinking Behavior”[Mesh] OR “alcohol use” OR “alcohol abuse” OR “nicotine use” OR “Marijuana Abuse”[Mesh] OR “Marijuana Smoking”[Mesh] OR “cannabis use” OR “Cocaine-Related Disorders”[Mesh] OR “cocaine use” OR “cocaine abuse”)) AND (varenicline OR “varenicline”[Supplementary Concept] OR nicotine replacement therapy OR “Bupropion”[Mesh] OR bupropion OR “topiramate”[Supplementary Concept] OR topiramate OR “acamprosate”[Supplementary Concept] OR acamprosate OR “Naltrexone”[Mesh] OR naltrexone OR anticraving OR “Cyanamide”[Mesh] OR cyanamide OR “Disulfiram”[Mesh] OR disulfiram OR antidipsotropic OR “Antipsychotic Agents”[Mesh] OR antipsychotics OR “Benzodiazepines”[Mesh] OR benzodiazepines OR lamotrigine OR “lamotrigine”[Supplementary Concept] OR valproate OR “Valproic Acid”[Mesh] OR divalproex OR “Lithium”[Mesh] OR lithium OR “Serotonin Uptake Inhibitors”[Mesh] OR “Serotonin Uptake Inhibitors”[Pharmacological Action] OR “duloxetine”[Supplementary Concept] OR duloxetine OR ssris OR “Antidepressive Agents, Tricyclic”[Mesh] OR “Antidepressive Agents, Tricyclic”[Pharmacological Action] OR tricyclic antidepressant OR nsri).

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

((((“Stress Disorders, Post-Traumatic”[Mesh] OR “Obsessive-Compulsive Disorder”[Mesh] OR “Panic Disorder”[Mesh] OR “Anxiety Disorders”[Mesh] OR posttraumatic stress disorder* OR obsessive compulsive disorder* OR panic disorder* OR anxiety disorder*)) AND (substance abuse OR substance dependence OR substance use OR comorbidity OR misuse OR co-occurr* OR coexist* OR concurren* OR dual diagnosis OR dual disorder OR dual pathology OR “Diagnosis, Dual (Psychiatry)”[Mesh])) AND (“Alcohol Drinking”[Mesh] OR “Drinking Behavior”[Mesh] OR “alcohol use” OR “alcohol abuse” OR “nicotine use” OR “Marijuana Abuse”[Mesh] OR “Marijuana Smoking”[Mesh] OR “cannabis use” OR “Cocaine-Related Disorders”[Mesh] OR “cocaine use” OR “cocaine abuse”)) AND (“Lithium”[Mesh] OR “Lithium Chloride”[Mesh] OR “Lithium Carbonate”[Mesh] OR lithium OR “Valproic Acid”[Mesh] OR valproate OR “lamotrigine 2-N-glucuronide”[Supplementary Concept] OR lamotrigine OR carbamazepine OR oxcarbazepine OR mood stabilizer*).

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

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

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

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

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

((((“Stress Disorders, Post-Traumatic”[Mesh] OR “Obsessive-Compulsive Disorder”[Mesh] OR “Panic Disorder”[Mesh] OR “Anxiety Disorders”[Mesh] OR posttraumatic stress disorder* OR obsessive compulsive disorder* OR panic disorder* OR anxiety disorder*)) AND (substance abuse OR substance dependence OR substance use OR comorbidity OR misuse OR co-occurr* OR coexist* OR concurren* OR dual diagnosis OR dual disorder OR dual pathology OR “Diagnosis, Dual (Psychiatry)”[Mesh])) AND (“Alcohol Drinking”[Mesh] OR “Drinking Behavior”[Mesh] OR “alcohol use” OR “alcohol abuse” OR “nicotine use” OR “Marijuana Abuse”[Mesh] OR “Marijuana Smoking”[Mesh] OR “cannabis use” OR “Cocaine-Related Disorders”[Mesh] OR “cocaine use” OR “cocaine abuse”)) AND (varenicline OR “varenicline”[Supplementary Concept] OR nicotine replacement therapy OR “Bupropion”[Mesh] OR bupropion OR “topiramate”[Supplementary Concept] OR topiramate OR “acamprosate”[Supplementary Concept] OR acamprosate OR “Naltrexone”[Mesh] OR naltrexone OR anticraving OR “Cyanamide”[Mesh] OR cyanamide OR “Disulfiram”[Mesh] OR disulfiram OR antidipsotropic).

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

((((Stress Disorders, Post-Traumatic[Mesh] OR “Obsessive-Compulsive Disorder”[Mesh] OR “Panic Disorder”[Mesh] OR “Anxiety Disorders”[Mesh] OR posttraumatic stress disorder* OR obsessive compulsive disorder* OR panic disorder* OR anxiety disorder*)) AND (substance abuse OR substance dependence OR substance use OR comorbidity OR misuse OR co-occurr* OR coexist* OR concurren* OR dual diagnosis OR dual disorder OR dual pathology OR “Diagnosis, Dual (Psychiatry)”[Mesh])) AND (“Alcohol Drinking”[Mesh] OR “Drinking Behavior”[Mesh] OR “alcohol use” OR “alcohol abuse” OR “nicotine use” OR “Marijuana Abuse”[Mesh] OR “Marijuana Smoking”[Mesh] OR “cannabis use” OR “Cocaine-Related Disorders”[Mesh] OR “cocaine use” OR “cocaine abuse”)) AND (“behavioral therapy” Or therapy OR “cognitive therapy” OR “social skills” OR “contingency management” OR “time out” OR “reinforcement programs” OR “token economy” OR self-help OR “motivational interview” OR mindfulness OR “cue exposure” OR self-control OR psychoeducation OR psychotherapy).

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

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

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

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

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

- Limits: Randomized Controlled Trial; +19 years.

Evaluation of the quality of the evidence and formulation of recommendations

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

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

External review and evaluation

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

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

Results

Study selection

Figure 1 outlines PRISMA flowchart leading to the study selection. The search yielded 204 studies. 39 studies were deemed eligible for further assessment. The final selection included 13 studies. Open-label, cohort or case-control studies, cross-sectional and observational studies, case reports, letters, posters and abstracts of presentations to specialist meetings and conferences were not included in the Guideline. Only articles published in English were included. Data were extracted from the included studies using a predefined template and the quality of each study was assessed using standard criteria. A summarized report of these studies can be found in Table 1.

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

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

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

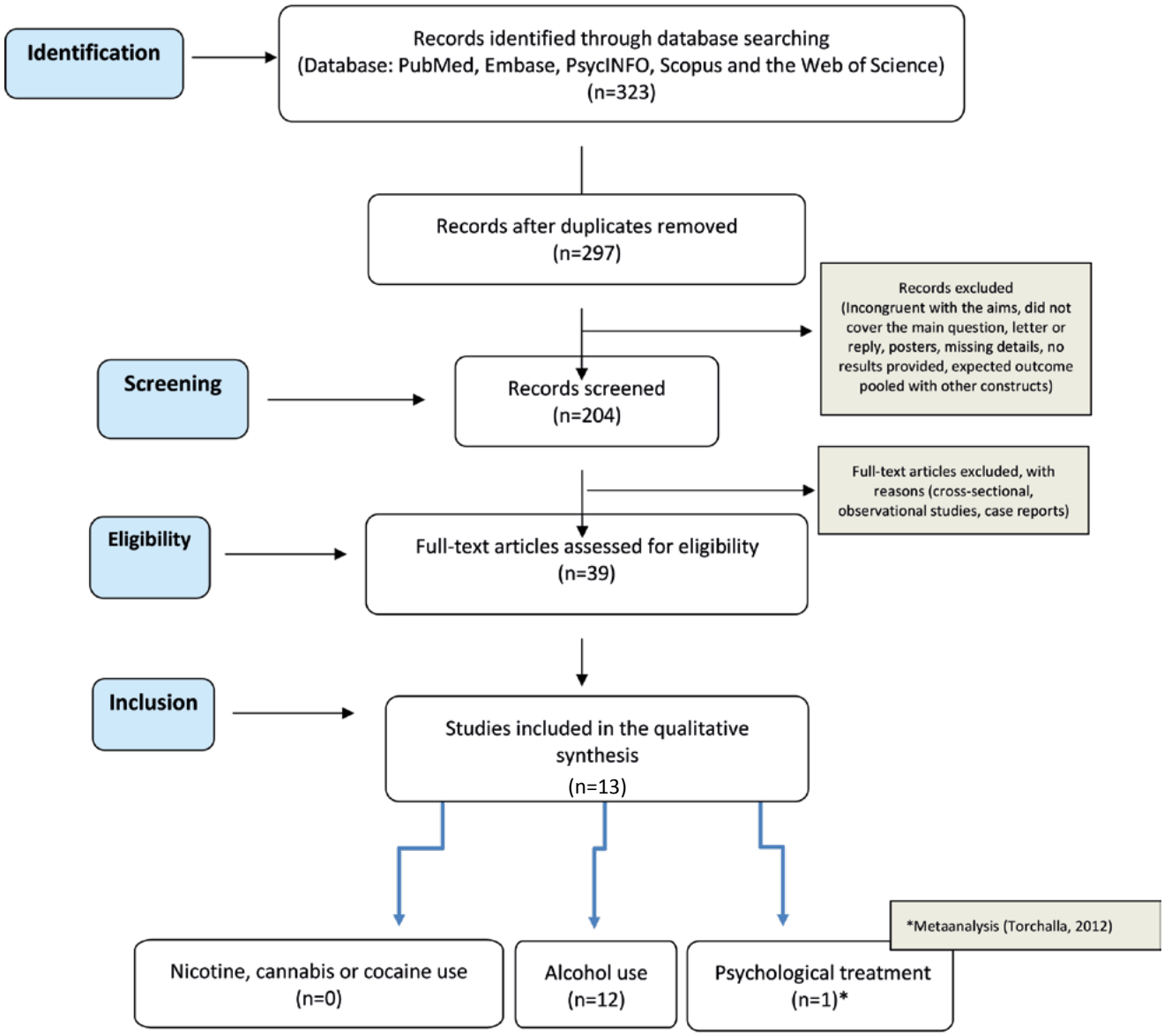

Figure 1. Flow chart of study selection process.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Recommendations

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

Conclusions

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

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

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

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

Our review highlights the need for more research in this area and for larger, multisite studies with generalizable samples to provide more definite guidance for clinical practice. This research should ensure adequate randomization, the use of an active comparator, and long-term follow ups, so as to establish the sustainability of treatment outcomes.

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Conflict of interests

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

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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 metaanalysis)

(((((("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., 2022) (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

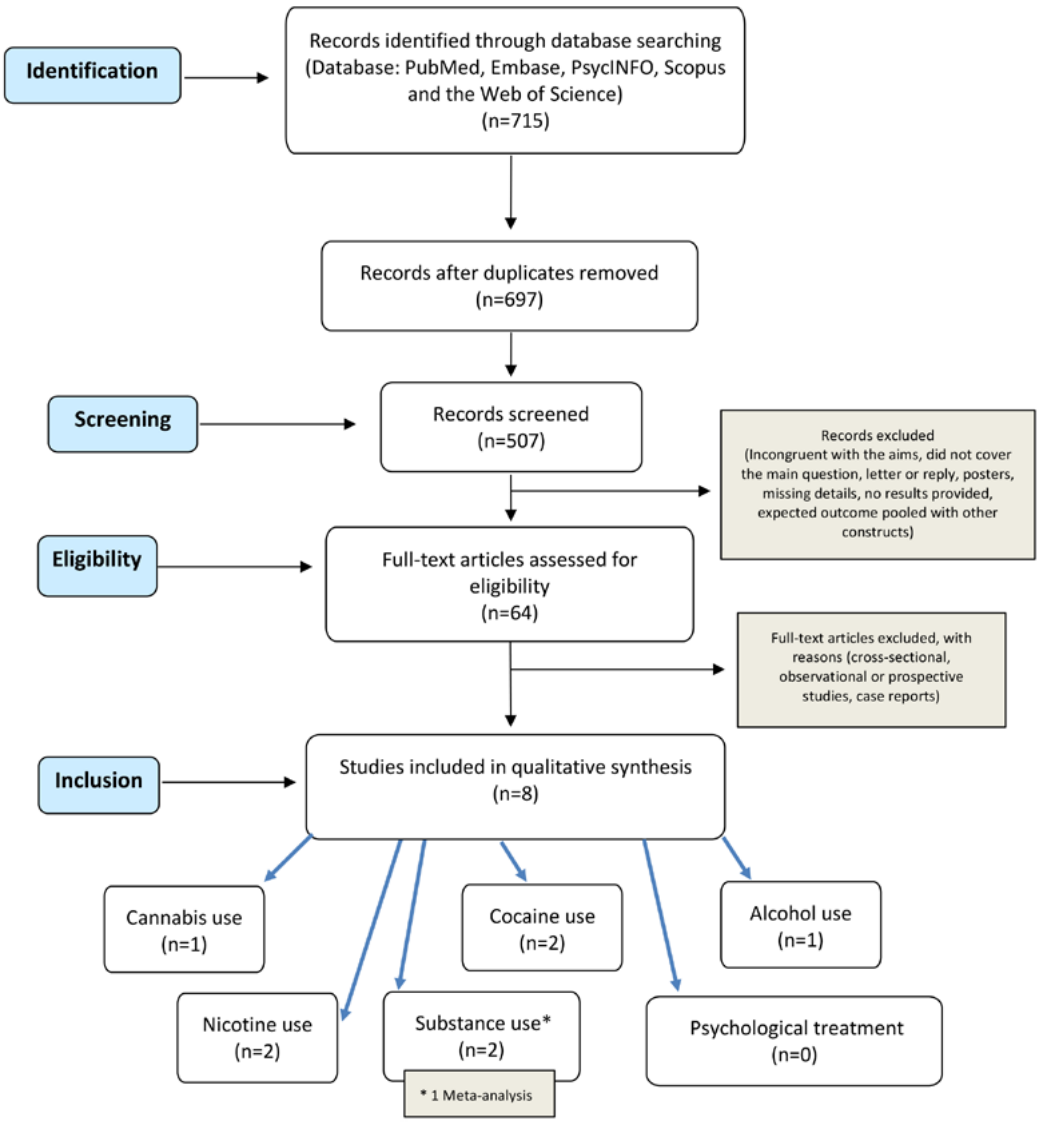

Figure 1. Flow chart of study selection process.

or case-control studies, cross-sectional and observational studies, case reports, letters, posters and abstracts of presentations to specialist meetings and conferences were not included in the Guideline. Only articles published in English were included. Data were extracted from the included studies using a predefined template and the quality of each study was assessed using standard criteria. A summarized report of these studies can be found in Table 1.

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).

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.

- 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 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 (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).

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 interests

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

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Ante la preparación de un artículo de cara a su publicación se deben revisar y aplicar las normas extensas, que pueden ser consultadas en www.adicciones.es

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Papel. La revista Adicciones está impresa en papel estucado fabricado con pastas libres de cloro (TCF).

Conflictos de intereses. La política de la revista es que en todos los artículos y editoriales conste expresamente la existencia o no de conflicto de intereses en el apartado correspondiente. Todos los conflictos de interés son importantes, pero especial cuidado hay que poner en el caso de haber recibido para el estudio financiación de la industria farmacéutica, alcoholera, tabaquera, etc. La revista Adicciones sigue en este tema las recomendaciones de ISAJE (International Society of Addiction Journals Editors). Tener conflicto de intereses no significa no poder publicar el artículo. En caso de duda sobre esta cuestión se debe contactar con el editor.

Autoría. Es muy importante que únicamente se consideren autores aquellos que han hecho sustanciales contribuciones: 1) a la concepción y diseño, adquisición de datos, o el análisis e interpretación de datos; 2) a la redacción del artículo o a su revisión crítica; y 3) que ha dado su aprobación de la versión que se publicará. Los autores deben asegurarse de que partes significativas del material aportado no ha sido publicado con anterioridad. En caso de que puedan tener dudas sobre el cumplimiento de esta norma, deberán presentar copias de lo publicado o de lo presentado para publicación a otras revistas antes de poder ser considerado el artículo para su revisión. En caso de dudas sobre alguno de los aspectos anteriores los autores deben consultar el acuerdo de Farmington al que está adherida la revista Adicciones (Anexo 1), las normas de "Sponshorship, authorship, and accountability" del International Committee of Medical Journal Editors (www.icmje.org/sponsor.htm) o las normas de publicación de la American Psychological Association, 6ª edición (2010) (www.apastyle.org). El editor de la revista puede dirigirse a los autores del artículo para que especifiquen cual ha sido la contribución de cada uno de ellos.

Preparación de manuscritos. Los autores deben seguir exclusivamente para la presentación de sus manuscritos las Normas de Publicación de la American Psychological Association (6ª edición, 2010; http://www.apastyle.org). Las excepciones a esta regla son mínimas y dependen sólo de las diferencias que puede haber en el uso del español y del inglés. Por ejemplo, los ingleses utilizan en la bibliografía el signo '&' antes del último autor, mientras que en español dicho signo se corresponde exactamente con la 'y' (por tanto los artículos en español utilizarán solo la 'y'); otra diferencia puede ser en los títulos de los artículos, puesto que en inglés se pone en mayúscula la primera letra de muchas de las palabras, mientras que en español sólo ponemos la primera…

NO existe un límite exacto de palabras para los trabajos que se presenten. Pero deberá cuidarse mucho que toda la información que se incluya sea estrictamente la necesaria.

Es importante que los artículos sean interesantes para la comunidad científica del campo de las adicciones. Se evitarán trabajos que se refieran a realidades muy concretas –a menos que precisamente en ello resida su interés-, o que sean básicamente descriptivos –a menos, nuevamente, que se trate de algo novedoso.

Artículos originales. Serán preferentemente trabajos de investigación clínicos o experimentales sobre el campo de las drogodependencias o las adicciones. Pero también pueden ser aceptados trabajos teóricos o de otro tipo.

Informes breves. En esta sección se considerarán los trabajos de investigación que por sus características especiales (series con número reducido de observaciones, casos clínicos, trabajos de investigación con objetivos y resultados muy concretos, estudios epidemiológicos descriptivos, primeros resultados de un estudio amplio, etc.) pueden ser publicados de forma abreviada y rápida.

Artículos de revisión. Presentarán la actualización de un tema de forma rigurosa y exhaustiva. Deberán regirse normalmente por metodologías sistematizadas. El contenido del artículo podrá llevar los apartados necesarios para la mejor comprensión de los lectores. En su parte final debe aparecer un apartado de discusión o conclusiones. La extensión preferiblemente no debería superar las 5.000 palabras, pero siempre que esté justificado, se admitirían revisiones más largas.

Cartas al Director. Tendrán normalmente un máximo de 800 palabras, 10 referencias y una tabla o figura. Pueden consistir en una presentación breve sobre algo novedoso, una investigación original, o la contestación o matización a un artículo publicado en la revista. Cuando sea éste el caso la carta tendrá que recibirse dentro de las 6 semanas subsiguientes a la publicación del artículo en el número de la revista

PRESENTACIÓN DE LOS TRABAJOS

Envío electrónico. La forma más rápida y preferente de enviar artículos para su revisión editorial es a través de www.adicciones.es. Allí encontrará todas las instrucciones a seguir y la forma de adjuntar el original. Todo el seguimiento del proceso de revisión y editorial se realizará a través de la web (a través de la plataforma de RECYT). Ésta es la única forma prevista para envío de artículos (pero si tiene alguna duda puede comunicarse con secretaria@adicciones.es). Será muy útil para facilitar el proceso de revisión que en el momento del envío del artículo proporcione a través de la misma plataforma información sobre por lo menos dos posibles revisores para su artículo (nombre, institución y correo electrónico). Estos revisores deberán ser expertos en el tema y no estar ligados a la investigación que se desarrolla en el trabajo presentado. Tampoco podrán pertenecer al actual Comité de Redacción o Editorial. La revista se reserva la decisión de utilizar o no dichos revisores propuestos. El editor señalará además normalmente otros revisores. Recordar que el proceso de revisión es anónimo para los autores. Caso de que no fuese posible por alguna razón o tuviese algún problema con el envío del artículo a través de la web, le agradeceremos que se ponga en contacto con secretaria@adicciones.es o al teléfono (+34) 971727434 o a Editor de Adicciones. Rambla, 15, 2ª, 3ª. 07003 Palma de Mallorca.

ESTRUCTURA DE LOS TRABAJOS ENVIADOS A LA REVISTA

Todas las hojas deberán ir numeradas correlativamente en la parte superior derecha. Cada parte del manuscrito empezará una página en el siguiente orden:

1. En la *primera página* del artículo se indicarán, en el orden que aquí se cita, los siguientes datos:

- Título del artículo, en minúsculas (en castellano e inglés) excepto la letra inicial.
- Nombre de los autores completo (no sólo iniciales), y uno o dos apellidos del/los autor/es (p. ej.: Miguel García o Miguel García Rodríguez o bien Miguel García-Rodríguez, teniendo en cuenta que la forma que hayan utilizado los autores es la que se enviará a las bases de datos) en minúsculas, excepto la letra inicial. Los distintos autores vendrán separados por punto y coma. Detrás del apellido de cada autor, sin espacio intermedio y en superíndice, deberá ir un asterisco de llamada (1 asterisco para el primero, 2 para el segundo, etc.). Estos asteriscos son necesarios para indicar en el siguiente punto la institución donde se ha realizado el trabajo.
- Precedidos por un asterisco o los que fuesen necesarios –según el punto anterior– se indicarán el nombre/s del centro/s donde se ha realizado el trabajo o donde trabajan los autores.

Al final de la primera página (no como 'nota al pie') se colocará este texto: "Enviar correspondencia a: ...", indicando el nombre, la dirección postal, correo electrónico u otra información mediante la cual el autor elegido podrá ser contactado. Este será

el autor al cual la secretaría se dirigirá durante el proceso de revisión, a menos que se acuerde mutuamente otra solución.

2. La *segunda hoja* del artículo incluirá un resumen del trabajo presentado, tanto en español como en inglés. Dicho resumen tendrá alrededor de 250 palabras. Siguiendo las normas de publicación internacional ya citadas, el resumen debe especificar los objetivos del estudio o investigación; la metodología fundamental utilizada; los principales resultados; y las conclusiones más importantes y/o novedosas. El resumen debe redactarse en uno o varios párrafos siguiendo las normas de publicación de la APA, sin atender a las divisiones de antecedentes, método, etc.

Después del resumen se incluirá un listado de alrededor de 5 Palabras clave en español y luego en inglés (Key words) en minúsculas y separadas por comas que, a ser posible, se adapten a las normalmente utilizadas en los índices al uso (ej., Index Medicus, Psychological Abstracts, Índice Médico Español).

3. La *tercera hoja* dará inicio al texto del artículo. Se recomienda la redacción del texto en impersonal. Conviene dividir claramente los trabajos en apartados, siguiendo, siempre que sea posible por las características del estudio, el esquema general siguiente: Introducción (no obstante la palabra introducción no se pondrá, pues se da por supuesta), Método, Resultados, Discusión, Reconocimientos, Conflicto de intereses y Referencias.

Introducción. Será breve y deberá proporcionar sólo la explicación necesaria para que el lector pueda comprender el texto que sigue a continuación. No debe contener tablas ni figuras, a menos que sean imprescindibles para la comprensión del texto. Debe incluir un último párrafo en el que se exponga de forma clara el o los objetivos del trabajo. Siempre que se pretenda publicar una observación muy infrecuente, debe precisarse en el texto el método de pesquisa bibliográfica, las palabras claves empleadas, los años de cobertura y la fecha de actualización.

Métodos. Se describirá claramente la metodología empleada (selección de la muestra, como se recogieron los datos, instrumentos de recogida de datos o de evaluación, temporalización,… Se deben identificar los métodos, instrumentos de evaluación, tratamientos, fármacos utilizados, aparatos, sistema de evaluación, pruebas estadísticas si son novedosas, métodos nuevos, etc. Debe especificarse el tipo de estudio (descriptivo, epidemiológico, experimental, ensayo clínico, etc.), sistema de asignación de los sujetos a grupos, aleatorización, etc. Cuando haya un protocolo debe citarse. Cuando los experimentos son realizados con animales o el ensayo es experimental en humanos debe especificarse explícitamente que se han seguido las normas éticas deontológicas, de investigación y que se han cumplido los convenios internacionales de experimentación animal o humana. Debe especificarse el tipo de análisis estadístico que se va a utilizar, describirlo cuando éste sea nuevo o poco conocido, e indicar el paquete estadístico que se va a utilizar. Se valorará positivamente si se ha conseguido la aprobación del estudio por algún comité ético o se podrá exigir cuando el estudio realizado lo requiera.

Resultados. Los resultados deben presentarse en una secuencia lógica en el texto, tablas y figuras. Utilice sólo aquellas tablas y figuras estrictamente necesarias, que expresen claramente los resultados del estudio. No duplique los datos en tablas y figuras. No repita en el texto todos los datos de las tablas y figuras, sólo los más importantes. Enfatice y resuma sólo las observaciones más importantes. Adicciones adopta el sistema convencional del 5% como valor para la significación estadística y no acepta tener en cuenta las tendencias para valores menores.

Los ensayos clínicos aleatorizados deben adecuarse a las guías CONSORT (www.consort-statement.org) y los estudios con diseños no experimentales a las guías TREND (www.trend-statement.org/asp/trend.asp) para la mayor claridad de los lectores y revisores del trabajo. Igualmente, se presentarán los estadísticos del tamaño del efecto.

Discusión. Enfatizará los aspectos nuevos e importantes del estudio y las conclusiones que se derivan del mismo. No repita en detalle los resultados que ha presentado en la sección anterior ni en la introducción. Destaque lo más importante y controvertido y relacionelo con otros estudios relevantes sobre el tema. No haga suposiciones si no se ven apoyadas por los datos. Cuando sea apropiado pueden incluirse recomendaciones. Indique las implicaciones de sus hallazgos y sus limitaciones (estas preferiblemente formarán un párrafo al final del artículo).

Reconocimientos. Este apartado se situará al final del texto del artículo y justo antes del apartado de Referencias. Cuando se considere necesario se citará a las personas, centros o entidades que hayan colaborado o apoyado la realización del trabajo. Pueden incluirse todas aquellas personas que hayan ayudado en la preparación del artículo, pero no con la intensidad requerida para ser considerados autores. Si el trabajo ha sido financiado se indicará la entidad financiadora.

Conflicto de intereses. Todos los artículos, editoriales, comentarios, opiniones, reseñas de libros y cartas que se publican en la revista estarán acompañados por una declaración sobre los posibles o reales conflictos de interés o una declaración de que los autores no tienen conflictos de intereses que declarar.

Referencias. Seguirán de forma estricta las normas de la American Psychological Association [American Psychological Association (2010). Publication Manual of the American Psychological Association (6th ed.). Washington, DC. http://www.apastyle.org

Tablas y figuras. Irán al final del texto, numeradas, y cada una en una página distinta, siguiendo el diseño propio de la APA.

EL PROCESO DE REVISIÓN DEL MANUSCRITO

Los artículos son enviados a la revista a través de la www.adicciones.es. Los autores reciben al enviar el artículo unas claves para poder entrar en la web y revisar la situación de su artículo. No obstante el editor de la revista enviará un mensaje cuando tenga una decisión tomada o quiera preguntar alguna cuestión. Una vez recibido el manuscrito en la Redacción de la Revista Adicciones empezará el proceso de revisión.

El Editor, normalmente consultando con los editores asociados, puede desestimar de entrada un artículo que entienda que claramente no reúne la calidad suficiente o no entra dentro de las prioridades de la revista. El editor puede rechazar de entrada aquellos artículos que no cumplan estrictamente dicha normativa, sin pasarlo a revisión.

Los manuscritos serán enviados por el Editor o los Editores Asociados a dos o más expertos en el tema (revisores), que harán los comentarios pertinentes sobre el mismo y que requerirán aquellos cambios que estimen necesarios; también pueden dar su opinión sobre la aceptación o rechazo del artículo. La última decisión, basada en el informe de los revisores, o del editor asociado que se hubiese responsabilizado de la revisión, será tomada por el Editor de la revista, que podrá consultar además a los Editores asociados. En todo el proceso de revisión se mantendrá el principio de confidencialidad por parte de los revisores hacia el trabajo que revisan, así como la confidencialidad de los nombres de los revisores entre ellos o ante los autores del manuscrito.

El resultado de la revisión del manuscrito será enviado al autor de correspondencia que viene en el artículo indicándole su aceptación, rechazo o la necesidad de someterse a una nueva revisión una vez tenidos en cuenta los comentarios de los revisores o del editor. El autor, si es el caso, deberá hacer los cambios señalados –cuando esté de acuerdo con ellos–, enviando:

- Una copia del manuscrito revisado.
- Otro documento en donde se exponga de forma detallada las principales modificaciones efectuadas, así como sus propios comentarios sobre los principales aspectos de la revisión, con los que obviamente puede estar en desacuerdo.

Una vez aceptado el artículo, se enviará a los autores las pruebas de imprenta para que las corrijan. Los autores son totalmente responsables de la versión final que se publique. Los autores pueden hacer el uso que crean pertinente para la difusión del artículo, siempre que quede clara toda la información necesaria acerca de la revista donde ha sido publicado.

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