

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-occur* 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-occur* 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-occur* 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-occur* 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: meta-analyses, 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 meta-analysis 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

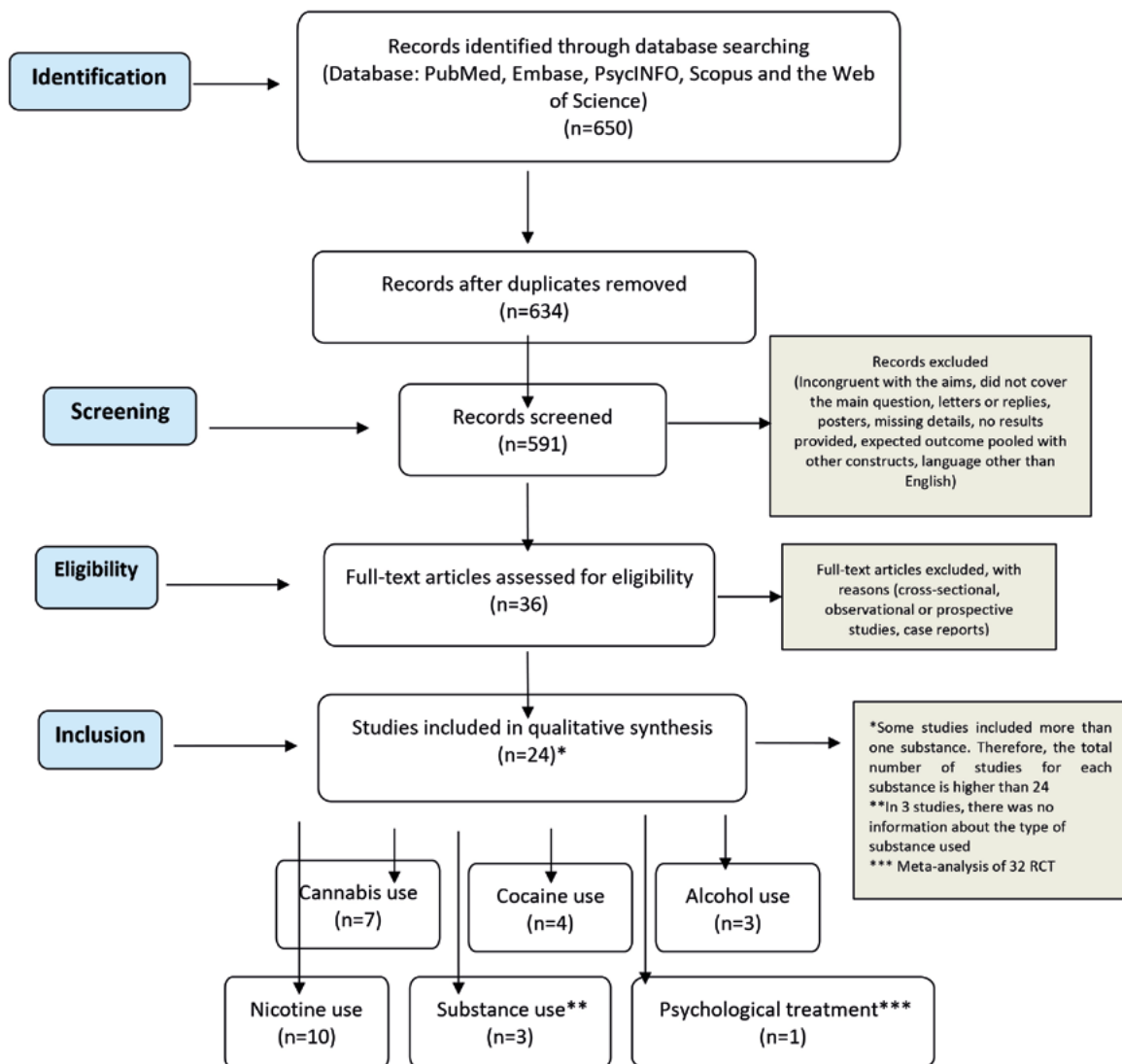


Figure 1. Flow chart of study selection process.

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. <i>Lilly Research Laboratories</i> 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. <i>Eli-Lilly</i> 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) (Akerle & Levin, 2007); three craving questionnaire (moderate quality of evidence) (Van Nimwegen et al., 2008); marijuana craving questionnaire (very low quality of evidence) (Akerle & 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 (Akerle & 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 <i>Eli Lilly</i> . 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 (Akerle & 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 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 previous month. <i>Lilly Research Laboratories</i> 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 (Akerle & 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 use (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) (Akerle & 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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