



Atypical Antipsychotic Drugs in Dual Diagnosis Patients: A Review

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Abstract

Introduction: Dual Diagnosis (DD), defined as the co-occurrence of a Substance Use Disorder (SUD) and a Severe Mental Illness (SMI), is associated with several negative outcomes. Typical antipsychotics (TAP) are not of great value for patients with DD as they are associated with poorer responses and can worsen SUD. Atypical antipsychotics (AAP) offer several advantages compared to TAP. In DD, they have been found to be effective in treating both, psychiatric symptoms and substance use. The aim of this article is to review the use of AAP for treating DD patients.

Methods: A search of MEDLINE, EMBASE and Pubmed was performed in order to identify publications that examined the use of AAP in the treatment of DD.

Results: The largest number of studies focus on clozapine, with consistently positive data. Data regarding aripiprazole are also consistent but less substantial. Olanzapine, risperidone and quetiapine have given inconclusive and inconsistent results. Finally, there is little use of amisulpride, ziprasidone, paliperidone and asenapine or it has not been documented.

Discussion: Today, there is a consensus on using AAT instead of TAP for treating patients with DD. Patients with DD show a poorer response to treatment with TAP, and TAP may even worsen the addictive behaviour. AAP are as effective as TAP in treating psychiatric symptoms, but they are more effective in reducing substance use in DD patients. Because with the exception of CLO none of the AAP have shown to be superior to the others, when choosing between the different AAP agents clinicians should take into account other variables such as medical comorbidity, possible pharmacological interactions of concomitant treatments and profile of side effects. Even though a growing body of evidence suggests the beneficial effects of AAP in DD patients, further randomized, blinded, controlled trials, with larger sample sizes and longer follow-ups are needed.

Keywords

Atypical antipsychotics, Dual diagnosis, Substance use disorder

Introduction

Dual diagnosis (DD) is traditionally defined as the co-occurrence of a Substance Use Disorder (SUD) and a Severe Mental Illness (SMI) [1]. Although in recent years the concept of DD has been extended and it is being used to define the co-occurrence of any mental illness and a SUD, in this review we will consider Schizophrenia (SCH) and related disorders, as well as Bipolar Disorder (BD) with concomitant SUD.

More than 50% of the patients with a psychiatric disorder meet DSM-IV criteria for alcohol and/or substance abuse and/or dependence [2]. The substances more commonly used by these patients are alcohol, followed by cannabis and cocaine [3]. Several complimentary hypotheses have been used to explain the comorbidity between SMI and SUD. Traditionally, the association between SUD and SMI was explained with the “self-medication” theory, which stated that patients use substances to relieve psychiatric symptoms or the side-effects of psychiatric medication [4]. However, in recent years, the neurobiological theory proposed by Green et al. (1999) is gaining importance in the field of DD. They suggest that there is a “reward deficiency syndrome” in people with SMI, so that they have a dysfunction in their dopamine (DA)-mediated mesocorticolimbic (MCL) reward pathways, and use alcohol and other drugs of abuse in order to ameliorate this dysfunction in the brain reward system [5].

Comorbid SUD among patients with SMI is associated with more negative outcomes such as more relapses [6], more admissions to hospital [7], poor response to treatments [8], non-compliance with

Citation: Marín-Mayor M, López-Álvarez J, López-Muñoz F, Arias-Horcajadas F, Rubio G (2015) Atypical Antipsychotic Drugs in Dual Diagnosis Patients: A Review. Int J Neurol Neurother 2:026. doi.org/10.23937/2378-3001/2/1/1026

Received: March 04, 2015: **Accepted:** March 27, 2015: **Published:** March 30, 2015

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the treatment [9], increased rates of suicidal ideation [10], increased rates of impulsive and violent behaviours [11], increased rates of neurological and psychiatric symptoms [12], and higher incidence of poverty, unemployment and social exclusion [13]. The demographic correlates of substance use are well documented and DD patients tend to be younger males, with a lower educational level, a family history of SUD, and a comorbid Antisocial Personality Disorder (ASPD) [14].

Typical antipsychotics (TAP), unfortunately, are often not of great value for patients with a SMI and a SUD. In fact, a poorer response to TAP has been described in patients with a past history of SUD [15,16]. In addition, an increase in cigarettes smoked after the initiation of haloperidol (HAL) treatment has also been reported [17]. Two main hypotheses have been proposed to explain this lack of efficacy of TAP in dual diagnosed patients: 1) TAP are associated with considerable side effects, such as extra pyramidal side effects (EPS) and dysphoria, so that DD patients would "self-medicate" in order to ameliorate these symptoms [18-20] and 2) they worsen the functioning of DA-mediated MCL brain reward circuits because of a potent D₂ receptor blockade action [5,21].

Atypical antipsychotics (AAP) offer several advantages over TAP: 1) they are effective in treating positive symptoms to the same extent as TAP; 2) they are as effective or superior to TAP in treating negative symptoms; 3) they exert antidepressant and mood stabilization actions; 4) they are effective in treating aggression and impulsivity; 5) they exhibit better tolerability, especially in terms of decreased EPS, tardive dyskinesia and hyperprolactinemia; 6) they diminish suicidality and 7) they are associated with an improvement in cognition. Furthermore, they have been reported to obtain some advantage in the treatment of SUD probably due to their mechanism of action, which includes less DA antagonism and pharmacological action on serotonin (5HT), histamine (HIS), and norepinephrine (NE) pathways [22,23].

The aim of this article is to review the use of AAP for treating DD, in order to critically discuss their effectiveness both in treating the psychiatric disorder and treating the SUD, their tolerability and their safety.

Methods

A search of MEDLINE, EMBASE and Pubmed (1980-present) was performed in order to identify English- and Spanish-language publications that examined the use of AAP in the treatment of DD. Major search terms included dual diagnosis, schizophrenia, schizoaffective disorder, bipolar disorder, SUD, on one hand, and atypical antipsychotics, clozapine (CLO), amisulpride (AMS), aripiprazole (ARI), asenapine (ASE), olanzapine (OLZ), paliperidone (PAL), quetiapine (QUE), risperidone(RIS) and ziprasidone (ZIP), on the other hand.

The inclusion criteria were the following: 1) studies that had been published in English or Spanish; 2) studies which included a sample or subsample of patients with a diagnosis of a Psychotic Spectrum Disorder such as Substance Induced Psychosis, Schizophrenia or Schizoaffective Disorder, and/or a Bipolar Disorder; 3) studies in which the presence of a SUD was specified; and 4) studies in which the efficacy and/or safety of the pharmacological intervention was described. Studies that did not follow the inclusion criteria were excluded. With the exception of reviews, all types of studies, regardless of their design, were reviewed and therefore included (case reports, case series, retrospective analyses, open, prospective case-control studies and prospective, randomised, double-blind controlled studies).

A careful review of the titles and abstracts of the total number of publications found in the literature search using all possible combinations of major search terms was carried out. Those studies that followed the inclusion criteria were selected and we read through the full text of those studies initially chosen. Review papers and the references of the selected studies were searched manually to identify papers not located in the electronic database search. The final sample

included: 25 studies on CLO (that have been described in detail in our previous work [24]), 20 studies on OLZ, 20 studies on RIS, 11 studies on QUE, 6 studies on ARI, 2 studies on AMS and one study on ZIP.

Results

Clozapine

Clozapine (CLO) is the AAP with the greater body of research regarding its use as a pharmacological agent for patients with DD. Results regarding CLO have been published in a previous work of our group [24]. To summarize, several case reports, case series, retrospective and prospective studies, comparing CLO to TAP or other AAP such as RIS, OLZ and ZIP have suggested that CLO may decrease the use of nicotine, alcohol, or other drugs of abuse among patients with DD, as well as craving for these drugs. It is also associated with an improvement of psychiatric symptoms and social functioning. In addition, it has been found that a history of SUD does not influence the positive response to CLO. However, clinicians are often hesitant to use CLO as a first-line treatment due to its undesirable side effects such as the risk for agranulocytosis and seizures, and the need for frequent monitoring [24].

Olanzapine

For Olanzapine (OLZ), a search was performed combining all possible major search terms: OLZ on one hand, and Dual Diagnosis or Psychosis, Schizophrenia, Schizoaffective Disorder, Bipolar Disorder and Substance Use Disorder, on the other. Of the total of 411 articles identified, 16 were suitable for our review. Four further studies were identified after reading through the full text of studies previously found. At the end of our search 20 studies met our inclusion criteria and were selected for our review.

OLZ is an AAP with a mechanism of action similar to CLO that has also shown some promising results when it comes to treat patients with a SMI and a comorbid SUD (Table 1). Two of the first authors that pointed out the efficacy of OLZ in treating patients with a SMI and a concomitant SUD were Noordsy and O'Keefe. They found that combining OLZ with case management and psychosocial rehabilitation was effective in reducing substance abuse severity by up to 20%, as well as improving psychopathology and psychosocial functioning, in a 6-month follow-up, naturalistic study which included 70 psychotic patients, 58 of whom had a diagnosis of SCH or Schizoaffective Disorder (SAD), and a comorbid SUD [25]. These results were extended by Littrell's group. They designed a 12-month prospective, open-label study in which 30 patients meeting DSM-IV criteria for SCH (n=22) or SAD (n=8) and comorbid alcohol or cocaine dependence were included. At the end of the study, 70% of the patients achieved early, full remission and the remaining 30% early, partial remission from substance abuse, with 100% showing sustained abstinence from cocaine use. In addition, significant improvements were described in psychopathology (positive, negative and general symptoms), hopefulness and reduction in antipsychotic-related side-effects [22]. More recently, a case report showed a reduction in cocaine craving and improvements in psychotic symptoms in a male patient with SAD who previously failed to improve while treated with depot HAL [26].

Comparative studies of OLZ and TAP, however, are inconclusive, with some reporting positive results on the use of OLZ for treating patients with DD, and others that have failed to find a beneficial response to OLZ compared to TAP in DD patients. On one hand, positive results have been found in a 6-month follow-up naturalistic study in which 104 psychotic outpatients (64 with SCH, 26 with SAD and 8 with Bipolar Disorder-BD-), 30 of whom had a comorbid alcohol abuse and 22 of whom had a drug abuse were switched to OLZ (range of dosage 5-40mg/day, mean dosage 15.28mg/day), and compared to 49 patients (26 with SCH, 13 with SAD and 6 with BD), 8 of whom had a comorbid alcohol abuse and 3 of whom had a drug abuse, who continued taking TAP. Patients in the OLZ group showed significantly greater improvements on the Brief Psychiatric Rating Scale(BPRS), in some items of the Mini Psychiatric Rating Scale

Table 1: Studies with olanzapine

Author; No. of patients	Design; Duration; Intervention	Outcomes	Results
Conley et al. (1998) [39] n=60	OL 7 weeks 60 TR-SCH patients, 23 with lifetime SUD OLZ (10-25mg/d)	Psychopathology (BPRS, CGI, SANS)	No differences between patients with and without SUD in outcomes evaluated (BPRS, CGI, SANS), thus same efficacy of OLZ in patients with additional SUD
Berk et al. (1999) [31] n=30	Pros, DB, RCT 4 weeks CIPD + CAA OLZ (10mg/d) (n=15) or HAL (10mg/d) (n=10)	Psychopathology (BPRS, CGI) Side effects (SAS, dose of BIP needed)	Comparable reduction of psychopathology, but more EPS with HAL
Noordsy and O'Keefe (1999) [25] n=70	Nat study 6 months 70 PSY patients, 58 with SCH or SAD + SUD OLZ (dosage N.S.) + Psychosocial RHB	Psychopathology Substance abuse	Reduction in alcohol and drug use and psychopathology
Littrell et al. (2001) [22] n=30	Pros, OL 12 months SCH or SAD + AUD or SUD Alcohol + Cocaine 100%, Cannabis 60%, Hallucinogens 10%, Amphetamines 10% OLZ (10-25mg/d)	Psychopathology (PANSS, HHI, service utilization) Substance abuse (SSAS, UTS, BAL) Safety (BAS, SAS, AIMS)	70% of the patients achieved abstinence and 30% partial substance abuse remission. Improvement of psychopathology ($p=0.048$) and EPS ($p<0.01$)
Noordsy et al. (2001) [27] n=153	Nat study, switch design 6 months PSY patients, 29% AA and 21% SA in the OLZ group, and 16% AA and 6% SA in the TAP group OLZ (dosage N.S.)	Psychopathology (MPRS, CGI) Psychosocial functioning (CMRS) Substance use (CMRS item 2)	Significant reduction in alcohol and substance use ($p<0.001$) and improvement in psychopathology ($p<0.01$) and psychosocial functioning ($p=0.09$)
Tsuang et al. (2002) [28] n=4	Pros, DB, OL 24 weeks SCH + COA OLZ (5-20mg/d) (n=2) or HAL (5-10mg/d) (n=2)	Psychopathology Cocaine use and craving	Reduction of psychopathology and cocaine use and craving with OLZ
Sattar and Bhatia (2003) [26] n=1	CR 6 months SAD + COD Switched to OLZ from depot HAL	Psychopathology Cocaine use and craving	Improvement in psychopathology and reduction in craving and substance use achieving abstinence
Green et al. (2004) [40] n=262	MC, Pros, DB, RCT 12 weeks FE-PSY, 37% with lifetime SUD and 7.6% with current abuse Cannabis 28%, Alcohol 21%, Cocaine 6%, Hallucinogens 5%, Opioids 1% OLZ (5-20mg/d, mean dosage 10.2mg/d) or HAL (2-20mg/d, mean dosage 4.8mg/d)	Psychopathology (PANSS, MADRS, CGI) Psychosocial and vocational functioning Substance use	Among the SUD-Group 27% were responders (23% OLZ vs. 31% HAL) as compared to 35% of non-SUD Group (38% OLZ vs. 32% HAL) Patients with comorbid AUD showed poorer response to OLZ (27%) than to HAL (9%) ($p<0.02$) Higher drop-out rate among SUD patients receiving HAL (49%) compared to OLZ (23%) ($p<0.04$)
Leelahanj et al. (2005) [30] n=58	Pros, DB, RCT 4 weeks AMP Psychosis OLZ (5-20mg/d) (n=29) vs. HAL (5-20mg/d) (n=29)	Clinical response Safety (SAS, BAS)	93% of the OLZ patients and 79.3% of the HAL patients clinically improved at endpoint. These differences were not statistically significant ($p=0.25$). The differences of mean change in the SAS significantly favored OLZ ($p<0.01$). The differences of mean change in the BAS favored OLZ ($p=0.02$)
Sayers et al. (2005) [32] n=24	Pros, DB, RCT 6 months SCH + COA OLZ (5-20mg/d) or HAL (5-20mg/d)	Psychopathology (BPRS, SAPS, SANS, HRSD) Cocaine use (UTS) Cocaine craving (VAS)	No significant differences in regard to cocaine use (UTS), although there was a significant reduction with OLZ and a significant increase with HAL of cocaine use compared to the amount at baseline ($p<0.05$). There was a significant increase of craving with OLZ ($p<0.05$). No differences in psychopathology were observed
Smelson et al. (2006) [29] n=31	Pros, DB, RCT 6 weeks SCH + SUD Cocaine 100% OLZ (5-20mg/d) or HAL (5-20mg/d)	Cocaine use (UTS) Cocaine craving (VCCQ) Psychopathology (PANSS)	Significant greater reduction of craving in the OLZ group ($p=0.04$). No significant differences in cocaine use and psychopathology
Stuyt et al. (2006) [38] n=55	Ret, OL 2 years SCH (61%) or SAD (54%) + SUD or AUD Polyvalent SUD (34%), Alcohol (27%), Cocaine (16%), other SUD (21%) OLZ (2.5-30mg/d, mean dosage 18.7mg/d) (n=15) or RIS (n=16) (2-8mg/d, mean dosage 3.9mg/d) or ZIP (60-160mg/d, mean dosage 132.8mg/d) (n=10) or TAP depot (n=10)	Retention rate Success in completing a DD Programme	RIS and ZIP had higher rates of retention compared to OLZ ($p=0.0002$ and $p=0.004$, for RIS and ZIP respectively) and TAP ($p=0.003$ and $p=0.03$, for RIS and ZIP, respectively). There were no significant differences in the length of stay were found between RIS and ZIP. 88% of RIS patients and 64% of ZIP completed the DD program, whereas only 40% of patients taking TAP and 33% of patients in the OLZ successfully completed the program. This difference in successful completion was statistically significant for RIS vs. OLZ ($p=0.02$) and TAP ($p=0.017$)
Gerra et al. (2007) [23] n=61	MC, Pros, OL 12 weeks Patients on MET or BUP treatment SSD + HD OLZ or HAL (N.S. dose)	Retention in treatment Psychopathology (SCL-90-R) Drug use (UTS) Craving reduction	Patients in the OLZ group remained significantly longer in treatment ($p=0.001$), had a significant superior decrease in the SCL-90 score ($p=0.001$) and more negative UTS ($p=0.04$)
Akelere and Levin (2007) [33] n=28	P, DB, RCT 14 weeks SCH + SUD Cannabis (93%), Cocaine (78%), Alcohol (4%) OLZ (5-20mg/d) or RIS (3-9mg/d)	Psychopathology (PANSS, HDRS, CGI) Substance use and craving (MCR, CCR, QSUI, UTS) Side effects (AIMS, SAS)	Trend for a greater reduction of cocaine positive urines and significantly less self-reported days of use (for any drug) ($p=0.02$) in the OLZ group. There was a significant reduction in cannabis craving in the RIS group, with no modifications in the OLZ group ($p=0.04$). There were no significant differences between groups in cocaine craving

Swart et al. (2008) [41] n=1432	Pros, RCT 18 months SCH, 643 with illicit SUD and 789 without illicit SUD Flexible doses of OLZ (mean dosage 20.1mg/day) (n=330) or QUE (mean dosage 538.9mg/day) (n=329) or RIS mean dosage 3.9mg/day) (n=333) or ZIP (112.8mg/day) (n=183) or TAP (n=257)	Discontinuation rate and time to discontinuation Psychopathology (PANSS, CGI, episodes of hospitalization)	Among non-users, OLZ was associated with significantly lower discontinuation rates and time to discontinuation compared to QUE ($p<0.001$), RIS ($p=0.01$), TAP ($p<0.001$), but not ZIP. Among illicit-drug users, no significant differences between treatment groups were found regarding discontinuation rates and time to discontinuation. OLZ group was associated with a greater psychopathological improvement as measured by the PANSS, CGI and number of hospitalizations, in both illicit-drug users and non-users, compared to the other treatment groups
Van Nimwegen et al. (2008) [34] n=128	MC, Pros, DB, RCT 6 weeks RO-SCH, 41.3% of whom used cannabis OLZ (5-20mg/d, mean dosage 11.1mg/d) (n=63) or RIS (1-5mg/d, mean dosage 3mg/d) (n=65)	Subjective well-being (SWN) Cannabis craving (OCDUS, DDQ)	Similar improvements in subjective well-being were found in both groups. Similar decrease in craving for cannabis was found in both treatment conditions
Kim et al. (2010) [37] n=139	Pros, RCT 8 weeks SCH + ND OLZ (n=32) or RIS (n=41) or ARI (n=31) or HAL (n=35)	Psychopathology (SANS, SAPS) EPS (AIMS) Severity of ND and cigarette craving (FTQ)	No significant differences in the degrees of change in psychiatric symptoms among the four groups. At 8 weeks, HAL was associated with higher EPS ($p<0.01$). HAL was associated with less reduction in the severity of ND ($p<0.01$) and cigarette craving ($p<0.01$) compared to AAP. Among AAP, RIS increased cigarette craving ($p=0.03$), there were no significant changes in ND severity and cigarette craving associated with OLZ, and ARI showed a reduction in both severity of ND and cigarette craving ($p<0.01$)
Sevy et al. (2011) [35] n=49	Pros, RCT 16 weeks FE-SCH (SCH, SCHD, SAD) + CAUD OLZ (2.5-20mg/d, mean dosage 15mg/d) (n=28) or RIS (1-6mg/d, mean dosage 4mg/d) (n=21)	Psychopathology (SADS-C+PD, CGI, SANS) Substance Use (SUQ)	OLZ group did not differ significantly from RIS group in initial response rates of positive symptoms and rates of cannabis use or alcohol use. Negative symptoms (global asociality-anhedonia) improved over time but did not differ between groups
Machielsen et al. (2012) [36] n=123	MC, Long, Nat study 6 years SCH, SCHD, SAD, DED or PDNOS + CAD CLO (mean dosage 350mg/d) (n=23) or RIS (mean dosage 3.46mg/d) (n=48) or OLZ (mean dosage 13.78mg/d) (n=52)	Cannabis craving (OCDUS-CAN)	There were significant differences in craving between RIS and CLO ($p=0.001$), and between RIS and OLZ ($p=0.025$), in favour of CLO and OLZ, which were associated with less craving. No significant differences were found between CLO and OLZ
Sani et al. (2013) [42] n=80	Pros, Obs, CC 8 weeks BD, 40 with SUD Add-on OLZ (5-20mg/d, mean dose 17.31mg/d)	Remission, response and relapse rates (YMRS, HDRS, BPRS) Days of substance abuse (TLFB) Craving (VAS)	Patients with SUD received significantly higher doses of OLZ compared to non-substance abusers. Remission, response and relapse rates were similar, with mood rating scores dropping significantly from baseline to end-point in both groups ($p<0.01$). In the SUD group there was a significant reduction in days of substance abuse ($p<0.01$) and craving ($p<0.03$)

AA: Alcohol Abuse, AIMS: Abnormal Involuntary Movement Scale, AMP: Amphetamine, ARI: Aripiprazole, AUD: Alcohol Use Disorders, BAL: Blood Alcohol Levels, BAS: Barnes Akathisia Scale, BD: Bipolar Disorder, BIP: Biperiden, BPRS: Brief Psychiatric Rating Scale, BUP: Buprenorphine, CAA: Cannabis abuse, CAD: Cannabis Dependence, CAUD: Cannabis Use Disorders, CC: Case-Control, CCR: Cocaine Craving Report, CGI: Clinical Global Impression, CIPD: Cannabis Induced Psychotic Disorder, CLO: Clozapine, CMRS: Case Manager Rating Scale, COA: Cocaine Abuse, COD: Cocaine Dependence, DB: Double-blinded, DED: Delusional Disorder, DDQ: Drug Desire Questionnaire, EPS: Extrapyramidal symptoms, FE-PSY: First Episode of Psychosis, FTQ: Fagerstrom Tolerance Questionnaire, HAL: Haloperidol, HDRS: Hamilton Depression Rating Scale, HD: Heroin Dependence, MADRS: Montgomery-Asberg Depression Rating Scale, MC: Multicenter, MET: Methadone, MPRS: Mini Psychiatric Rating Scale, HHI: Herth Hope Index, MCR: Marijuana Craving Report, ND: Nicotine Dependence, NAT: Naturalistic, N.S: Not specified, Obs: Observational, OCDUS: Obsessive Compulsive Drug Use Scale, OCDUS-CAN: Obsessive Compulsive Drug Use Scale, cannabis version, OL: Open label, OLZ: Olanzapine, PANSS: Positive and Negative Syndrome Scale, PDNOS: Psychotic Disorder NOS, Pros: Prospective, PSY: Psychotic Disorder, QSIUL: Quantitative Substance Use Inventory, RCT: Randomized controlled trial, RHB: Rehabilitation, RIS: Risperidone, RO-SCH: Recent Onset Schizophrenia, SA: Substance Abuse, SAD: Schizoaffective Disorder, SADS-C+PD: Schedule for Affective Disorders and Schizophrenia- Change Version with psychosis and disorganization items, SANS: Scale for the Assessment of Negative Symptoms, SAPS: Scale for the Assessment of Positive Symptoms, SAS: Simpson Angus Scale, SCH: Schizophrenia, SCHD: Schizophreniform Disorder, SCL-90-R: Symptoms Checklist 90, SSAS: Schizophrenia/Substance Abuse Schedule, SSD: Schizophrenic Spectrum Disorders, SUD: Substance Use Disorder; SUQ: Substance Use Questionnaire, SWN: Subjective Well Being Under Neuroleptics Scale, TAP: Typical Antipsychotics, TLFB: Timeline Follow-Back, TR-SCH: Treatment Resistant Schizophrenia, UTS: Urine Toxicological Screens, VAS: Visual Analogue Scale, VCCQ: Voris Cocaine Craving Questionnaire, YMRS: Young Mania Rating Scale.

(MPRS) and in the Clinical Global Impression (CGI), and significant improvements in both alcohol ($p<0.01$) and drug ($p=0.01$) outcomes compared to the control group. However, this study was limited because the OLZ group and the control group were not comparable in terms of the rates of substance use [27]. A wide range of studies have focused on the use of OLZ for treating Cocaine Use Disorders (COUD), some with positive findings. In a small pilot double-blinded trial that included 4 SCH patients with comorbid cocaine abuse, who were assigned to receive OLZ (5-20mg/day) (n=2) or HAL (5-10mg/day) (n=2), OLZ was associated with significant reductions in psychopathology and cocaine use and craving [28]. In addition, Smelson et al. conducted a 6-week, prospective, double-blind, randomized controlled trial using a cue-exposure paradigm, in which 31 SCH patients with comorbid cocaine dependence were assigned to receive OLZ (5-20mg/day) or HAL (5-20mg/day). OLZ was associated with a significant reduction in the cue elicited-craving ($p=0.04$), and patients in the OLZ group had lower scores in the Positive and Negative Symptoms Scale (PANSS), General Psychopathology Subscale scores ($p=0.07$) and fewer positive urine toxicology screens

(UTS) (12.5% and 40%, respectively, $p=0.20$) compared to patients in the HAL group, although differences in the two last outcomes were not statistically significant [29]. There is also a 4-week, double-blind comparison study of OLZ with HAL in the treatment of amphetamine psychosis [30]. This study included 58 patients that suffered from an amphetamine psychosis episode who were randomly assigned to OLZ (n=29) (5-20mg/day) or HAL (n=29) (5-20mg/day). Although no significant differences were found in terms of clinical response between OLZ and HAL ($p=0.25$), and both treatments were effective since the first week, with 93% of the patients on OLZ vs. 79.3% of the patients on HAL showing a clinical improvement at the study endpoint, OLZ was superior to HAL in treatment safety with lower frequency and severity of EPS [30]. Another group of comorbid pathology where OLZ has shown to have a potential beneficial effect in terms of increasing retention and negative UTS, and improving psychopathology and tolerability, is in patients with a Schizophrenic Spectrum Disorder (SSD) and concomitant heroin dependence. In a 12-week, prospective, observational trial of opioid agonist substitution treatment in combination with OLZ (n=35) or HAL (n=26), which

included 61 patients who met DSM-IV criteria for heroin dependence (HD) and the criteria for SSD (SCH, Schizotypal, SAD or BD), OLZ was associated with significantly greater rates of retention in treatment ($p<0.001$), greater improvements in psychopathology, measured by a decrease in Symptoms Checklist-90 total scores ($p<0.001$), greater rates of early full substance abuse remission and partial substance abuse remission achievement ($p=0.04$), and lesser adverse events [23].

On the other hand, despite these positive results, several studies have not found statistically significant differences between OLZ and TAP in treating patients with a SMI and concomitant SUD. In a randomized, double-blind, controlled trial in which 30 patients who met DSM-IV criteria for Cannabis Induced Psychotic Disorder (CIPD) were randomly allocated to receive either OLZ (10mg/day) ($n=15$) or HAL (10mg/day) ($n=15$), no significant differences between the two groups were found in terms of psychopathology as measured by the BPRS ($p=0.70$) and the CGI ($p=0.21$), although HAL was associated with significantly more EPS, as measured by the Simpson Angus Scale (SAS) ($p=0.014$) and the dose of biperiden used ($p=0.027$) [31]. In addition, in a prospective, double-blind, randomized controlled trial with a sample of 24 SCH patients and current COA in the last 6 months, who were allocated either OLZ (10-20mg/day) or HAL 10-20mg/day), no significant differences in the proportion of positive UTS were found and, unexpectedly, craving for cocaine was rated as significantly lower by patients on HAL than those on OLZ ($p<0.05$). OLZ and HAL were equivalent in treating psychotic and depressive symptoms and, with exception of abnormal movements, which were significantly higher in the HAL group ($p<0.05$), both treatments were equally tolerated [32].

Comparative studies with other AAP have focused nearly exclusively on comparing OLZ to RIS, with most studies reporting a similar efficacy between both treatments for DD patients [33-35], and some finding a beneficial response of OLZ over RIS in treating this population [36]. The efficacy of OLZ (5-20mg/day) ($n=14$) and RIS (3-9mg/day) ($n=14$) was evaluated in a 14-week double blind, randomized-controlled study with a sample of 28 patients with SCH or SAD and current cocaine and/or marijuana abuse or dependence. The study had three phases: a two-week assessment phase, a two-week cross-taper phase onto OLZ/RIS, and a ten-week period of maintenance on OLZ/RIS. The proportion of positive UTS decreased over time for both groups with a trend towards a greater reduction for the OLZ group compared to the RIS group. In addition, patients in the OLZ group reported, on average, significantly fewer days of use than patients in the RIS group ($p=0.02$). In the last six weeks, reductions of cannabis craving were more likely for the RIS group compared to the OLZ group ($p=0.04$), although there was no group difference in the proportion of negative cannabis UTSs [33]. In addition, van Nimwegen et al. carried out a 6 week, double-blind randomized trial which included 128 young adults with recent onset SCH or related disorders, 41.32% of whom had a comorbid cannabis use disorder (CAUD). OLZ and RIS were found to be equally effective in terms of improving subjective well-being and decreasing cannabis craving [34]. These results were replicated in an additional a 16-week, randomized, controlled trial, with a sample of 49 first-episode patients with a diagnosis of SCH, Schizophreniform Disorder (SCHD) or SAD and a co-occurring lifetime diagnosis of CAUD, who were assigned to receive treatment either with OLZ ($n=28$) or RIS ($n=21$). No significant differences were observed in the initial response rates of positive and negative symptoms [35]. Finally, a multisite, longitudinal, naturalistic cohort study that included 123 patients who met criteria for a non-affective psychotic disorder and a concomitant CAD, found that cannabis craving, assessed with the Obsessive Compulsive Drug Use Scale (OCDUS) cannabis specific version (OCDUS-CAN), was significantly ($p=0.025$) less in patients treated with OLZ (mean dosage 13.78mg/day) ($n=52$) compared to patients treated with RIS (mean dosage 3.46mg/day) ($n=48$), with no significant differences in cannabis craving compared to CLO (mean dosage 350mg/day) ($n=23$). OLZ was considered an intermediate agent between RIS and CLO in treating cannabis craving [36]. However, OLZ has been found to be less effective compared to other

AAP in two studies [37,38]. Recently, Kim et al. have conducted an 8-week, prospective trial where OLZ has shown intermediate results compared to other AAP. The study included 139 SCH patients with comorbid ND who were randomized to receive OLZ ($n=32$), RIS ($n=41$), ARI ($n=31$) or HAL ($n=35$). When analyzing severity of ND and cigarette craving, OLZ was not associated with significant changes in these two variables, whereas RIS increased cigarette craving ($p=0.03$), and ARI was associated with a reduction in both, severity of ND and cigarette craving ($p<0.01$) [37]. In addition, in a retrospective study of 95 patients with schizophrenic spectrum disorder and concomitant SUD, OLZ (mean dosage 18.7mg/day) ($n=15$) was associated with a shorter length of stay and lower rates of successful treatment completion, similar to TAP ($n=10$), compared to RIS (mean dosage 3.9mg/day) ($n=16$) and ZIP (mean dosage 132.8mg/day) ($n=15$) [38].

Regarding studies that have evaluated how a history of SUD influences the response to OLZ, studies are contradictory. On one hand, in a 7-week, open label study that included 60 TR-SCH patients of whom 23 (38%) had a concomitant history of substance abuse, switching to OLZ up to 25mg/day resulted in similar outcomes between substance-abusing patients and non-substance abusers in the total BPRS, CGI and negative symptoms, as well as no increase in side effects, despite the fact that at baseline patients who had previously abused substances had lower CGI scores, less negative symptomatology and a higher rate of tardive dyskinesia [39]. However, on the other hand, Green et al. have reported opposite results. They carried out a multicentre, double-blind, controlled trial, with a sample of 262 patients with a first-episode SCH, SAD or SCHD, 37% of whom had a comorbid lifetime SUD and 7.6% a current abuse, being the substances used cannabis (28%), alcohol (21%), cocaine (6%), hallucinogens (5%) and opiates (1%). Patients were randomized to receive either OLZ (5-20mg/day) or HAL (2-20mg/day). At 12-week follow-up, 96 patients with a comorbid SUD were compared to 166 patients without such comorbidity and it was found that among the SUD group, 27% of the patients were responders (23% in the OLA and 31% in the HAL group), as compared to the 35% of the patients in the non-SUD group (38% for OLZ and 32% for HAL), and that AUD status significantly affected the probability of a response, with 27% of the patients with alcohol use from the HAL group responding to treatment as compared with only 9% of the patients of the OLZ group ($p<0.02$). The authors pointed out, nevertheless, that there were significant higher drop-out rates in the HAL group for patients with a SUD, so that only 51% of the patients in the HAL group completed the study compared to 77% of patients in the OLZ group ($p<0.04$) [40]. In addition, a sub-analysis of the Clinical Antipsychotic Trials of Intervention effectiveness (CATIE) project, which include 1432 SCH patients, 643 illicit drug users and 789 non-users, who were randomized to receive flexible doses of OLZ (mean dosage 20.1mg/day) ($n=330$), QUE (mean dosage 538.9mg/day) ($n=329$), RIS mean dosage 3.9mg/day) ($n=333$), ZIP (112.8mg/day) ($n=183$) and a TAP ($n=257$) reported that among non-users, OLZ was associated with significantly lower discontinuation rates and time to discontinuation compared to QUE ($p<0.001$), RIS ($p=0.01$), TAP ($p<0.001$), but not ZIP. However, this apparent superiority of OLZ over the other treatments was attenuated and, in the illicit-drug users group, no significant differences between treatment groups were found regarding discontinuation rates and time to discontinuation. OLZ group was associated with a greater psychopathological improvement as measured by the PANSS, CGI and number of hospital admissions, in both illicit-drug users and non-users, compared to the other treatment groups. The authors concluded that the lesser adherence to OLZ among illicit-drug users could be due to idiosyncratic reasons [41].

Only one Italian group has focused on the treatment of patients with BD and a concomitant SUD. They carried out an 8-week, prospective, observational, case-control study with a sample of 80 hospitalized patients with a diagnosis of BD and a current manic or mixed episode, 40 of whom had a SUD and 40 of whom were non-substance abusers. They received OLZ (5-20mg/day, mean dose

17.31mg/day) through an add-on method. Although the SUD group received significantly higher doses of OLZ compared to the non-substance abusers ($p<0.002$), remission, response and relapse rates were similar, with mood rating scores dropping significantly from baseline to end point in both groups ($p<0.001$). In addition, in the SUD group, there was a significant reduction in days of substance abuse ($p<0.01$) and craving ($p<0.03$) [42].

To summarize, regarding OLZ's efficacy in the treatment of DD, results are inconsistent and inconclusive. Although most of the studies agree on the effectiveness of OLZ for treating psychotic symptoms and the only study that has been carried out in bipolar population found OLZ to be effective in the treatment of mood symptoms, results regarding substance use and craving are contradictory, with some studies reporting an improvement in drug use and craving parameters, and others that do not find significant improvements or even a worsen in these parameters. In addition, results should be interpreted with caution due to methodological issues that are described in detail in the discussion section. Regarding safety and tolerability, in those studies in which they were explored [21,23,30-33,35], OLZ demonstrated to be safe in general. Compared to TAP and RIS, OLZ was associated with less EPS [21,30-33]. Common side effects associated to OLZ were sedation and weight gain [21,23,35], although these side effects did not affect retention rates.

Risperidone

Regarding risperidone (RIS), a search was performed combining all possible major search terms: RIS on one hand, and Dual Diagnosis or Psychosis, Schizophrenia, Schizoaffective Disorder, Bipolar Disorder and Substance Use Disorder, on the other. Of the total of 391 articles identified, 17 were suitable for our review. Three further studies were identified after reading through the full text of studies previously found. At the end of our search, 20 studies met our inclusion criteria and were selected for our review.

Several case reports, case series, open studies and controlled studies have evaluated the efficacy of RIS in treating patients with DD (Table 2). The first to report on the effectiveness of RIS in treating patients with a SMI and concomitant SUD was Huang, who conducted a 3-month follow-up study in which 7 patients meeting criteria for SCH and AD

were successfully treated with RIS and exhibited a decrease in alcohol consumption [43]. Subsequently, Albanese et al. presented the results of a small study in which RIS was given as an adjunctive therapy at a dosage ranging from 2 to 8mg/day (mean dosage 3.6mg/day) to 14 patients with SMI (Major Depression with psychotic symptoms, n=8; BD, n=3; Posttraumatic Stress Disorder (PTSD), n=3; SCH, n=1; SAD, n=1) and a concomitant SUD (alcohol, n=5; polysubstance, n=3; alcohol and cocaine, n=3; cocaine, n=2; opioids, n=1). It was found that 11 out of 14 patients exhibited a significant clinical improvement in behaviour and symptoms within 4 weeks of the beginning of the treatment [44]. In a more recent study by the same author, an open-label, naturalistic study in which 16 male patients with cocaine dependence and comorbid psychiatric disorder were started on RIS (mean starting dose 2.3mg/day), it was described that 81% of the patients were rated as improved or much improved on the CGI scale, and all patients reported mild or no craving at the end of the study [45]. Two-month therapy with RIS (8mg/day) was also found to be effective in reducing cocaine craving and cocaine use, as well as psychiatric symptoms, after switching from TAP in 2 SCH patients with comorbid cocaine dependence [46]. Furthermore, RIS was also found to be effective in a case report of a 23-year-old male diagnosed with SCH and with a 5-year history of opioids and stimulants dependence. He was initially treated with OLZ 20mg/day for a period of 6 weeks without a positive response. After being switched to RIS 4mg/day, psychopathology and substance use subsided, and the patient reported diminution of craving and relief from psychopathology-related anxiety. This asymptomatic state lasted for the 10 months follow-up [47]. A Spanish group conducted a 6-month follow-up study with a sample of 180 psychotic patients and opioid abuse or dependence. RIS (0.5-12mg/day) improved disability, psychotic symptoms and tolerability of these patients. RIS also reduced the rates of opioid abuse patients from 39% at baseline to 18% at month 6 [48]. In addition, another Spanish group has reported a significant reduction in the rates of patients abusing cocaine (from 98.7% to 17.7%), cannabis (from 52.1% to 27.1%) and alcohol (from 68.5% to 33.3%) in a 6-month follow-up, open label, prospective, multicenter study with a sample of 146 patients that met criteria for a psychotic disorder and stimulants abuse or dependence [49,50].

Two comparative studies with TAP have also found RIS to be useful in treating patients with a DD. The first one was a 6-week,

Table 2: Studies with risperidone

Author; No. of patients	Design; Duration, Intervention	Outcomes	Results
Huang (1996) [43] n=7	Nat study 3 months 7 SCH + AD RIS (dose N.S.)	Alcohol use	Reduction in alcohol use
Berk et al. (2000) [54] n=30	Pros, DB, RCT 4 weeks CIPD + CAA RIS (6mg/d) (n=15) or HAL (10mg/d) (n=15)	Psychopathology (BPRS) Side effects (EPS)	No differences in the reduction of psychopathology, no differences in EPS
Gupta and Basu (2001) [47] n=1	CR 10 months SCH + OD RIS (4mg/day)	Psychopathology Substance use Craving	Reduction of psychopathology, substance use and craving
Albanese (2001) [44] n=14	Nat study, CS 9 weeks 7 SCH and SAD + SUD Alcohol (57%), Cocaine (36%), Opiate (7%), polyvalent (21%) Add-on RIS (2-8mg/d, average 3.6mg/d)	Clinical response Tolerability	11 of 14 patients showed clinical improvement. RIS was well tolerated
Casas et al. (2001) [48] n=180	OL 6 months PSY + OA or OD RIS (0.5-12mg/d, average 2.4mg/d)	Psychopathology (BPRS, CGI, DDS-SV) Opiate use Side effects (UKU)	Improvement in psychopathology and reduction in opiate use from 39% to 18% Reduction in neurological side effects ($p<0.0001$)
Bobes et al. (2001) [49] n=146	Pros, MC, OL 6 months PSY + SA or SD RIS (N. S. dose)	Psychopathology (BPRS, CGI, DAS) Side effects (UKU) Cocaine and cannabis use	Rates of patients using cocaine decreased from 89.7% to 17.7% and rates of patients using cannabis decreased from 52.1% to 27.1%, being these differences statistically significant ($p<0.0001$)
Gutierrez et al. (2001) [50] n=146		Alcohol use	Rates of patients using alcohol was reduced from 68.5% to 33.3%, being these differences statistically significant ($p<0.0001$)

Smelson et al. (2002) [51] n=18	Pros, OL 6 weeks SCH + SUD Cocaine (100%) RIS (6mg/d) (n=8) or TAP (n=10)	Psychopathology (PANSS) Substance use Substance craving (VCCQ)	Reduction in psychopathology (trend towards significance in the PANSS negative ant total subscale), of substance use and craving
Tsuang et al. (2002) [28] n=2	CR 2 months SCH + COD RIS (8mg/d)	Psychopathology Cocaine use and craving	After switching from TAP to RIS there were no changes of craving and cocaine use, as well as of psychopathology
Green et al. (2003) [55] n=41	Ret, OL 12 months SCH or SAD + SUD or AUD Alcohol (78%), Cannabis (51%) RIS (average 3.9mg/d) (n=8) or CLO (average 440mg/d) (n=33)	Substance use	Significantly more patients stopped SU with CLO (54%) than with RIS (12.5%)
Rubio et al. (2006) [52] n=115	MC, OL, RCT 24 weeks SCH + SUD LAR (47mg/2 weeks) + RIS (3.4mg/d) (n=57) or depot ZUC (200mg/3 weeks) + Oral ZUC (15mg/d) (n=58)	Substance use (UTS) Psychopathology (PANSS) Side effects Compliance	Significantly less drug use (fewer positive UTS), greater improvement in psychopathology (PANSS), less EPS and better compliance with LAR
Stuyt et al. (2006) [38] n=55	Ret, OL 2 years SCH (61%) or SAD (54%) + SUD or AUD Polyvalent SUD (34%), Alcohol (27%), Cocaine (16%), other SUD (21%) OLZ (2.5-30mg/d, mean dosage 18.7mg/d) (n=15) or RIS (n=16) (2-8mg/d, mean dosage 3.9mg/d) or ZIP (60-160mg/d, mean dosage 132.8mg/d) (n=10) or TAP depot (n=10)	Retention rate Success in completing a DD Programme	RIS and ZIP had higher rates of retention compared to OLZ (p=0.0002 and p=0.004, for RIS and ZIP respectively) and TAP (p=0.003 and p=0.03, for RIS and ZIP, respectively). No significant differences in length of stay were found between RIS and ZIP. 88% of RIS patients and 64% of ZIP completed the DD program, whereas only 40% of patients taking TAP and 33% of patients in the OLZ successfully completed the program. This difference in successful completion was statistically significant for RIS vs OLZ (p=0.02) and TAP (p=0.017)
Albanese and Suh (2006) [45] n=16	Nat study N.S. duration DD (N.S.) + COD RIS (mean dose 2.3mg/d)	Overall functioning (CGI) Craving Safety (AIMS) Compliance	81% of the patients improved in the CGI scale, 100% of the patients reported mild or no craving, 88% completed the programme
Akelere and Levin (2007) [33] n=28	P, DB, RCT 14 weeks SCH + SUD Cannabis (93%), Cocaine (78%), Alcohol (4%) OLZ (5-20mg/d) or RIS (3-9mg/d)	Psychopathology (PANSS, HDRS, CGI) Substance use and craving (MCR, CCR, QSUI, UTS) Side effects (AIMS, SAS)	Trend for a greater reduction of cocaine positive urines and significantly less self-reported days of use (for any drug) (p=0.02) in the OLZ group. There was a significant reduction in cannabis craving in the RIS group, with no modifications in the OLZ group (p=0.04). There were no significant differences between groups in cocaine craving
Kim et al. (2008) [56] n=61	Pros, Nat, Obs 2 years SCH + AUD CLO (mean dosage 423.6mg/d) (n=25) or RIS (mean dosage 7.6mg/d) (n=36)	Hospitalization rates Time to hospitalization	CLO treated patients were readmitted to hospital significantly later than the RIS treated patients (p=0.045). At the end of the study, 75% of the RIS treated patients had been admitted to the hospital, compared to 48% of patients of the CLO treated patients
Van Nimwegen et al. (2008) [34] n=128	MC, Pros, DB, RCT 6 weeks RO-SCH, 41.3% of whom used cannabis OLZ (5-20mg/d, mean dosage 11.1mg/d) (n=63) or RIS (1-5mg/d, mean dosage 3mg/d) (n=65)	Subjective well-being (SWN) Cannabis craving (OCDUS, DDQ)	Similar improvements in subjective well-being were found in both groups. Similar decrease in craving for cannabis was found in both treatment conditions
Kim et al. (2010) [37] n=139	Pros, RCT 8 weeks SCH + ND OLZ (n=32) or RIS (n=41) or ARI (n=31) or HAL (n=35)	Psychopathology (SANS, SAPS) EPS (AIMS) Severity of ND and cigarette craving (FTQ)	No significant differences in the degrees of change in psychiatric symptoms among the four groups. At 8 weeks, HAL was associated with higher EPS (p<0.01). HAL was associated with less reduction in the severity of ND (p<0.01) and cigarette craving (p<0.01) compared to AAP. Among AAP, RIS increased cigarette craving (p=0.03), there were no significant changes in ND severity and cigarette craving associated with OLZ, and ARI showed a reduction in both severity of ND and cigarette craving (p<0.01)
Sevy et al. (2011) [35] n=49	Pros, RCT 16 weeks FE-SCH (SCH, SCHD, SAD) + CAUD OLZ (2.5-20mg/d, mean dosage 15mg/d) (n=28) or RIS (1-6mg/d, mean dosage 4mg/d) (n=21)	Psychopathology (SADS-C+PD, CGI, SANS) Substance Use (SUQ)	OLZ group did not differ significantly from RIS group in initial response rates of positive symptoms and rates of cannabis use or alcohol use. Negative symptoms (global sociality-anhedonia) improved over time but did not differ between groups
Machielsen et al. (2012) [36] n=123	MC, Long, Nat study 6 years SCH, SCHD, SAD, DED or PDNOS + CAD CLO (mean dosage 350mg/d) (n=23) or RIS (mean dosage 3.46mg/d) (n=48) or OLZ (mean dosage 13.78mg/d) (n=52)	Cannabis craving (OCDUS-CAN)	There were significant differences in craving reduction between RIS and CLO (p=0.001), and between RIS and OLZ (p=0.025), in favour of CLO and OLZ. No significant differences were found between CLO and OLZ

Farnia et al. (2014) [53] n=45	Pros, DB, RCT 1 year follow-up AMP induced psychosis RIS (4mg/d) or ARI (15mg/d)	Psychopathology (SANS, SAPS)	SANS and SAPS scores decreased significantly in both groups. Mean SAPS score reduction was greater in the RIS group ($p < 0.001$). Mean SANS score reduction was greater in the ARI group ($p = 0.08$)
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AD: Alcohol Dependence, AIMS: Abnormal Involuntary Movement Scale, AMP: Amphetamine, ARI: Aripiprazole, AUD: Alcohol Use Disorder, BPRS: Brief Psychiatric Rating Scale, CAA: Cannabis Abuse, CAD: Cannabis Dependence, CAUD: Cannabis Use Disorders, CCR: Cocaine Craving Report, CGI: Clinical Global Impression, CIPD: Cannabis Induced Psychotic Disorders, CLO: Clozapine, COD: Cocaine Dependence, CR: Case Report, CS: Case Series, DAS: Depression Anxiety Stress Scale, DB: Double Blinded, DED: Delusional Disorder, DD: Dual Diagnosis, DDQ: Drug Desire Questionnaire, DDSS-SV: Desire to Drink Scale, Spanish Version, EPS: Extrapyramidal Side Effects, FE-SCH: First Episode of Schizophrenia, FTQ: Fagerstrom Tolerance Questionnaire, HAL: Haloperidol, LAR: Long-acting RIS, MC: Multicenter, MCR: Marijuana Craving Report, ND: Nicotine Dependence, Nat: Naturalistic, N.S.: Not specified, OA: Opioid Abuse, HDRS: Hamilton Depression Rating Scale, OCDUS: Obsessive Compulsive Drug Use Scale, OCDUS-CAN: Obsessive Compulsive Drug Use Scale, Cannabis Version, OD: Opioid Dependence, OL: Open Label, OLZ: Olanzapine, PANSS: Positive and Negative Symptoms Rating Scale, PDNOS: Psychotic Disorder NOS, PICD: Psychotic Induced Cannabis Disorder, Pros: Prospective, PSY: Psychotic Disorder, QSUI: Quantitative Substance Use Inventory, RCT: Randomized Controlled Trial, Ret: Retrospective, RIS: Risperidone, RO-SCH: Recent Onset Schizophrenia, SA: Stimulant Abuse, SADS-C+PD: Schedule for Affective Disorders and Schizophrenia- Change Version with psychosis and disorganization items, SANS: Scale for the Assessment of Negative Symptoms, SAPS: Scale for the Assessment of Positive Symptoms, SAS: Simpson Angus Scale, SD: Stimulant Dependence, SAD: Schizoaffective Disorder, SCH: Schizophrenia, SCHD: Schizophreniform Disorder, SU: Substance Abuse, SUD: Substance Use Disorder, SUQ: Substance Use Questionnaire, SWN: Subjective Well-Being Under Neuroleptics scale, TAP: Typical Antipsychotics, UKU: Udvælg for Undersøgelse, UTS: Urine Toxicological Screenings, VCCQ: Voris Cocaine Craving Questionnaire, ZIP: Ziprasidone, ZUC: Zuclopentixol.

open-label, pilot study that compared RIS (up to 6mg/day) (n=8) with TAP (n=10) in a sample of 18 withdrawn cocaine-dependent SCH patients. It was found that individuals treated with RIS had significantly less cue-elicited craving on the intensity ($p=0.005$) and depression ($p=0.031$) items, and less substance abuse relapse (12.5% in the RIS group, 70% in the TAP group, $p=0.025$) at study completion compared to TAP. In addition, they showed a trend towards greater reduction in negative ($p=0.068$) and global ($p=0.079$) symptoms of SCH [51]. The second one was a 6-month follow-up, open-label, randomized, controlled study in which 115 patients with SCH and SUD were allocated in two treatment groups: Long-acting RIS (LAR) (47.2mg per 15 days and 3.4mg/day of oral RIS) (n=57) or zuclopentixol depot (ZUC) (200mg/ 21 days and 15mg/day of oral ZUC) (n=58). LAR patients presented significantly fewer positive UTS ($p=0.005$), showed improved scores on the PANSS ($p=0.02$) and had a better compliance with a Substance Abuse Management Program ($p=0.001$) [52]. In addition, when compared to other AAP, as said above, RIS (mean dosage 3.9mg/day) (n=16), together with ZIP (mean dosage 132.8mg/day) (n=15), was found to be associated with a longer length of stay compared to OLZ (mean dosage 18.7mg/day) ($p=0.0002$ and $p=0.004$, for RIS and ZIP respectively) (n=15) and TAP (n=10) ($p=0.003$ and $p=0.03$, for RIS and ZIP, respectively), in a retrospective study of 95 patients with schizophrenic spectrum disorder and concomitant SUD. Moreover, RIS and ZIP were associated with higher rates of successful treatment completion. 88% of RIS patients and 64% of ZIP completed the DD program, whereas only 40% of patients taking TAP and 33% of patients in the OLZ successfully completed the programme. This difference in successful completion was statistically significant for RIS vs. OLZ ($p=0.02$) and TAP ($p=0.017$) [37]. Finally, there is a very recent one-year follow-up, randomised controlled trial in which 45 patients with an amphetamine-induced psychosis were randomly allocated to ARI (15mg/day) or RIS (4mg/day) over a period of 6 weeks, where it was found that both, ARI and RIS were effective in treating psychotic symptoms, although RIS had the greater effect on positive psychotic symptoms ($p<0.001$), whereas ARI was more effective on treating negative symptoms ($p=0.08$) [53].

Despite these positive findings, other studies have failed to find a RIS effective when treating dually diagnosed patients. In a randomized, controlled study where 30 patients with cannabis-induced psychotic disorder were included, no significant differences were found in terms of reduction of psychopathology and EPS between RIS (6mg/day) (n=15) and HAL (10mg/day) (n=15) [54]. With regard to comparison studies with CLO, RIS has failed to show more effectiveness when compared to CLO in two studies [55,56]. In the first study, RIS (n=8) was found to be less effective than CLO (n=33) in a 1-year retrospective survey which included 41 patients with SCH or SAD and comorbid alcohol and/or cannabis disorder, in terms of achieving abstinence from alcohol and cannabis use. Abstinence rates were significantly higher in patients treated with CLO than in those treated with RIS (54% vs. 13%, $p=0.05$) [55]. In addition, in a 2-year, prospective, naturalistic, observational, community-survival analysis study of 61 schizophrenic patients with concomitant AUD, patients

receiving CLO (n=25) and RIS (n=36) were analyzed, and it was found at the end of the study that 75% of the patients treated with CLO were readmitted to hospital significantly later than the RIS treated group ($p=0.045$), and that at the end of the study 75% of the RIS treated patients had been admitted to the hospital compared to only 48% of the CLO treated patients [56]. Finally, a multisite, longitudinal, naturalistic cohort study that included 123 patients who met criteria for a non-affective psychotic disorder and a concomitant CAD, found that cannabis craving, assessed with the Obsessive Compulsive Drug Use Scale (OCDUS) cannabis specific version (OCDUS-CAN), was significantly ($p=0.001$) lesser in patients treated with CLO (mean dosage 350mg/day) (n=23) compared to patients treated with RIS (mean dosage 3.46mg/day) (n=48) [36]. When compared to OLZ, some studies have found similar efficacy in several variables such as psychotic symptoms and substance use [35] and subjective well-being and cannabis craving [34], but there are several studies that have reported an increase in cannabis [33,36] and cigarette [37] craving, compared to OLZ [33,36,37] or ARI [37].

To sum up, studies involving RIS must be interpreted with caution because again, results are inconclusive. Although the majority of case reports, open studies and comparative studies with TAP agree on the effectiveness of RIS in treating psychotic symptoms in DD patients, RIS does not seem to offer a great advantage when it is compared to other AAP. In fact, in most of the studies in which it is compared to other AAP, RIS is not associated with a greater improvement in substance use parameters and craving, and sometimes it even worsens them. Although further studies are needed, LAR could be a promising option for treating DD patients as it has been found to be effective in treating psychotic symptoms as well as in improving substance use, probably because it increases treatment adherence. Regarding safety and tolerability issues, RIS is generally well tolerated according to most of the studies [44,45,48-50,52,54]. However, it is sometimes more frequently associated to sedation and EPS.

Quetiapine

With regard to quetiapine (QUE), the search performed combining all possible major search terms: QUE on one hand, and Dual Diagnosis or Psychosis, Schizophrenia, Schizoaffective Disorder, Bipolar Disorder and Substance Use Disorder, on the other, identified a total of 300 articles, 11 of which were suitable for our review. No further articles were found after reading through the full text.

QUE has shown promising results in most of the studies published to date, mainly in patients with SCH or BD and concomitant SUD (Table 3). Several studies have focused on the use of QUE in general SUD in DD patients. Weisman et al. reported the case of a SCH male with a concurrent alcohol and cocaine abuse who was successfully treated with QUE (400mg/day) for more than 5 months [57]. Concurrently, a 12-week, open, randomized, pilot study that included 24 patients with SMI [BD (n=13), SAD (n=6), SCH (n=3) and Major Depressive Disorder (MDD) (n=2)] and comorbid SUD [cocaine dependence (n=18), amphetamine dependence (AMD) (n=3), cocaine abuse (n=2) and amphetamine abuse (AAM) (n=1)]

Table 3: Studies with quetiapine

Author; No. of patients	Design; Duration, Intervention	Outcomes	Results
Brown et al. (2002) [66] n=17	OL, Add-on QUE 12 weeks BD + COD QUE (mean dosage 229.4mg/d)	Psychopathology (HDRS, YMRS, BPRS) Cocaine Craving (CQC) Cocaine use (UTS)	Significant improvement in psychiatric symptoms ($p<0.01$) and cocaine craving ($p=0.05$). No significant changes in cocaine use
Weisman (2003) [57] n=1	CR 1 year SCH + AA and COA QUE (400mg/d)	Psychopathology Social functioning Alcohol and cocaine use	Reduction of psychopathology and improvement of social functioning. Reduction in alcohol and cocaine use
Brown et al. (2003) [58] n=24	OL, Pros, RCT, switch study 12 weeks PSY (9 with SCH or SAD) + SUD Cocaine (69%), Amphetamine (14%) Non-TAP (n=12), QUE (mean dose 394mg/d) (n=8/12) or TAP (n=12)	Psychopathology (HDRS, BPRS) Cocaine craving (CQC) Cocaine or amphetamines use (self-reported money spent on substance use, UTS)	After discontinuing TAP and switching to QUE there was a significant improvement in psychopathology ($p<0.05$) and a significant craving reduction ($p<0.01$), with no significant differences in the amount of drug use
Longoria et al. (2004) [61] n=17	OL, add-on study 12 weeks BD + COD QUE (mean dosage 239mg/d)	Psychiatric symptoms (YMRS, HDRS, BPRS) Alcohol use (alcohol drinks/week, days/week of alcohol use) Alcohol craving (VAS)	QUE was associated with significant reductions in craving ($p=0.02$), days/week of alcohol use ($p=0.04$) and psychiatric symptoms ($p<0.01$). Depressive symptoms significantly correlated with craving ($p=0.029$)
Potvin et al. (2004) [65] n=8	OL study 6 months SCH (n=4) or BD (n=4) + CAD QUE (dosage N.S.)	Cannabis use	Weekly cannabis use was reduced in 97.3% at the end of the study
Potvin et al. (2006) [59] n=34	OL study 12 weeks SSD + SUD Cannabis (n=15), alcohol (n=10), other psychoactive substances (n=9) QUE (200-800mg/d)	Drug Use (TLFB, UTS, GGT) Severity of drug use (AUS, DUS) Craving (VAS, PACS) Psychiatric and depressive symptoms (PANSS, CDSS) Cognition (CANTAB)	Overall, severity of SUD improved ($p<0.05$), fewer days/week were spent on SUD. Money/week spent on alcohol significantly diminished ($p<0.05$), but money/week spent on cannabis did not diminish significantly. Craving for alcohol did not improve significantly, but craving for cannabis significantly diminished ($p<0.05$) There were significant improvements in psychopathology ($p<0.01$) and cognition ($p<0.05$)
Potvin et al. (2008) [60] n=24		Peripheral ECB	No significant changes in ECB levels were observed during QUE treatment
Brown et al. (2008) [63] n=115	Pros, R, PC, Add-on study 12 weeks BD outpatients + AA or AD QUE (up to 600mg/d) or PLA	Psychiatric symptoms (YMRS, HDRS) Alcohol use	HDRS scores decreased significantly more in the QUE group compared to the PLA group ($p<0.05$). No significant differences were found in the decrease of the YMRS scores and in alcohol use
Martinotti et al. (2008) [62] n=28	OL, FD study 16 weeks Recently detoxified BD (n=16) and SAD (n=12) + AD QUE (300-800mg/d)	Relapse rate (number of drinking days) Craving (OCDS, VAS) Psychopathology (BPRS, HDRS, YMRS, CGI)	42.8% of patients remained alcohol free at the end of the study. 32.1% relapsed. Significant reductions from baseline to exit were observed in craving ($p<0.005$), psychopathology ($p<0.0001$) and number of drinking days/week ($p=0.005$)
Steadman et al. (2010) [64] n=176	MC, DB, RPCT 12 weeks Outpatient BD + AD Treatment with LIT (n=185) or VAL (n=177) + QUE (300-800mg/d) (n=159) or PLA (n=169)	Change in the proportion of heavy drinking days (TLFB) Psychopathology (CGI, HARS)	No significant differences in the proportion of heavy drinking days between QUE and PLA. No significant differences in improvement in psychopathology
Zhurnitsky et al. (2011) [67]	CC study 12 weeks DD (n=26), SCH without SUD (n=23), SUD without SCH (n=24) QUE (mean dosages in the three groups: 554, 478 and 150mg/d, respectively)	Neurological and psychiatric symptoms (PANSS, ESRS, BAS) Substance use (TLFB, UTS)	DD and SCH patients were receiving significantly higher doses of QUE ($p=0.0001$). DD patients had significantly higher parkinsonism ($p=0.02$) and depression ($p=0.005$). DD patients had significantly higher SUD severity compared to SUD patients ($p<0.001$)

AA: Alcohol Abuse, AD: Alcohol Dependence, AUS: Alcohol Use Scale, BAS: Barnes Akathisia Scale, BD: Bipolar Disorder, BPRS: Brief Psychiatric Rating Scale, CAD: Cannabis Dependence, CANTAB: Cambridge Neuropsychological Test Automated Battery, CC: Case-Control, CDSS: Calgary Depression Scale for Schizophrenia, CGI: Clinical Global Impression, COA: Cocaine Abuse, COD: Cocaine Dependence, CQC: Cocaine Craving Questionnaire, CR: Case Report, DB: Double blinded, DD: Dual Diagnosis, DUS: Drug Use Scale, ECB: Endogenous Cannabinoids, ESRS: Extrapyramidal Symptoms Rating Scale, FD: Flexible dose, GGT: GammaGlutamyltranpeptidase, HARS: Hamilton Anxiety Rating Scale, HDRS: Hamilton Depression Rating Scale, LIT: Lithium, MC: Multicenter, OCDS: Obsessive Compulsive Drinking Scale, OL: Open label, PACS: Penn Alcohol Craving Scale, PANSS: Positive and Negative Symptoms Scale, Pros: Prospective, PSY: Psychotic Disorder, QUE: Quetiapine, PLA: Placebo, RCT: Randomized Controlled Trials RPCT: Randomized Placebo Controlled Trials, SAD: Schizoaffective Disorder, SCH: Schizophrenia, SSD: Schizophrenic Spectrum Disorders, SUD: Substance Use Disorder, TAP: Typical Antipsychotics, TLFB: Timeline Follow Back, UTS: Urine Toxicological Screens, VAL: Valproate, VAS: Visual Analogue scale, YMRS: Young Mania Rating Scale

were randomized to continue taking TAP (n=12) or to discontinue TAP (n=12), switching in some cases to QUE (mean dosage 394mg/day) (n=8). Patients who were switched to QUE had significant reductions in drug craving, being this reduction more prominent at week 3 ($p<0.01$). They also showed significant improvements in psychopathology ($p<0.05$) compared with those that continued treatment with TAP. However, reduction in craving was not followed by a reduction in substance use [58]. In addition, in a 12-week, open-label trial in which 24 SSD patients with comorbid SUD [cannabis (n=15), alcohol (n=10), other psychoactive substances (n=9)], were switched to QUE (200-800mg/day, mean dosage 545.8mg/day), it was found an overall improvement in the severity of substance abuse, in terms of a reduction in positive UTS, plasmatic GGT levels, weekly

days spent in drug abuse and a decrease in the weekly money spent in psychoactive substances. In the case of alcohol, cravings did not improve significantly over time, but weekly money spent on alcohol significantly diminished ($p<0.05$). Regarding cannabis, cravings significantly diminished during QUE therapy ($p<0.05$), but not money spent per week on cannabis. In addition, cognition ($p<0.01$), psychiatric symptoms ($p<0.01$) and EPS ($p<0.05$) significantly improved at the end of the study [59]. In a further analysis over this sample, there was no significant reduction in endogenous cannabinoids levels in this group (its augmentation is thought to play an important role in an enhance sensitivity to psychoactive substances in patients with schizophrenia) after QUE therapy [60].

Regarding alcohol, all the studies conducted to date are in BD DD patients and most of them have found a positive effect of QUE over alcohol outcomes. The first to report on the effectiveness of QUE in treating patients with BD and AD were Longoria et al. They carried out a 12-week, add-on study which included 17 patients with BP and AD. QUE (mean dosage 239mg/day) was found to be effective in decreasing craving for alcohol ($p=0.02$), number of days of alcohol use per week ($p=0.04$) and intensity of psychiatric symptoms ($p<0.01$). However, drinks of alcohol per week did not decline significantly. No significant correlations were found between changes in alcohol craving or use, and psychiatric symptoms, with the exception of depressive symptoms and craving ($p=0.029$) [61]. Subsequently, an Italian group has reported that 43% of 28 DD recently detoxified alcoholic patients (BD, n=16; SAD, n=2), remained totally alcohol free after 16-weeks of treatment with QUE (300-800mg/day). QUE therapy was also associated with significant reductions in the number of drinking days per week, alcohol craving and psychiatric symptoms intensity ($p<0.005$). Changes in alcohol withdrawal and craving were correlated with psychiatric symptoms, being the highest level of correlation for the item of insomnia [62]. More recently, Brown et al. reported an improvement in depressive symptoms, but no significant effect on improvement in manic symptoms or alcohol consumption compared to PLA, following 12 weeks of treatment with QUE (titrated to 600mg/day) in a sample of 115 outpatients with BD and AA or AD [63]. However, adding QUE (300-800mg/day) to lithium (LIT) or valproate (VAL) was not been found to be effective in reducing the proportion of heavy drinking days and improving psychiatric symptoms in a 12-week, placebo-controlled trial, which included 362 patients with BD and concomitant AD [64]. With regard to cannabis, there is only one small, open-label study published to date, where a 6 month therapy with QUE was associated with a reduction of 97.3% of weekly cannabis use in a sample of 8 psychotic patients (SCH, n=4; BD, n=4), and CAD [65]. Finally, Brown et al. carried out a 12-week, open-label, add-on study, where QUE was associated with significant improvements in psychopathology ($p<0.01$) and craving scores ($p=0.05$), in a sample of 17 outpatients with BD and concomitant COD. However, no significant decrease in cocaine use was observed in terms of money spent on drugs, days of drug use and negative UTS [66].

In the most recent study, a case-control study, conducted in DD patients treated with QUE, Zhomitsky et al. compared several

outcomes in terms of neurological and psychiatric symptoms, as well as substance use and severity of addiction, in a sample of patients with a DD (SCH and SUD) (n=26), patients with SCH without a SUD (n=23) and patients with SUD without SCH (n=24). They received QUE for 12 weeks. At the end of the study, SUD patients improved significantly more than DD patients in SUD severity ($p<0.001$), although at baseline DD had a lower severity of SUD compared to SUD patients ($p<0.001$). In addition, DD patients had significantly more EPS than SCH patients at baseline ($p=0.03$) and significantly more EPS than SUD at endpoint ($p=0.02$). They had also more depressive symptoms at baseline and endpoint ($p=0.005$), and positive symptoms at endpoint ($p<0.001$), compared to SUD and SCH patients [67].

To summarize, although QUE in general has brought promising results in the field of the treatment of DD, further studies are needed. QUE has shown to be effective for treating psychiatric symptoms, specially psychotic and depressive symptoms. It has also been reported an improvement in cognition associated to QUE. With regard to substance use and craving most of the studies have focused in AUD, although there are studies that explore the use of QUE in cannabis and cocaine use disorders. QUE has generally been associated with improvements in substance use and craving, but this fact must be analysed cautiously because there are some studies that fail to find a positive effect on these parameters, and QUE has not demonstrated to be an effective augmentation strategy when added to lithium and/or valproate in DD patients. With regard to safety and tolerability issues, the majority of studies conclude that QUE is a well-tolerated pharmacological agent [59,62,64,66]. Generally side effects are mild and are not associated with the discontinuation of QUE treatment. The most frequent side effects associated with QUE are sedation, somnolence, dizziness, dry mouth and blurred vision. In addition, most of the studies agree on the association of QUE with weight gain, although mild. Finally, QUE seems not to increase EPS and rather reduce them according to some studies.

Aripiprazole, amisulpride and ziprasidone

Aripiprazole (ARI) is an AAP that acts as a D_2 receptor partial agonist and has been approved for the treatment of SCH and mania. To date, there are only one case report and four studies evaluating the effectiveness of ARI in treating DD patients (Table 4). Warsi et al. reported the case of a 39 year-old man diagnosed with SCH and

Table 4: Studies with aripiprazole, amisulpride and ziprasidone

Author; No. of patients	Design; Duration, Intervention	Outcomes	Results
ARIPIPRAZOLE			
Warsi et al. (2005) [68] n=1	CR 2 months SCH + AD ARI (20mg/d)	Psychiatric symptoms (BPRS) Daily alcohol used Alcohol craving (PCS, SRCS)	ARI was associated with an improvement in psychiatric symptoms, cessation of daily alcohol intake and reduction in alcohol craving
Beresford et al. (2005) [69] n=10	Pros, OL study 8 weeks SCH + COD ARI (maximum 15mg/d)	Psychiatric symptoms (BPRS) Cocaine and alcohol craving (UTS, BCRS)	Positive UTS dropped significantly ($p<0.001$) Mean cocaine ($p=0.026$) and alcohol ($p=0.006$) craving scores significantly declined Declining psychosis scores were significantly associated with declining cocaine and alcohol craving ($p<0.01$)
Brown et al. (2005) [70] n=20	OL study 12 weeks BD (n=19) or SAD (n=1) + AD (n=17) and/or COUD (n=9) ARI (up to 30mg/d)	Psychiatric symptoms (YMRS, HDRS, BPRS) Substance craving (VAS) Substance use (days of use/week, money spent on substances/week and UTS)	ARI was associated with significant improvements in psychiatric symptoms ($p<0.05$), significant reductions in alcohol craving ($p=0.003$) and money spent on alcohol/ week ($p=0.042$) and significant reductions in cocaine craving ($p=0.014$). No significant changes were observed in days/week of alcohol and cocaine use, and in money spent on cocaine/week
Kim et al. (2010) [37] n=139	Pros, RCT 8 weeks SCH + ND OLZ (n=32) or RIS (n=41) or ARI (n=31) or HAL (n=35)	Psychopathology (SANS, SAPS) EPS (AIMS) Severity of ND and cigarette craving (FTQ)	No significant differences in the degrees of change in psychiatric symptoms among the four groups. At 8 weeks, HAL was associated with higher EPS ($p<0.01$). HAL was associated with less reduction in the severity of ND ($p<0.01$) and cigarette craving ($p<0.01$) compared to AAP. Among AAP, RIS increased cigarette craving ($p=0.03$), there were no significant changes in ND severity and cigarette craving associated with OLZ, and ARI showed a reduction in both severity of ND and cigarette craving ($p<0.01$)

Bruno et al. (2014) [71] n=20	OL study 8 weeks SAD + OD + MMT ARI (10mg/d) + TOP (200mg/d)	Tapering and suppression of MET	ARI + TOP was effective to achieve MET suppression reducing clinical symptoms
Farnia et al. (2014) [53] n=45	Pros, DB, RCT 1 year follow-up AMP induced psychosis RIS (4mg/d) or ARI (15mg/d)	Psychopathology (SANS, SAPS)	SANS and SAPS scores decreased significantly in both groups. Mean SAPS score reduction was greater in the RIS group ($p < 0.001$). Mean SANS score reduction was greater in the ARI group ($p = 0.08$)

AMISULPRIDE

Dervaux and Cazali (2007) [72] n=1	CR Over 25 months SCH + AD CLO (600-1200mg/d) + AMS (600mg/d)	Psychopathology Alcohol addictive behaviour	CLO + AMS was effective in controlling psychiatric symptoms and alcohol addictive behaviour
Máñez et al. (2010) [73] n=97	Pros study 9 months SUD (alcohol, cannabis, cocaine and heroin + psychotic symptoms AMS in two ranges (100-300mg/D or >400mg/d, mean dose 493.5 ± 197.1mg/d)	Psychosocial distress Craving Psychosocial functioning	Overall improvement in their psychological distress, a decrease in craving and an improvement in their psychological and psychosocial functioning

ZIPRASIDONE

Stuyt et al. (2006) [38] n=55	Ret, OL 2 years SCH (61%) or SAD (54%) + SUD or AUD Polyvalent SUD (34%), Alcohol (27%), Cocaine (16%), other SUD (21%) OLZ (2.5-30mg/d, mean dosage 18.7mg/d) (n=15) or RIS (n=16) (2-8mg/d, mean dosage 3.9mg/d) or ZIP (60-160mg/d, mean dosage 132.8mg/d) (n=10) or TAP depot (n=10)	Retention rate Success in completing a DD Programme	RIS and ZIP had higher rates of retention compared to OLZ ($p = 0.0002$ and $p = 0.004$, for RIS and ZIP respectively) and TAP ($p = 0.003$ and $p = 0.03$, for RIS and ZIP, respectively). No significant differences in length of stay were found between RIS and ZIP. 88% of RIS patients and 64% of ZIP completed the DD program, whereas only 40% of patients taking TAP and 33% of patients in the OLZ successfully completed the program. This difference in successful completion was statistically significant for RIS vs OLZ ($p = 0.02$) and TAP ($p = 0.017$)
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AAP: Atypical Antipsychotics, AD: Alcohol Dependence, AIMS: Abnormal Involuntary Movement Scale, AMP: Amphetamine, AMS: Amisulpride, AR: Aripiprazole, BCRS: Brief rating craving scale, BD: Bipolar Disorder, BPRS: Brief Psychiatric Rating Scale, CLO: Clozapine, COD: Cocaine Dependence, COUD: Cocaine Use Disorder, CR: Case Report, DB: Double blinded, DD: Dual Diagnosis, EPS: Extrapyramidal Symptoms, FTQ: Fagerstrom Tolerance Questionnaire, HAL: Haloperidol, HDRS: Hamilton Depression Rating Scale, MET: Methadone, MMT: Methadone Maintenance Treatment, ND: Nicotine Dependence, OD: Opioid Dependence, OL: Open Label, OLZ: Olanzapine, PCS: Pennsylvania Craving Scale, Pros: Prospective, RCT: Randomized Controlled Trial, Ret: Retrospective, RIS: Risperidone, SAD: Schizoaffective Disorder, SANS: Scale for the Assessment of Negative Symptoms, SAPS: Scale for the Assessment of Positive Symptoms, SCH: Schizophrenia, SRCS: Self-report Craving Scale, SUD: Substance Use Disorder, TAP: Typical Antipsychotics, TOP: Topiramate, UTS: Urine Toxicological Screens, VAS: Visual Analogue Scale, YMRS: Young Mania Rating Scale, ZIP: Ziprasidone

concurrent AD, who was treated with ARI at a dosage of 20mg/day during 2 months, and improved in psychiatric symptoms and severity of AD, his daily intake of alcohol stopping and his alcohol craving being reduced [68]. Regarding the four other studies, the first study was an 8-week, prospective, open-label study which included 10 patients diagnosed with SCH and COD. ARI, given at a maximum dose of 15mg/day, was associated with a significant drop in the positive UTS ($p < 0.001$) that was evident after 2 weeks of having initiated ARI treatment, and a decrease in craving scores for cocaine ($p = 0.026$) and alcohol ($p = 0.006$). A reduction in psychotic symptoms was correlated with reduced cocaine and alcohol craving ($p < 0.01$) [69]. Brown et al. conducted a 12-week, open-label study with a sample of 20 antipsychotic-treated patients with BD and SAD and current substance abuse, who were switched to ARI using an overlap and taper method. ARI was found to be effective in improving psychiatric symptoms of mania ($p = 0.021$) and depression ($p = 0.002$). In addition, in 17 patients who had a current alcohol dependence, a significant reduction in the money spent on alcohol ($p = 0.042$) and alcohol craving ($p = 0.003$) was observed. In the case of the 9 patients who had cocaine-related disorders, it was found a significant reduction in cocaine craving ($p = 0.014$), but no in cocaine use [69]. ARI has also found to be effective in reducing the severity of nicotine dependence (ND) and cigarette craving ($p < 0.01$) compared to other AAP (OLZ and RIS) and TAP, in an 8-week, prospective trial that included 139 SCH patients with comorbid ND [37]. Very recently, combining ARI (10mg/day) with topiramate (TOP) (up to 200mg/day) during 8 weeks, for treating 20 patients with SAD and concomitant opioid dependence undergoing Methadone Maintenance Treatment (MMT) (80mg/day), in order to taper MET until suspension at week 4 by 3mg/day, was found to be effective in reducing clinical symptoms and achieving a rapid tapering off of MMT [71]. Finally, as said above, a one-year follow-up, randomised controlled trial which included 45 patients with an amphetamine-induced psychosis who were randomly allocated to ARI (15mg/day) or RIS (4mg/day) over a period of 6 weeks, found ARI and RIS to be equally effective

in treating psychotic symptoms, although ARI was more effective on treating negative symptoms ($p = 0.08$) [55]. ARI has been associated only with mild side effects which not caused discontinuation of the treatment, such as insomnia, stiffness, tremor, dry mouth, sedation and restlessness [70].

Only one case report and a Spanish study have been published to date regarding the use of amisulpride (AMS) in DD patients (Table 4). The case report was of a 47-year-old SCH male with a comorbid severe alcohol dependence who was effectively treated when AMS (600mg/day) was added to his treatment with CLO (600-1200mg/day), improving of his resistant symptoms and his alcohol addictive behavior [72]. In addition, an experimental, prospective study including 97 outpatients with SUD (alcohol, heroin, cocaine or cannabis) that had overcome detoxification, and presented symptoms of paranoid ideas, hostility, severe irritating or impulsive behaviors, interpersonal sensitivity, and/or hearing or visual hallucinations, found that 9 month treatment with AMS standardized in two ranges (100-300mg/day or more than 400mg/day, mean dose 493.5 ± 197.1mg/day) was associated with an overall improvement in psychological distress, a decreased in craving and an improvement in psychological and social functioning [73]. As described above, in regard to ZIP (Table 4), ZIP (mean dosage 132.8mg/day) (n=14) was associated with a significant longer length of stay and higher rates of successful treatment completion, similar to RIS (mean dosage 3.9mg/day) (n=16), compared to OLZ (mean dosage 18.7mg/day) (n=15) and TAP (n=10) in a sample of 95 patients with SCH (n=42), SAD (n=48) or psychotic disorder NOS (n=5) and concomitant SUD [PSD (34%), AD (27%) and COD (16%)] treated in a 90-day, inpatient, DD treatment programme [38]. No studies have been identified with asenapine and paliperidone.

Conclusions

To date, although DD in clinical settings is the norm and not the exception, there is relatively very little research in this field. However,

among the pharmacological agents that have been more widely studied we find the group of the antipsychotics. Today, there is a consensus in using AAP instead of TAP for treating patients with a SMI and a comorbid SUD. This is because it has been reported that patients with DD show a generally poorer response to treatment with TAP [16]. Studies comparing TAP and AAP in DD patients have reported that AAP are as effective as TAP in treating psychiatric symptoms, but they offer more effectiveness in reducing substance use [74]. However, these results have not always been replicated [75].

With regard to AAP, the largest number of studies available is for CLO. The data on the beneficial effect of CLO are consistently positive, although the lack of prospective, controlled, randomized trials limits the conclusions that can be drawn. However, clinicians are often hesitant to use CLO as a first-line treatment due to several undesirable side effects including the risk for agranulocytosis and the consequent need for blood tests [14]. Data regarding ARI are also quite consistent but less substantial, as there have not yet been a great number of studies carried out in DD patients using this pharmacological agent. OLZ, RIS and QUE have given inconclusive and discrepant results, with some studies reporting on a beneficial effect of these agents for treating patients with a DD, and others that have failed to find a positive effect on this population. Finally, the use of AMS, ZIP, PAL and ASE is yet poor or not documented.

Despite a growing body of evidence suggesting the beneficial effects of AAP in DD patients, interpretation of the published literature remains limited due to methodological issues that include small sample sizes, short follows-up, low attrition rates and the lack of randomized, controlled and blinded methodological designs. This is generally due to the specific features of DD patients who are more difficult to engage and retain in trials, and associate higher rates of treatment non-compliance.

To conclude, to date, when choosing between the different AAP agents, clinicians may need to rely on indirect data provided by case reports, open label, retrospective and prospective studies such as those described in detail throughout this review. Because with the exception of CLO none of the AAP have shown to be superior to the others, when choosing between the different AAP agents clinicians should take into account other variables such as medical comorbidity, possible pharmacological interactions of concomitant treatments and profile of side effects.

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