

Clozapine use in Dual Diagnosis Patients

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Abstract: *Background:* 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 and in DD patients 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 clozapine (CLO) for treating DD patients.

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

Results: There is consistent data in regard to the efficacy of CLO in the treatment of DD patients in both studies with and without comparison to TAP and other AAP. These positive results have been found for different substances of abuse and in different SMI. However, there is a lack of randomized, placebo-controlled trials in this field.

Conclusions: CLO has been found to be at least as effective as TAP and other AAP in treating psychiatric symptoms, but it has shown itself to be more effective in reducing substance use in DD patients. Several hypotheses have been proposed to explain this effectiveness: 1) amelioration of reward system dysfunction in the dopamine-mediated mesocorticolimbic circuits; 2) improvement of negative symptoms, and relief of anxiety, depression and dysphoria; 3) improvement of cognitive dysfunction associated with DD; and 4) reduction of craving. CLO might be considered as a pharmacological agent for use in patients with DD, although safety issues, such as the risk of agranulocytosis and seizures must be taken into account. Even though there is a growing body of evidence suggesting the beneficial effects of CLO in DD patients, further randomized, blind, controlled trials, with larger sample sizes and longer follow-ups are needed.

Keywords: Clozapine, Dual diagnosis, Substance use disorder, Atypical antipsychotics.

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 is being used to define the co-occurrence of any mental illness and a SUD, in this review we will consider schizophrenia and related disorders, with concomitant SUD.

It is estimated that 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 most commonly used by these patients are alcohol, followed by cannabis and cocaine [3]. The demographic correlates of substance use are well documented and people with SMI that have concomitant SUD tend to be younger men, with a lower educational level, a family history of SUD, and comorbidity with a behaviour disorder such as an antisocial personality disorder (ASPD) [4].

Several hypotheses have been used to explain the co morbidity between SMI and SUD. Traditionally, the association between substance abuse and SMI was explained by the "self-medication" theory, which stated that patients used substances to relieve psychiatric symptoms or the side-effects of psychiatric medication [5]. However, in recent years, the neurobiological

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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 they have a dysfunction in their dopamine (DA)-mediated mesocorticolimbic (MCL) reward pathways, and they use alcohol and other drugs of abuse in order to ameliorate this dysfunction in the brain reward system [6].

Comorbid SUD among patients with SMI is associated with more negative outcomes such as poor response to treatments [7], more relapses [8], more admissions to hospital [9], non-compliance with treatment [10], increased rates of suicidal ideation [11], increased rates of impulsive and violent behaviours [12], increased rates of neurological and psychiatric symptoms [13], and increased rates of poverty, unemployment and social exclusion [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] and even an increase in number of cigarettes smoked after the initiation of haloperidol (HAL) treatment [17]. Two main hypotheses have been proposed to explain this lack of efficacy of TAP in DD patients: 1) TAP are associated with considerable side effects and it has been postulated that patients with the co-occurrence of a SMI and a SUD may use substances to “self-medicate” side-effects produced by TAP, such as extra pyramidal side-effects (EPS) and dysphoria [18-20] and 2) they worsen the functioning of DA-mediated MCL brain reward circuits because of a potent D₂ receptor blockade action [6, 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. They have been reported to offer some advantages in the treatment of SUD probably due to their mechanism of action, which includes less DA antagonism and pharmacological action on serotonin (5-HT), histamine (HIS), and norepinephrine (NE) pathways [22, 23].

CLO is considered to be the “prototypical” AAP and has one of the most complex pharmacological profiles of all the AAP. It produces weak blockade of D₂ receptor and potent blockade of the serotonergic 5-HT_{2A} and the NA α_1 and α_2 receptors, and it ameliorates the deficits in both the mesocortical and mesolimbic DA neuronal projections [24]. Although it has been considered the “gold standard” for the treatment of schizophrenia and related disorders, in clinical practice CLO is not used as a first-line treatment due to several undesirable side effects including the risk of agranulocytosis and seizures, and the consequent need for regular blood draws to assess blood abnormalities [25].

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

METHODS

A search of MEDLINE (1980-present), EMBASE (1980-present) and Pubmed (1980-present) was performed in order to identify English- and Spanish-language publications that examined the use of CLO in the treatment of DD. Major search terms included dual diagnosis, schizophrenia, schizoaffective disorder, bipolar disorder, SUD, on one hand, and AAP and CLO on the other.

RESULTS

Clozapine (CLO) is the AAP with the greatest body of research regarding its use as a pharmacological agent for patients with DD. Several case reports, case series, retrospective studies and prospective studies have suggested that CLO may decrease the use of nicotine, alcohol, or other drugs of abuse among patients with DD.

Regarding nicotine, retrospective and cross-sectional studies have found an overall decrease in smoking [26, 27] and less smoking compared with DD patients taking TAP [28-31] or risperidone (RIS) [32]. McEvoy reported a decrease in the drive to smoke in 8 out of 10 treatment-resistant schizophrenic (TR-SCH) smoker patients after 12 weeks of CLO treatment [26]. Subsequently, another group reported that 11 out of 13 schizophrenic patients, eight of whom had a history of another SUD [alcohol (n=6), cannabis (n=6), cocaine (n=2), heroin (n=1), hallucinogens (n=2)], reduced or stopped smoking after taking CLO. These patients did

not associate their decrease in smoking with a reduction in cigarette craving, rather they attributed it to an improvement in their ability to plan and budget, as well as becoming more concerned about the cost of cigarettes and physical health [27]. Switching from HAL to CLO (plasmatic levels 1200 ng/ml) was associated with a reduction of 25-35% in smoking in a sample of 12 schizophrenic patients [28]. In addition, these results were supported by two studies in which switching from TAP to CLO was associated with a significant ($p=0.025$) decrease in the daily amount of cigarettes smoked in a sample of 18 schizophrenic patients and comorbid nicotine dependence (ND) [30], and in a sample of 55 smokers of a total of 70 TR-SCH patients [29]. It was also reported that smokers had a greater therapeutic response to CLO compared to non-smokers [29]. More recently, a retrospective study in which hospitalized, schizophrenic patients who were divided into three treatment groups: TAP ($n=15$), CLO ($n=6$) or other AAP ($n=16$), found that smoking prevalence differed significantly among the three treatment groups ($p<0.001$), CLO being the pharmacological agent that was associated with a significantly lower incidence of smoking compared to TAP ($p<0.03$) or other AAP ($p=0.042$) [33]. Finally, a Canadian group has conducted two small studies switching from depot TAP to CLO [31] and adding CLO to RIS [32]. In both studies it was demonstrated that patients receiving treatment with CLO smoked less, as they showed significantly lower levels of expired carbon monoxide (CO) ($p<0.01$ and $p=0.03$, respectively) and significantly less self-reported smoking, assessed by the Fagerstrom Test for Nicotine Dependence (FTND) ($p=0.08$ and $p=0.04$, respectively) as compared to patients on depot TAP or RIS alone.

Regarding alcohol and other substances of abuse, a series of case reports and case series studies beginning in the mid-1990s, suggested that CLO was effective in patients with a co-occurring SMI and SUD, and that it appeared to reduce substance use. The first to report on the effectiveness of CLO in treating patients with a DD were Yovell and Opler (1994). They reported the case of a 37-year-old male diagnosed with Schizoaffective Disorder (SAD) and comorbid Cocaine Dependence (COD) who showed a reduction in psychotic symptoms, an improvement in social functioning and a reduction in cocaine craving and craving for other substances after CLO at doses of 600 mg/day was initiated [34]. Concurrently, CLO (500 mg/day, up to 6 months) was also found to be effective in decreasing psychotic symptoms and, in turn,

abstinence from alcohol, in two 40-year-old males with TR-SCH and chronic alcohol abuse (AA) [35]. In addition, CLO was effective in preventing relapse in alcohol or drug use in a TR-SCH patient with poly-drug abuse (PDA) [36]. Finally, the psychotic symptoms of a patient with a TR-SCH and comorbid alcohol (AA) and cocaine (COA) abuse were stabilized and the patient remained abstinent from alcohol and cocaine use after initiating CLO at dosages of 550 mg/day [37]. There are also two recent case reports in which augmentation strategies for CLO have been proposed for treating schizophrenic patients with comorbid Alcohol Use Disorders (AUD). In the first one, three TR-SCH patients with a concomitant alcohol dependence (AD) were successfully treated adding lamotrigine (LAM) (200-300 mg/day) to their previous treatment with CLO (300-600 mg/day), and such treatment led to the improvement of the psychopathology and significantly reduced craving ($p<0.05$) [38]. In the second one, a 47-year-old schizophrenic male with severe, comorbid alcohol dependence was treated effectively when amisulpride (AMS) (600 mg/day) was added to his treatment with CLO (600-1200 mg/day), improving his resistant schizophrenia symptoms and behaviour in relation to alcohol [39].

Results of case reports have been consolidated in several retrospective and naturalistic studies where CLO has also been found to be effective for treating patients with a SMI and a comorbid SUD. In a retrospective survey that included 58 patients diagnosed with schizophrenia or SAD and a comorbid SUD [alcohol (20%), cannabis (3%), cocaine (13%) and PSA (24%)], it was found that more than 85% of 36 patients who initiated treatment with CLO decreased their alcohol and substance consumption, and 72% of them achieved abstinence. In addition, of those patients who were not actively using substances at the beginning of the study none restarted substance use. Moreover, in those patients that remained in treatment, the reduction of substance use significantly correlated with an improvement in global clinical symptoms ($p=0.002$) [40]. These results were extended in a 3-year-follow-up-naturalistic study in which 151 patients with schizophrenia or SAD with a comorbid alcohol (69.5%) or other SUD [cannabis (31.8%) and cocaine (11.3%)] were included. Among 36 patients switched to CLO, significant improvement was described in substance abuse stage ($p=0.003$), and the severity of alcohol ($p=0.004$) and drug ($p=0.0001$) use, and the number of drinking days ($p=0.0002$) and days of drug abuse ($p=0.0003$) significantly decreased. At the end of

the study, 79% of the patients receiving CLO were in remission from their AUD compared to 33.7% of patients who were not on CLO ($p=0.001$), and 65% of patients receiving CLO were in remission from the SUD, compared to only 29.6% of patients not taking CLO ($p=0.032$). The relationship between a greater length of time on CLO and the likelihood of remission of SUD at 3-year follow-up tend toward significance for alcohol ($p=0.07$), but not for other drugs ($p=ns$). Improvement in alcohol and substances of abuse parameters was associated with an improvement in psychopathology, especially regarding symptoms of anergia ($p=0.002$), but not symptoms of thought disorder ($p=ns$) [41].

In comparative studies, CLO has been shown to be more effective than TAP and other AAP in treating patients with a concomitant SMI and SUD. Regarding TAP, in a retrospective study that included 204 patients with a schizophrenic spectrum disorder (SSD) the rates of concurrent SUD decreased from 57% to none in the 35 patients taking CLO, whereas they decreased from 50% to 13% among the 169 patients taking TAP, suggesting that CLO was more effective in treating SUD [42]. In addition, very recently, a 3-month treatment with CLO has been compared with a 3-month treatment with TAP in an experimental study in which 43 patients diagnosed with SCH or SAD and a concomitant SUD including AA (42% CLO, 69% TAP), AD (25% CLO, 15% TAP), cannabis abuse (CAA) (33% CLO, 46% TAP), cannabis dependence (CAD) (25% CLO, 15% TAP), poly substance dependence (PSD) (25% CLO, 23% TAP), cocaine abuse (COA) (8% CLO, 15% TAP), COD (8% CLO, 8% TAP), heroin abuse (HA) (8% CLO), hallucinogen abuse (8% TAP) and inhalant abuse (8% TAP), were tested with an odour hedonic task. They found that CLO, compared to TAP, was significantly ($p=0.01$) associated with a broader and stronger experience of rewarding olfactory stimuli and, subsequently, it could ameliorate the dysfunction of the brain reward system of patients with DD, thus reducing their substance abuse [25]. Regarding other AAP, in a retrospective study which included 41 patients with schizophrenia or SAD and comorbid alcohol and/or cannabis use disorders treated with either RIS ($n=8$) or CLO ($n=33$) for at least one year, abstinence rates were significantly higher in patients treated with CLO than in those treated with RIS (54% vs. 13%, $p=0.05$) [43]. In addition, in a 2-year prospective, naturalistic, observational study, which included 61 patients with schizophrenia and AUD, cases receiving CLO ($n=25$) or RIS ($n=36$) were analysed, and it was found that at the end of the study,

patients treated with CLO were readmitted to hospital significantly later than the RIS treated group ($p=0.045$). Also 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 [44]. More recently, two studies have explored the use of CLO in DD patients with comorbid cannabis use disorders (CAUD), comparing it to RIS and OLZ on one hand [45], and to ziprasidone (ZIP) on the other [46]. The first study that was a multisite, longitudinal, naturalistic cohort study which included 123 patients who met criteria for a non-affective psychotic disorder and a concomitant CAD, found that there was significantly less cannabis craving ($p=0.001$), assessed by the Obsessive Compulsive Drug Use Scale (OCDUS) cannabis specific version (OCDUS-CAN), in patients treated with CLO (mean dosage 350 mg/day) ($n=23$) compared to patients treated with RIS (mean dosage 3.46 mg/day) ($n=48$), although significant differences between CLO and OLZ (mean dosage 13.78 mg/day) ($n=52$) in craving were not found [45]. The second one was a 12-month, randomized, controlled trial in which 30 patients with SCH and comorbid CAUD were randomized to receive either CLO ($n=14$) (50-425 mg/day, mean dosage 225 mg/day) or ZIP ($n=16$) (80-400 mg/day, mean dosage 200 mg/day). Both, CLO and ZIP were equally effective in reducing the frequency of cannabis use during follow-up. The reduction of cannabis use was already seen at the 3-month follow-up examination and was stable over the period of the 12 months. However, regarding psychotic symptoms, there was a stronger decline in positive symptoms in patients treated with CLO ($p=0.05$). Despite these positive results, CLO was also associated with significantly more side effects, especially hyper salivation ($p=0.017$) and overall poorer compliance with treatment ($p=0.024$). Some of these CLO side effects such as sedation were reported to help diminish craving in some patients. The fact that this study used lower dosages of CLO compared to the previous ones, could have explained the non-superiority of CLO compared to ZIP [46]. All these results have been replicated in a prospective, 10-year follow-up study with a sample of 223 outpatients, of whom 95 met criteria for schizophrenia or SAD and experienced a 6-month remission from their SUD. There were three treatment groups: TAP ($n=62$), CLO ($n=25$) or other AAP ($n=8$). Patients taking CLO, at a mean dose of 417 mg/day, were significantly less likely to experience substance abuse relapse 1 year after remission ($p=0.003$) and 2 years after remission ($p=0.05$) [47].

Table 1: Clinical Studies with Clozapine on Dual Diagnosis

Author N° patients	Design; Duration; Intervention	Outcomes	Results
Yovell and Opler (1994) N=1	CR 4 weeks SAD + COA and poly-substance use CLO (600 mg/d)	Psychotic symptoms Social functioning Cocaine use and craving	Reduction of psychopathology and cocaine use
Albanese <i>et al.</i> (1994) N=2	CR Up to 6 months TR-SCH + AUD and poly- substance use CLO (500 mg/d)	Psychotic symptoms Alcohol use	Reduction of psychopathology and alcohol abstinence after switching from TAP
Buckley <i>et al.</i> (1994) N=118	Ret, OL 6 months TR-SCH or TR-SAD, 29 with comorbid SUD Alcohol (11%) CLO (dose N.S.)	Psychotic symptoms and psychosocial functioning	Similar improvement in psychopathology and psychosocial functioning in patients with SUD and without SUD Reduction of substance use and craving
Marcus and Snyder (1995) N=16	CS Duration N.S. SCH, 13 with ND, 8 with another SUD: Alcohol (n=8), Cannabis (n=6), Cocaine (n=2), Heroine (n=1), Hallucinogens (n=1) CLO (dose N.S.)	Smoking reduction or cessation Psychotic symptoms	Smoking reduction or cessation in 11 out of 13 patients. Improvement in psychotic symptoms
McEvoy <i>et al.</i> (1995) N=12	Nat study 12 week SCH + ND CLO (dose N.S.)	Smoking reduction	25-35% decrease in smoking
George <i>et al.</i> (1995) N=29	Ret study N.S. SCH + ND CLO (dose N.S.)	Smoking reduction	Smoking reduction in all the patients ($p=0.025$)
Buckley (1998) N=1	CR 3 years TR-SCH + poly- substance use (alcohol, cannabis and cocaine) CLO (dose N.S.)	Relapse in drug abuse	No relapse of alcohol and drug use under CLO treatment
Lee <i>et al.</i> (1998) N=204	Ret study N.S. SCH + SUD CLO (n=35) or TAP (n=169)	% of reduction of SU	57% to none in SU in the CLO group and from 50% to 13% in the other group
McEvoy <i>et al.</i> (1999) N=70	Nat study 12 weeks TR-SCH, 55 smokers CLO (dose N.S.)	Response to CLO Smoking reduction	Smokers showed a greater response to CLO. They smoked less under treatment with CLO compared to treatment with TAP
Tsuang <i>et al.</i> (1999) N=1	CR N.S. TR-SCH + COUD and AUD CLO (550 mg/d)	Psychotic symptoms Alcohol and cocaine use	Psychiatrically stable and abstinent from alcohol and cocaine after switching to CLO
Volavka <i>et al.</i> (1999) N=331	Ret study 6 months SCH or SAD +/- SUD CLO (dose N.S.)	Psychopathology and psychosocial functioning	Similar improvement in psychopathology and psychosocial functioning in substance abusers and non-substance abusers
Combs and Advokat (2000) N=39	Nat study Duration N.S. SCH or SAD + ND TAP (n=15) or CLO (n=6) or other AAP (n=18)	Smoking behaviour (Self- reports and Observer- reports) Psychopathology (BPRS) Cognitive abilities (WAIS) Side effects (AIMS)	Smoking prevalence differed significantly among the three groups ($p<0.001$). CLO was associated with a significantly lower incidence of smoking than either TAP ($P<0.003$) or other AAP ($p=0.042$)

(Table 1): Continued.

Author N° patients	Design; Duration; Intervention	Outcomes	Results
Drake <i>et al.</i> (2000) N=151	Pros, OL, Ret analysis of subgroups 3 years SCH or SAD + AUD or SUD CLO (n=36) or non-CLO (n=115) (dose N.S.)	Alcohol and substance use, and days of alcohol use and drug use (TLFB, UTS, AUS, DUS, SATS) Psychopathology (BPRS)	CLO was associated with a significant improvement of substance abuse stage (p=0.003), and a decrease in the severity of alcohol (p=0.004) and drug (p=0.0001) use, and the number of drinking days (p=0.0002) and days of drug abuse (p=0.0003). 79% of patients receiving CLO were in remission from their AUD compared to 33.7% of patients who were not on CLO (p=0.001), and 65% of patients receiving CLO were in remission from the SUD, compared to 29.6% of patients not taking CLO (p=0.032)
Zimmet <i>et al.</i> (2000) N=58	Ret, OL study Over 3 years SCH or SAD + SUD CLO (dosage N.S.)	Psychotic symptoms Substance Use	More than 85% of patients on CLO decreased their alcohol and substance consumption, 72% of them achieving abstinence. The reduction of substance use significantly correlated with an improvement in global clinical symptoms (p=0.002)
Procyshyn <i>et al.</i> (2001) N=N.S.	Cross Sectional Duration N.S. SCH + ND CLO or Depot TAP	Self-reported smoking (FTND) Expired CO	Significant reduction in expired CO (p<0.01) and a trend toward significance in self-reported smoking (p=0.08) in patients taking CLO compared to patients taking Depot TAP
Procyshyn <i>et al.</i> (2002) N=14	Cross Sectional Duration N.S. SCH + ND RIS alone or RIS and CLO	Self-reported smoking (FTND)) Expired CO	Significant reduction in expired CO (p=0.03) and in self-reported smoking (p=0.04) in patients taking CLO and RIS compared to patients taking RIS alone
Green <i>et al.</i> (2003) N=41	Ret study 1 year SCH or SAD + AUD or CAUD CLO (n=33) (mean dose 439.6 mg/d) or RIS (n=8) (mean dose 3.9 mg/d)	Alcohol/Cannabis use Abstinence rates	Abstinence rates were significantly higher in patients treated with CLO (54%) than in those treated with RIS (13%) (p=0.05)
Kelly <i>et al.</i> (2003) N=45	OL 5 years TR-SCH, 19 with comorbid SUD	Psychopathology Readmission rates	Better treatment response in patients with comorbid SUD. Similar rates of readmission at 1-year follow-up
Kalyoncu <i>et al.</i> (2005) N=3	CS TR-SCH + AUD CLO + LAM	Alcohol consumption Alcohol craving (OCDS)	CLO + LAM was effective in treating AD A significant reduction in alcohol craving was observed (p<0.05)
Brunette <i>et al.</i> (2006) N=95	Pros, follow-up study 10 years SCH or SAD + SUD, 6-month abstinence Alcohol (74.8%), other drugs (41.9%) CLO (mean dosage 484 mg/d) (n=25) or TAP (n=62) or other AAP (n=8)	Relapse rates at 1 and 2-year follow-up	Significantly less substance abuse relapse with CLO compared to TAP and other AAP at 1-year (p=0.003) and 2-year follow-up (p=0.05)
Dervaux and Cazali (2007) N=1	CR Over 25 months SCH + AD CLO (600-1200 mg/d) + AMS (600 mg/d)	Psychopathology Addictive behaviour regarding alcohol	CLO + AMS was effective in controlling psychiatric symptoms and addictive behaviour regarding alcohol
Kim <i>et al.</i> (2008) N=61	Pros, Nat, Obs 2 years SCH + AUD CLO (mean dosage 423.6 mg/d) (n=25) or RIS (mean dosage 7.6 mg/d) (n=36)	Hospitalization rates Time until 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 hospital, compared to 48% of patients treated with CLO

(Table 1): Continued.

Author N° patients	Design; Duration; Intervention	Outcomes	Results
Machielsen <i>et al.</i> (2012) N=123	MC, Long, Nat study 6 years SCH, SCHD, SAD, DelD or PDNOS + CAD CLO (mean dosage 350 mg/d) (n=23) or RIS (mean dosage 3.46 mg/d) (n=48) or OLZ (mean dosage 13.78 mg/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
Mesholam-Gately <i>et al.</i> (2014) N=27	Experimental 3 months SCH or SAD + SUD CLO (n=13) or TAP (n=14) compared to HC	Odour hedonic task	CLO treatment is associated with broadening and strengthening the hedonic experience of rewarding olfactory stimuli and in this way, it could ameliorates some aspects of abnormal brain reward functioning in subjects with SCH + SUD
Schnell <i>et al.</i> (2014) N=30	RCT 12 months SCH + CAUD CLO (n=14) (50-425 mg/d, mean dosage 225 mg/d) or ZIP (n=16) (80-400 mg/d, mean dosage 200 mg/d)	Cannabis use (average of frequency use, UTS) Psychiatric symptoms (PANSS, MADS, GAF) Treatment compliance (drug plasma levels) Side-effects (UKU)	Cannabis use was reduced in both groups during follow-up, with no significant differences between the two groups. CLO was associated with significantly fewer positive symptoms ($p=0.05$), but more side effects ($p=0.017$) and poorer compliance ($p=0.024$), compared to ZIP

AD= Alcohol Dependence; AIMS= Abnormal Involuntary Movement Scale; AMS= Amisulpride; ASI= Addiction Severity Index; AUD= Alcohol Use Disorder; AUS= Alcohol Use Scale; BPRS= Brief Psychiatric Rating Scale; CAUD= Cannabis Use Disorder; CLO= Clozapine; CO= carbon monoxide; COA= Cocaine Abuse; COUD= Cocaine Use Disorder; CR= Case Report; CS= Case Series; DelD= Delusional Disorder; DUS= Drug Use Scale; FTND= Fagerstrom Test for Nicotine Dependence; GAF= Global Assessment of Functioning Scale; HC= Healthy controls; LAM= Lamotrigine; Long= Longitudinal; MADS= Montgomery Asberg Depression Scale; MC= Multicentre; Nat= Naturalistic; ND= Nicotine Dependence; N.S.= Not specified; Obs= Observational; OCD= Obsessive Compulsive Drinking Scale; OCDUS-CAN= Obsessive Compulsive Drug Use Scale, cannabis version; OL= Open Label; PANSS= Positive and Negative Symptoms Scale; PDNOS= Psychotic Disorder Not Specified; Pros= Prospective; Ret= Retrospective; RIS= Risperidone; SAD= Schizoaffective disorder; SATS= Substance Abuse Treatment Scale; SCH= Schizophrenia; SCHD= Schizophreniform Disorder; SU= Substance Use; SUD= Substance Use Disorder; TAP= Typical Antipsychotics; TLFB= Timeline Follow Back TR-SAD= Treatment Resistant Schizoaffective Disorder; TR-SCH= Treatment Resistant Schizophrenia; UKU= UKU Side Effect Rating Scale; UTS= Urine Toxicological Screenings; WAIS= Wechsler Adult Intelligence Scale; ZIP= Ziprasidone.

A history of SUD does not appear to influence the response to CLO in DD patients. This fact has been proved in several studies. In a 6-month-follow-up prospective study in which 118 treatment-resistant patients who met DSM-III-R criteria for schizophrenia or SAD, 29 patients with a past or current SUD showed less psychopathology and better psychosocial functioning at baseline, and after 6 months of CLO therapy they had similar levels of improvement in these parameters compared to the group of patients without a history of SUD [48, 49]. In addition, in a sample of 331 patients who suffered from schizophrenia or SAD, after a period of 6 months of treatment with CLO, substance abusers and non-substance abusers showed similar improvements in measures of psychopathology and psychosocial functioning [50]. Finally, in an open-label study a better response was found to CLO treatment in schizophrenic patients with comorbid substance abuse compared to non-abusing patients, in terms of a lower total Brief Psychiatric Rating Scale (BPRS) score, although readmission rates at 1-year follow-up were similar in both groups (23% and 21% respectively, $p=ns$) [51].

DISCUSSION

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 antipsychotics. Today, there is a consensus on 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]. In addition, TAP has been found to be ineffective in terms of reducing alcohol or substance abuse, and they sometimes even worsen addictive behaviours [17]. 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 [52]. However, these results have not been always replicated [53].

In regard to CLO, the data on the beneficial effect 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 clozapine as a first-line treatment due to several undesirable side effects such as the risk of agranulocytosis and seizures and the need for frequent monitoring [24]. In addition, many patients will not comply with the required laboratory blood tests or will not tolerate other common side effects of CLO such as hyper salivation, sedation and weight gain [46].

Although the mechanism by which CLO reduces substance abuse among patients with SMI remains unclear, several nonexclusive hypotheses have been proposed to explain the superiority of AAP over TAP in treating DD patients. Firstly, CLO has a unique action on the DA-mediated MCL system. It may reduce alcohol and SUD in SMI patients through its varied actions on multiple neurotransmitter systems, particularly its potent blockade of α_2 -NE receptors and increase in NE levels, its potent 5-HT₂ antagonism and its weak blockade of D₂ receptors. These actions would have a normalizing effect on the signal detection capabilities of a dysfunctional MCL brain reward system [6]. In addition, CLO lacks EPS and exerts a positive effect on psychotic positive and negative symptoms, relieving as well symptoms such as anxiety, all of which have been associated with an increase in substance use in DD patients as a way of "self-medication" [5, 27, 43, 46]. In addition, CLO has been shown to improve some aspects of cognitive dysfunction associated with SMI, which are aggravated when a concurrent SUD is present [54]. These findings have led to speculation that patients taking CLO would have more cognitive resources to avoid substance use and would be more aware of their psychiatric illness [27]. Specifically, in regard to CLO, it has been suggested that the greater frequency of clinic visits when being treated with CLO could contribute to increasing abstinence [44]. Some authors have suggested that the superior effect of CLO in the DD population might have been due to a selection bias by which prescribers select patients for CLO treatment who have less severe psychotic symptoms, are more compliant or have a less severe SUD [45]. However, this hypothesis has not been confirmed by other authors [47]. Finally, although results are inconclusive and contradictory, it has been proposed that another pathway by which CLO could help to reduce substance use in the DD population is through a direct effect on craving reduction. This effect is thought to be due to a lower occupancy rate of the D₂ receptor, higher dissociation rate of the D₂ receptor and the higher D₁/D₂ receptor occupancy associated to CLO [45].

Despite a growing body of evidence suggesting the beneficial effects of CLO 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 blind methodological designs. This is generally due to the specific features of DD patients who are more difficult to engage and retain in trials, and associated higher rates of treatment non-compliance.

However, CLO may be considered as a pharmacological strategy in DD patients, as it covers both aspects of the treatment of this population. It is effective in reducing psychiatric symptoms and it has been found to be effective in reducing use of several substances such as nicotine, alcohol, cannabis and polysubstances. In addition, it has been found that a history of SUD does not influence the positive response to CLO. Although undesirable side-effects such as agranulocytosis and seizures have led to restriction in its use, generally these studies tend to find positive results with moderate-high doses of CLO perhaps increasing the risk of lack of tolerability, as CLO side effects are dose-dependent. This drawback can be solved by carefully monitoring CLO in clinical settings.

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