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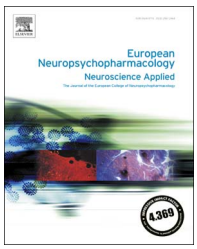

REVIEW

Clozapine use in patients with schizophrenia and a comorbid substance use disorder: A systematic review

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Abstract
Lifetime prevalence of substance use disorders (SUD) in patients with schizophrenia is nearly 50%. Nicotine, alcohol, and cannabis are the substances most frequently used, with a high percentage of poly-substance users. There are few available data about pharmacological approaches in this population. Amongst antipsychotics, clozapine shows positive evidence in the literature. The aim of the present article is to provide systematic review on the efficacy of clozapine in SUD improvement in schizophrenic patients. PRISMA recommendations were followed (PROSPERO id: CRD42017059299). Five studies for nicotine use and nine studies for SUD (other than nicotine) were analyzed. Regarding nicotine use, results from randomized controlled trials (RCT) have found a decrease in nicotine use after 12 weeks of 200–600 mg/day clozapine, as compared with lower doses. In SUD improvement (other than nicotine), RCT have shown superiority of clozapine when compared with risperidone, in short-term studies (from 4 to 12 weeks) performed in cannabis users. In long-term studies (1 year), clozapine was equal to ziprasidone in reducing cannabis use and equal to treatment as usual in reducing alcohol use. We conclude that positive results on nicotine use are scarce and derived from studies with a low degree of evidence. Evidence of clozapine on SUD (other than nicotine) is stronger, especially when clozapine is compared with first generation antipsychotics in poly-substance users. When

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compared with second generation antipsychotics, clozapine was superior to risperidone but equal to olanzapine or ziprasidone in poly-substance and cannabis users.

1. Introduction

Lifetime prevalence of substance use disorders (SUD) in patients with schizophrenia is nearly 50%, a percentage three times higher than in general population (Moore et al., 2012). SUD in patients with schizophrenia has a negative impact in treatment compliance, cognitive performance, functional prognosis and quality of life of these patients (Najt et al., 2011; Wobrock and Soyka, 2008). Indeed mortality ratios are even higher when there is a comorbid SUD (Hjorthøj et al., 2015). The substances most commonly used by patients with schizophrenia are nicotine (80–95%), followed by alcohol (20–60%), cannabis (12–42%), cocaine (15–50%) (de Leon and Diaz, 2005; Moore et al., 2012) and amphetamines (10–25%); moreover, a high percentage of patients present a poly-substance use. Despite this evidence, pharmacological treatment options of patients with schizophrenia and a SUD (Dual Diagnosis –DD- patients) are still challenging (Potvin et al., 2003; Wobrock and Soyka, 2008), as these subjects are usually excluded from pharmacological trials to avoid confounding effects and high rate of dropouts. As a consequence, there are few available data about pharmacological approaches in this psychiatric population and it is difficult to obtain clear guidance about the clinical management of these patients.

So far, some antipsychotic medications have shown to be effective as treatment of both conditions individually, that is, the schizophrenic disorder and the SUD (Lalanne et al., 2016). First generation antipsychotics (FGA) do not seem to have any beneficial effect in improving SUD in patients with schizophrenia (San et al., 2007; Green et al., 2008, 2015), and they are associated with even more consumption (Meszaros et al. 2011). Evidence related to the use of second generation antipsychotic (SGA), such as risperidone, olanzapine, quetiapine and aripiprazole, in these DD patients is mixed and not promising (San et al., 2007). In addition, in a meta-analysis of patients with cocaine and psychostimulant use without any other mental illness, antipsychotic medications did not improve craving or abstinence (Kishi et al., 2013). Consequently, although prescription of antipsychotics in patients with schizophrenia and SUD has been proposed, randomized controlled trials (RCT) have failed to ensure their positive effects in substance use behaviour.

Clozapine remains the only molecule where current literature retrieves some positive evidence of a substantial improvement of SUD in schizophrenic patients (San et al., 2007; Agid et al., 2010). The mechanisms that render clozapine superiority to other antipsychotics for the treatment of these patients are yet not fully understood. Clozapine reduction of the euphoric features and psychotic symptoms induced by addictive substances, such as the paranoid ideas triggered by cocaine use, has been suggested (Farren et al., 2000). Clozapine performs a relatively weak blockade and rapid dissociation from dopamine D2 receptors and a potent blockade of the serotonergic 5-HT_{2A} and the noradrenergic 1 and 2 receptors which might reduce substance craving (Green et al., 1999; Seeman, 2014). In addition, the enhancing effect of clozapine on glutamatergic NMDA mechanisms may alleviate substance use craving (Schwieler et al., 2008). Like other SGAs, clozapine is less disruptive to cognitive functions, thus enabling the use of coping skills learned during the psychotherapeutic SUD treatment (Wobrock and Soyka, 2008). Furthermore, researchers have found that N-desmethylclozapine (NDMC), the main metabolite of clozapine and a potent and efficacious muscarinic receptor agonist, is the specific molecular agent responsible for the distinctive efficacy of clozapine in the treatment of refractory schizophrenic patients (Weiner et al., 2004). The unique efficacy of clozapine in the treatment of SUD as compared to other SGA (Kelly et al., 2012) might also be explained partly by the special molecular structure of NDMC, which is not found in any of the SGA.

Overall, it has been observed that SUD improve significantly (by around 85%) when patients suffering from schizophrenia and a SUD switch from FGA to clozapine (Zimmet et al., 2000; San et al., 2007). However, the demonstrated efficacy of clozapine in the treatment of these DD patients mainly derives from uncontrolled observational studies and case series supporting its beneficial effects on psychopathology, craving or substance use. The aim of the present article is to provide a systematic literature review on the efficacy of clozapine treatment in the improvement of substance use and/or craving in patients with schizophrenia and a comorbid SUD.

2. Experimental procedures

The review was registered with the International Prospective Register of Systematic Reviews (PROSPERO), an international database of prospectively registered systematic reviews in health and social care based in the United Kingdom (id: CRD42017059299). Study methods and results follow recommendations of the PRISMA group for reporting systematic reviews (Moher al., 2009).

2.1. Search strategy, eligibility criteria, and search procedures

Following the PRISMA guidelines (Moher et al., 2009), we systematically searched in the electronic databases PubMed, Embase, PsyINFO, Scopus and Web of Science for articles about the use of clozapine for the treatment of substance use and/or craving in adult patients suffering from schizophrenia (and related disorders) and a comorbid SUD.

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