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Pharmacotherapy of Co-Occurring Schizophrenia and Substance Use Disorders

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Abstract

Substance use disorders, common in patients with schizophrenia, can lead to poor outcomes. Here we review the literature on the use of antipsychotics in patients with co-occurring schizophrenia and substance use disorder as well as evidence for the use of adjunctive pharmacological treatments targeting substance use in these patients. We also discuss a neurobiological formulation suggesting that the cooccurrence of these disorders may be related to a dysfunction in the dopamine mediated brain reward circuitry. Typical antipsychotics do not appear to decrease substance use in this population. Randomized, controlled trials provide some support for use of the atypical antipsychotic clozapine for co-occurring cannabis use disorder, naltrexone and disulfiram for alcohol use disorder, and also nicotine replacement therapy, sustained-release bupropion and varenicline for tobacco use disorder. Nonetheless, data regarding treatment in patients with these co-occurring disorders are still limited, and many studies reported to date have been either underpowered or did not include a control condition. Further research is needed to evaluate optimal pharmacotherapeutic strategies for this population.

Keywords

Schizophrenia; Substance use disorder; Antipsychotic; Brain reward; Clozapine

Introduction

Schizophrenia, characterized by hallucinations, delusions, and disorganized behavior and thinking, occurs in 1 % of the population. Nearly 50 % of people with schizophrenia have a lifetime substance use disorder [1], a rate three to four times higher than the general population [2]. Patients with schizophrenia and co-occurring substance use disorders (i.e.,

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Compliance with Ethics Guidelines: Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

"dual diagnosis" patients) have more severe psychiatric symptoms [3], are less treatment compliant [4], and have increased rates of hospitalization [5] compared to those with schizophrenia alone. Moreover, patients with schizophrenia die approximately 25 years prematurely, often due to heart disease, cancer, cerebrovascular disease, and lung disease, which can all be caused or exacerbated by substance use [6•, 7].

Several theories attempt to explain the high co-occurrence of schizophrenia and substance use disorders. In the neural stress diathesis model, neurobiological vulnerability interacts with environmental stressors, including substance use, to lead to substance use disorder in vulnerable individuals [8, 9]. In support of this model, substance use has been associated with a greater likelihood of the development of schizophrenia [10], and the "high output" variant of the catechol-o-methyl transferase (COMT) gene in adolescent cannabis users has been associated with the onset of psychotic symptoms in adulthood [11•]. Moreover, those with schizophrenia appear to be more vulnerable to the detrimental effects of substance use [12].

The self-medication hypothesis [13] proposes that individuals with schizophrenia use substances to ameliorate symptoms of schizophrenia or side effects of medications used to treat schizophrenia [14]. Although individuals with schizophrenia subjectively report improvements in sleep, mood, and other symptoms with substance use, substance use does not always correlate with symptom severity and studies have been unable to confirm the self-medication hypothesis as the cause of elevated rates of substance use in this population [15, 16].

Green and colleagues [17••] and others [18••] propose a third model. This reward circuitry dysfunction model postulates that a dysregulation in the dopamine-mediated mesocorticolimbic brain reward pathway underlies the cooccurrence of schizophrenia and substance use disorders, and that substance use may temporarily ameliorate this deficit, though substance use also worsens symptoms and the course of schizophrenia [19].

Optimal treatment for co-occurring schizophrenia and substance use disorder involves coordinated psychotherapy, psychosocial interventions, and pharmacotherapy [20]. Although motivational enhancement, cognitive behavioral therapy, group counseling, contingency management, supported employment, assertive community treatment, and long term residential treatment can improve outcomes in dual diagnosis patients treated with antipsychotics, many patients do not respond and relapse rates are high [21, 22]. Thus, there is clearly a need for better treatments. In this review we discuss evidence supporting the pharmacologic management of substance use in patients with co-occurring schizophrenia and substance use disorders and we discuss future directions toward the development of improved pharmacotherapies. Since antipsychotics are the first line of treatment for people with schizophrenia, we first review their use in this population. Then we discuss other pharmacotherapeutic strategies and also touch upon the possible use of neurostimulating treatments.

Antipsychotics

Typical Antipsychotics

Typical antipsychotics, which share a common mechanism of potent antagonism of the dopamine D2 receptor, appear to be less effective in those with co-occurring psychotic and substance use disorders than in those with psychosis alone [23]. In most (but not all, [24]) studies, these agents do not decrease and may actually increase substance use and craving [25–27]. Green and others suggested that the potency of the dopamine D2 receptor blockade produced by typical antipsychotics, while responsible for antipsychotic effects, might inhibit the ability of these medications to limit substance use [17••, 28].

Atypical Antipsychotics

Atypical or “second generation” antipsychotics share a common mechanism of a weaker dopamine D2 blockade and/or a broader base of pharmacological action than typical antipsychotics, which may be of particular significance in the treatment of patients with co-occurring substance use disorders [17••]. Here we review data on clozapine, risperidone, olanzapine, quetiapine and aripiprazole. We are not aware of data published on the impact of the other atypical antipsychotics on substance use disorders in patients with schizophrenia.

Clozapine—The atypical antipsychotic clozapine can effectively reduce psychotic symptoms in patients with schizophrenia, but its use has been limited to patients who are refractory to other pharmacotherapies because of its side effect profile. This includes weight gain, sedation, seizures, and the risk of agranulocytosis, which requires regular blood count monitoring [29]. Unlike the typical agents, however, there is some evidence that clozapine may decrease substance use in patients with schizophrenia.

Two small chart reviews showed possible benefits of clozapine for decreasing substance use [30, 31]. In 151 prospectively followed patients with schizophrenia or schizoaffective disorder and substance use disorder, a higher proportion of patients receiving clozapine versus those taking another atypical antipsychotic achieved remission from a drug (64 % vs. 30 %) or alcohol use disorder (79 % vs. 34 %) [32•]. Following the same group over the next year showed that those in remission and treated with clozapine had lower rates of relapse to substance use (8 %) than those treated with other antipsychotics (40 %) [33]. Another open prospective study showed a reduction in cigarette smoking as demonstrated by lower expired carbon monoxide (effect size ∼0.8) among those taking clozapine compared to those treated with typical antipsychotics [34].

Two small randomized, controlled trials have been completed. In the first, 31 subjects with schizophrenia and cannabis use disorder were randomized to clozapine or continued on their current antipsychotic for twelve weeks [35]. The clozapine group used less cannabis than the other group (effect size ∼0.6). In the second trial including 28 patients with schizophrenia and cannabis use disorder, those randomized to clozapine demonstrated a larger decrease in subjective cannabis craving and a larger decrease in bilateral insula activation during a cannabis word Stroop task compared to those randomized to risperidone [36•].

While the basis of clozapine's apparent ability to decrease substance use is not known, Green and colleagues hypothesized that it could be due to clozapine's broad spectrum pharmacological effects, including its weak blockade of the dopamine D2 receptor, potent blockade of the norepinepherine alpha-2 receptor, and its ability to increase norepinepherine levels in the brain and plasma. They further suggested that these combined effects of clozapine may ameliorate a deficiency in the mesocorticolimbic reward circuitry postulated to occur in people with schizophrenia [17••, 19]- consistent with the findings by Machielsen and colleagues [36•].

Risperidone—Given the beneficial effects of clozapine, a number of studies assessed whether other antipsychotics share clozapine's ability to decrease substance use in patients with schizophrenia. This is of particular importance because clozapine tends to be used infrequently, given its side effects. While some suggested that the atypical antipsychotic risperidone might reduce craving and relapse more than haloperidol in patients with schizophrenia and cocaine use disorder (e.g. [37]), subsequent studies comparing risperidone to other atypical agents have been less promising. Risperidone appears less able to limit alcohol and cannabis use [31] and craving [36•, 38] than clozapine, and it demonstrates no benefit compared to olanzapine in reducing cannabis use in patients with schizophrenia [39, 40].

In patients with tobacco use disorder, however, those treated with group therapy and nicotine replacement therapy and also taking atypical antipsychotics, including risperidone (N= 18), had a 55.6 % smoking cessation rate (vs. 22.2 % in those taking typical antipsychotics (N=27)). Patients on risperdone and olanzapine had the highest quit rates [41•].

Given poor adherence to oral medications common in patients with schizophrenia [42], studies have assessed long-acting, injectable risperidone. Results in patients with co-occurring disorders conflict. In an open six month trial of 115 patients with schizophrenia and substance use disorder, those treated with long acting injectable risperidone had fewer positive urine drug screens compared to those treated with the long acting injectable typical antipsychotic, zuclopenthixol, although the difference was small [43]. Green and colleagues randomized 95 patients to treatment with either oral risperidone or long acting injectable risperidone to treat alcohol use disorder in patients with schizophrenia. The study suggested that, while patients in both groups continued drinking, those treated with injectable risperidone used less alcohol than those treated with oral risperidone [44•]. Moreover, a post-hoc analysis of alcohol use in a different one-year study comparing long-acting injectable risperidone to oral antipsychotic treatment in patients with unstable schizophrenia showed that scores on the alcohol composite index of the Addiction Severity Index favored people assigned to long-acting injectable risperidone [45]. However, Leatherman and colleagues, who randomized 396 patients with schizophrenia or schizoaffective disorder to long acting risperidone or an oral atypical antipsychotic, found no difference in substance use outcomes between the groups [46].

Olanzapine—Data regarding efficacy of olanzapine in patients with co-occurring schizophrenia and substance use disorders are similarly mixed. In one small observational study, substance abuse declined with olanzapine [47]. Other naturalistic studies, however,

did not find improvements in substance use among patients switched to olanzapine compared to those maintained on typical antipsychotics [48, 49]. In a longitudinal, naturalistic cohort study of 123 patients with cannabis use disorder and a psychotic disorder [38], olanzapine treatment led to less cannabis craving compared to risperidone but did not differ from clozapine in its effect on cannabis craving [38].

Two rigorous trials comparing olanzapine to haloperidol in patients with schizophrenia found conflicting results for cocaine craving along with no significant change in cocaine positive urine drug screens [50, 51]. Two randomized trials showed that olanzapine did not convey an advantage over risperidone in reducing cannabis use among schizophrenia patients [39, 40]. However, the study of nicotine replacement therapy mentioned above reported higher rates of smoking cessation among patients on risperdone and olanzapine compared to those on typical antipsychotics [41•].

Quetiapine—Although initial research on effects of quetiapine on alcohol drinking in the general population was promising, a recent randomized controlled trial showed that this medication did not improve drinking outcomes more than placebo in patients with alcohol dependence [52]. While two small, open label studies of quetiapine for patients with schizophrenia and substance use disorder found improvements in severity of substance use [53] and mean days of drinking per week [54], no randomized, controlled trials of quetiapine have been completed in this population.

Aripiprazole—The data on aripiprazole are also limited. Two small, open label trials showed reductions in cocaine and alcohol craving [55, 56]; one also showed reduction in dollars spent on alcohol but not a reduction in cocaine use [56], and the other showed a reduction in cocaine positive urine tests [55]. In an open label trial of 139 patients with schizophrenia and tobacco use disorder randomly assigned to haloperidol, risperidone, olanzapine, or aripiprazole, subjects on aripiprazole (N=31) showed a decrease in tobacco craving and nicotine dependence [57].

Summary of Data on Antipsychotics—While typical and atypical antipsychotics effectively reduce psychotic symptoms in patients with schizophrenia, research has not demonstrated an optimal antipsychotic treatment for patients with co-occurring schizophrenia and substance use disorders. Typical antipsychotics do not appear to decrease substance use, although preliminary studies suggest clozapine may be effective in treating these dual diagnosis patients. Further research is needed to clarify clozapine's optimal use in this population. Research on risperidone, olanzapine, quetiapine, and aripiprazole thus far has been less promising and, to our knowledge, no data have been published on the possible role of the other, newer atypical antipsychotics in such patients.

Adjunctive Treatments

There are a number of pharmacologic agents available for use in treating substance use disorders that have been used as adjunctive agents to antipsychotics in patients with schizophrenia and co-occurring substance use disorders. The Food and Drug Administration has approved three drugs for the treatment of alcohol use disorder - disulfiram (Antabuse),

naltrexone (ReVia, Vivitrol), and acamprosate (Campral); three drugs for the treatment of opioid use disorder - methadone (Dolophine), buprenorphine (Suboxone, Subutex), and naltrexone; and three drugs for the treatment of tobacco use disorder - nicotine (e.g. Nicorette), bupropion (Zyban), and varenicline (Chantix). Other agents used in the treatment of substance use disorders including anticonvulsants, tricyclic antidepressants, cannabinoids, and neurostimulation treatments are also discussed here.

Disulfiram

Disulfiram inhibits the enzyme aldehyde dehydrogenase to prevent the breakdown of acetaldehyde to acetate. After consuming alcohol while taking this medication, acetaldehyde accumulates in the body, causing patients to experience symptoms such as flushing, changes in blood pressure, sweating, headache, palpitations, nausea and vomiting. Multiple studies have shown that short-term, supervised use of disulfiram among motivated patients deters alcohol use [58].

Despite early reports that disulfiram may exacerbate psychiatric symptoms, a retrospective chart review suggested that disulfiram can be a safe and effective adjunctive treatment in patients with schizophrenia and alcohol use disorder [59]. In a randomized trial comparing disulfiram, naltrexone, and the combination of disulfiram and naltrexone to placebo, patients with psychotic illness and alcohol use disorder (N=66) treated with disulfiram had more days of abstinence and fewer heavy drinking days, with no change in psychotic symptoms compared to placebo [60•].

Naltrexone

Naltrexone, a competitive antagonist at μ-opioid receptors, decreases the pleasant and euphoric effects of drinking [61] through indirect action on the dopamine mediated pathway from the ventral tegmental area to the nucleus accumbens, the primary pathway involved in reinforcement, motivation, and reward anticipation [62]. Naltrexone reduces heavy drinking and the number of drinking days in alcohol dependent patients in the general population but does not significantly enhance abstinence [63].

For patients with schizophrenia, an early, small, open label trial was promising [64]. Following this, the trial in psychotic patients noted above (a randomized trial comparing disulfiram, naltrexone, and the combination of disulfiram and naltrexone to placebo) found that patients treated with naltrexone had more days of abstinence and fewer heavy drinking days as compared to those treated with placebo, with no change in psychotic symptoms [60•]. The same research group also demonstrated the efficacy of naltrexone in this population with apparent safety in a small, placebo controlled double blind study of naltrexone and cognitive behavioral therapy in 31 patients with schizophrenia and alcohol use disorder [65]. Patients treated with naltrexone had significantly fewer drinking days, fewer heavy drinking days, and reported less craving than did those treated with placebo, with no worsening psychosis. A long-acting, injectable form of naltrexone is available [66], but to our knowledge it has not been studied in patients with schizophrenia and alcohol disorders.

Acamprosate

Acamprosate is thought to restore the balance between inhibitory and excitatory systems [67] involved in the negative reinforcing effects of alcohol and the response to alcohol cues [68]. It may also reduce the rewarding effects of alcohol [69]. Studies in those with alcohol use disorder found that acamprosate reduces the risk of relapse after detoxification from alcohol and increases cumulative abstinence time [70].

Only one small, randomized trial (N=23) of the effect of acamprosate on alcohol drinking patients with schizophrenia and co-occurring alcohol use disorder has been reported, showing that acamprosate was not more effective than placebo in reducing drinking among these patients [71]. There was also no effect on psychotic symptoms or cognitive function [72].

Anticonvulsants

Some anticonvulsants have shown promise in the treatment of alcohol dependence, but none are currently FDA approved for this use. Topiramate, believed to antagonize glutamate receptors and facilitate $GABA_A$-mediated currents [73], appears to reduce heavy drinking in alcohol dependent patients but is often not well tolerated [74]. Valproate, an anticonvulsant and mood stabilizer, may increase time to relapse to heavy drinking in abstinent alcohol dependent patients [75] and reduce heavy drinking in patients with bipolar disorder [76]. Lastly, in a recent study, the anticonvulsant levitiracetam was reported ineffective for the treatment of alcohol dependence in a multisite trial [77]. To our knowledge, none of these medications has been studied in people with schizophrenia and substance use disorders.

Tricyclic Antidepressants

Two small studies published more than 20 years ago demonstrated that tricyclic antidepressants may have a role as an adjunctive treatment (added to typical antipsychotics) in individuals with schizophrenia and substance use disorders [78, 79]. Interestingly, recent animal research in alcohol drinking hamsters (used to model some aspects of alcohol drinking in people with schizophrenia) by our group suggests that the combination of the tricyclic antidepressant desipramine with the antipsychotic risperidone can reduce alcohol drinking more than either drug alone [80]. Feasibility trials are underway to assess the value of this combination in patients with schizophrenia and alcohol use disorder.

Opioid Substitution Therapy

To our knowledge there are no published trials of methadone or buprenorphine for the treatment of patients with schizophrenia and co-occurring opioid use disorder. There have been, however, brief reports suggesting that these medications may be helpful in this population [81, 82].

Cannabinoids

The endocannabinoid system modulates dopamine transmission leading to the notion that targeting cannabinoid receptor activity may be beneficial for the treatment of substance use disorders. Despite encouraging data from animal studies, a placebo-controlled double blind

study of the cannabinoid inverse agonist rimonabant in alcohol dependent patients (without a co-occurring psychiatric disorder) demonstrated that it did not prevent relapse to alcohol use [83]. Recently however, Fischer and colleagues (2014) reported on a preliminary imaging study suggesting that smoked cannabis or oral tetrahydrocannabinol, the primary psycho-active agent in cannabis, partially corrects a brain reward system deficit in patients with schizophrenia and co-occurring cannabis use disorder [84]. These data, if confirmed by future research, may suggest that a low dose of a cannabinoid agonist, given with an antipsychotic, could be tested in an attempt to decrease cannabis use in patients with schizophrenia.

Nicotine Replacement Therapy

In two open studies of nicotine replacement therapy for tobacco use disorder, nicotine patch, gum or both given with weekly group counseling led to abstinence in 12-13 % of smokers with schizophrenia over a six month follow-up period [85, 86]. Another longitudinal study in 68 smokers with schizophrenia assigned to 8 weeks of nicotine patch found that 23.1 % achieved continuous abstinence at 3 month follow up compared to 0 % in the control group [87]. Lastly, in a randomized, controlled trial of nicotine replacement with eight weeks of psychotherapy, compared to treatment as usual in patients with a psychotic disorder, rates of abstinence did not significantly differ between groups; however, the treatment group had a greater reduction in smoking at 3 months (43.5 % reduced cigarette consumption by at least 50 %, compared to 16.6 % of the comparison group) [88].

Novel strategies to treat tobacco use disorder in patients with schizophrenia are being explored. In a small, controlled study, Tidey and colleagues demonstrated the potential benefits of very low nicotine content cigarettes [89]. Moreover, one early observational study of electronic-cigarettes (not approved by the Food and Drug Administration as a cessation strategy) showed that 50 % of smokers with schizophrenia had a 50 % reduction in smoking and 14.3 % achieved abstinence at 1 year [90]. Over the coming years, we can anticipate more innovative uses of nicotine to decrease tobacco smoking.

Varenicline

Varenicline, a partial nicotinic receptor agonist [91], may affect dopamine release in the ventral tegmental area and striatum of the mesocorticolimbic reward pathway in response to nicotine [92]. Although a number of studies have demonstrated a role for this medication as an aid in smoking cessation, varenicline carries a Food and Drug Administration black box warning due to reports of depression and suicidal ideation associated with its use, often deterring providers from using varenicline in patients with co-occurring psychiatric disorders. However, a number of studies over the past few years demonstrated that varenicline appears to safely reduce smoking in patients with schizophrenia. A small trial using varenicline as an adjunctive treatment with healthy lifestyle intervention was promising [93] and was followed by two studies of smokers with schizophrenia treated with varenicline and cognitive behavioral therapy for twelve weeks. In one study, 47.3 % achieved at least two consecutive weeks of continuous abstinence at week 12 [94] and in the second, 60.4 % met criteria for two week point prevalence abstinence at week twelve [95].

Two randomized double-blind studies provided further evidence for its use in this population. The first, a 12-week trial, found that varenicline treatment was associated with a 19 % smoking cessation rate as compared to 4.7 % for placebo at 12 weeks [96]. The rate of adverse events was similar between the groups, with no significant change in psychotic or other mood symptoms. The second, a relapse prevention study in patients with severe mental illness (91 % with schizophrenia spectrum disorders) reported that after a year, point prevalence abstinence rates in those maintained on varenicline were higher than in those treated with placebo after an initial response to varenicline (60 % vs. 19 %) [97••]. There was a similar rate of adverse events in both groups without a change in psychotic or other mood symptoms between groups. A possible benefit of varenicline is that it may attenuate nicotine withdrawal-related cognitive dysfunction [98, 99] and improve performance on cognitive measures [100–102] in smokers with schizophrenia.

Varenicline is also being explored as a treatment for other substance use disorders. A recent, multi-site, randomized, controlled trial showed that varenicline reduced heavy drinking more than placebo in people with alcohol use disorders [103]. However, there has been limited study of varenicline for alcohol use disorder in schizophrenia. The one reported randomized, placebo controlled pilot trial, recruiting only 10 patients, suggested some promise. Although its tolerability was lower than reported in studies of its use for treating tobacco use disorder in patients with schizophrenia, the number of drinks was numerically lower in the group receiving varenicline [104] suggesting that future studies are warranted.

Bupropion

The antidepressant bupropion has been shown to decrease smoking in patients with schizophrenia. A small, 12 week, placebo controlled trial (N=19) suggested that bupropion plus cognitive behavioral therapy facilitated smoking cessation (11 % vs. 0 %) or reduction (66 % vs. 11 %) [105] with the majority of those who achieved at least a 50 % reduction able to maintain this reduction at two years [106]. Two larger placebo controlled trials showed that bupropion in combination with psychotherapy (N=53 and N=32) improved abstinence compared to placebo and psychotherapy (16-50 % on bupropion vs. 0–12.5 % on placebo), but these effects did not persist after treatment with bupropion ended [107, 108]. However, prolonged use of bupropion (12 months) may help to sustain smoking abstinence [109]. Moreover, there is evidence that combining bupropion with nicotine replacement therapy [110•] may improve outcomes.

Neurostimulation Therapies

There is recent interest in the use of transcranial magnetic stimulation (TMS) in the treatment of substance use disorders. Preliminary research suggests that stimulation over the dorsolateral prefrontal cortex can reduce cravings for substances, including alcohol and cigarettes, in people without schizophrenia [111, 112]. One small, randomized study in male patients with schizophrenia and co-occurring tobacco use disorder (N=35) with TMS showed a reduction of tobacco use during the treatment period among those receiving the active compared to the sham treatment [113]. Lastly, while case reports regarding the potential use of deep brain stimulation for severe substance use disorders have been

appearing, (for review, see [114]), randomized trials in patients with or without schizophrenia have not been completed.

Summary and Recommendations

Substance use disorders commonly co-occur and contribute to a greater overall risk of morbidity and mortality in individuals with schizophrenia. Thus, optimal treatment for patients with schizophrenia must address and treat these co-occurring disorders. While the etiology of substance use in this population is not well understood, it may involve a dysfunction in the dopamine-mediated mesocorticolimbic brain reward pathway. Although preliminary data about the use of the atypical anti-psychotic clozapine appears to be promising for the treatment of co-occurring schizophrenia and substance use disorder, no fully powered, randomized trials of clozapine in this population have been published, thus cautious use of clozapine in dual diagnosis patients is appropriate. Randomized trials suggest the potential value of the adjunctive agents naltrexone and disulfiram for co-occurring schizophrenia and alcohol use disorder as well as bupropion and varenicline for co-occurring tobacco use disorder. Given the clinical significance of co-occurring substance use disorder in patients with schizophrenia, further research is needed before the field has a full list of effective pharmacologic treatment approaches for this population.

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