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Substance abuse and schizophrenia: Pharmacotherapeutic intervention

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Abstract

Substance use disorder is common in patients with schizophrenia and dramatically worsens their outcome. The typical antipsychotic medications, introduced over 50 years ago, are effective for the treatment of psychosis but may have only limited efficacy in patients with these co-occurring disorders because patients continue to use substances while taking them. In preliminary studies, however, several of the atypical antipsychotic medications have shown promise for reducing alcohol and drug use in patients with schizophrenia. A neurobiologic formulation is discussed, suggesting that the use of substances in patients with schizophrenia may be based on a dysfunction within the dopamine-mediated brain reward circuitry, and that clozapine in particular, may potentially ameliorate this dysfunction and lessen the desire for substance use. Medications for the treatment of alcohol use disorders, such as disulfiram, naltrexone and acamprosate, as well as other adjunctive medications, may also be useful. Further studies are required to establish a solid evidence base of best practices for the use of medications in these patients.

Keywords

Schizophrenia; Substance Abuse; Brain Reward; Atypical Antipsychotics; Clozapine

1.0 Introduction

Schizophrenia is a chronic illness characterized by hallucinations, delusions, disorganized thinking or behavior, and associated disability that occurs in approximately 1% of the population worldwide. Nearly 50% of people with schizophrenia, including those within their first episode (usually occurring in late adolescence or early adulthood) have a lifetime history of substance use disorder, a rate at least 3 times as high as seen in the general population (Regier et al., 1990). Alcohol, cannabis and cocaine tend to be the primary substances of abuse. In addition, 70% to 90% of patients with schizophrenia smoke cigarettes, as compared to approximately 21% of the people within the general U.S. population (Centers for Disease Control and Prevention, 2005). Patients with schizophrenia and co-occurring alcohol and/or drug use disorders have a poorer long-term course than patients with schizophrenia without co-occurring substance use disorder: they have increased symptoms (Swartz et al., 2006),

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decreased adherence to treatment (Owen, Fischer, Booth, & Cuffel, 1996), increased mental illness relapses (Linszen, Dingemans, & Lenior, 1994), hospitalizations (Brady et al., 1990; Drake & Brunette, 1998; Gupta, Hendricks, Kenkel, Bhatia, & Haffke, 1996; Richard, Liskow, & Perry, 1985), violence (Abram & Teplin, 1991; Swanson, Holzer, Ganju, & Jono, 1990) and victimization (Goodman et al., 2001; Hiday, Swartz, Swanson, Borum, & Wagner, 1999), as well as homelessness (Caton, Shrout, Eagle, Opler, & Felix, 1994), an increased risk of HIV, hepatitis B and hepatitis C infections (Cournos & McKinnon, 1997; Rosenberg, Goodman et al., 2001), and a higher level of suicidality than patients without substance use disorder (Green, Salomon, Brenner, & Rawlins, 2002; Potvin, Stip, & Roy, 2003). In recent years, evidence-based practices for the care of patients with co-occurring schizophrenia (and other severe mental illness) and substance use disorders have been developed that integrate pharmacotherapy, psychosocial treatment and substance abuse services (Brunette, Drake, Lynde, & IDDT Group, 2002; Drake et al., 2001; Mueser, Noordsy, Drake, & Fox, 2003). However, most pharmacotherapy treatment guidelines for patients with schizophrenia and co-occurring substance use disorder are still in their infancy. In this article, we review theories that have attempted to elucidate the basis of substance use disorder in patients with schizophrenia. Then, we describe the effects of antipsychotic medications, indicating that some of these medications may be more helpful than others in this population, and we also note the potential role of other adjunctive medications for these patients. Lastly, we describe how one neurobiological theory about the basis of substance use disorder in patients with schizophrenia may allow us to understand the actions of medications that may be useful in the treatment of these patients.

2.0 The basis of substance use disorder in patients with schizophrenia

A number of theories have been advanced to explain the frequent association of substance use disorder and schizophrenia. Several groups have proposed that substance use can trigger the onset of schizophrenia in vulnerable individuals (Degenhardt, Hall, & Lynskey, 2003; Fowles, 1992; Walker & Diforio, 1997). A number of reports suggesting that patients with schizophrenia and a history of substance use disorder may have an earlier age of onset of schizophrenia would appear consistent with this possibility (Addington & Addington, 1998; Alterman, Ayre, & Williford, 1984; Green et al., 2004; Mueser et al., 1990; Salyers & Mueser, 2001; Tsuang, Simpson, & Kronfol, 1982; Weller, Ang, Latimer-Sayer, & Zachary, 1988). In addition, most investigators, report that patients with schizophrenia experience negative effects following the use of even small quantities of substances (D'Souza et al., 2005; Drake, Osher, & Wallach, 1989; Gonzalez, Bradizza, Vincent, Stasiewicz, & Paas, 2006; Treffert, 1978). Moreover, a recent report (Caspi et al., 2005) that adolescent cannabis use is associated with the development of psychosis in those who have a “high output” variant of the gene for catechol-o-methyl transferase (COMT) suggests an important gene-environment interaction in this risk.

The self-medication hypothesis suggests that individuals with schizophrenia may use substances to alleviate distressing psychiatric symptoms (Khantzian, 1985, 1997) or the uncomfortable neurologic side effects of antipsychotic medications (Potvin, Pampoulova et al., 2006; Siris, 1990). Despite the appeal of this explanation, studies that have tried to confirm this hypothesis have failed to do so (Blanchard, Brown, Horan, & Sherwood, 2000; Brunette, Mueser, Xie, & Drake, 1997; Buckley, 1998; Kirkpatrick et al., 1996; Lysaker, Bell, Beam-Goulet, & Milstein, 1994; Mueser et al., 1990; Scheller-Gilkey, Thomas, Woolwine, & Miller, 2002). Thus, while patients with dual disorders report that use of substances subjectively lessens social problems, insomnia and low mood similar to people with primary substance use disorders, the self-medication hypothesis does not appear to be an adequate causal explanation for the elevated rates of substance use disorder in schizophrenia.

Green and colleagues (Green, Zimmet, Strous, & Schildkraut, 1999; Roth, Brunette, & Green, 2005) and others (Chambers, Krystal, & Self, 2001) have proposed an alternative, neurobiological hypothesis. This formulation, based on a series of animal studies (Svensson et al., 1995), suggests that the dysregulated dopamine-mediated mesocorticolimbic brain pathways that are thought to underlie the symptoms of schizophrenia are also the basis of a brain reward circuit deficit in these patients. Green et al. have further proposed that substances of abuse transiently lessen this deficit (and thus allow patients with schizophrenia to enjoy normal activities) while, unfortunately, they also worsen the course of schizophrenia (Green, Zimmet, Strous, & Schildkraut, 1999; Roth, Brunette, & Green, 2005). Studies are underway to confirm the existence of this brain reward circuit deficiency in patients with schizophrenia.

3.0 Therapeutic approaches

3.1 Psychosocial treatment

Patients with co-occurring substance use disorder and schizophrenia are optimally treated in integrated programs that combine and coordinate psychotherapy, psychosocial treatments for mental illness and substance abuse counseling, and the use of medications for the mental illness and the addiction (Brunette, Drake, Lynde, & IDDT Group, 2002; Drake, Mueser, Brunette, & McHugo, 2004; Mueser, Noordsy, Drake, & Fox, 2003). These “integrated” treatment programs, implemented by multidisciplinary teams of case managers, therapists and psychiatric prescribers, optimally involve comprehensive services (e.g., pharmacotherapy, rehabilitation and social support interventions) that match the patient's level of motivation, are tailored to the individual patient, and are offered with a long-term treatment perspective. Patients with co-occurring disorders benefit from standard psychosocial services for schizophrenia, such as supported employment and assertive community treatment, but these services have minimal impact on substance use itself (Drake, O'Neal, & Wallach, In press). The most effective specific integrated interventions for substance abuse in patients with schizophrenia include group counseling with cognitive-behavioral and motivational components (Bellack, Bennett, Gearon, Brown, & Yang, 2006; Weiss et al., In press), contingency management (Drebing et al., 2005; Ries et al., 2004), and, for patients who do not respond to less intensive interventions, long-term residential programs (Brunette, Mueser, & Drake, 2004).

3.2 Use of medications in patients with schizophrenia and co-occurring substance use disorder

Antipsychotic medications, first introduced for the treatment of patients with schizophrenia over 50 years ago, serve as the core pharmacologic intervention for most patients with schizophrenia. All of these medications clearly reduce symptoms of schizophrenia and improve patient functioning, but their side effects vary. The older antipsychotics (typical antipsychotics) are associated with movement disorders and neurologic side effects (Stroup, Kraus, & Marder, 2006) and tend to have modest ability to improve negative symptoms of schizophrenia (reduced motivation, emotion, and communicativeness) (Corrigan, Reinke, Landsberger, Charate, & Toombs, 2003). Moreover, the typical antipsychotics are thought to be only modestly helpful in dual disorder patients (Bowers, Mazure, Nelson, & Jatlow, 1990): they do not decrease substance abuse in these patients, and there is some suggestion that they may even worsen substance abuse in some of them (Brady et al., 1990; Dixon, Haas, Weiden, Sweeney, & Frances, 1991; McEvoy, Freudenreich, Levin, & Rose, 1995).

3.3 Atypical antipsychotic medications

Six new medications, the atypical antipsychotic medications, were introduced in the U.S. beginning in 1989 with the availability of clozapine. Although clozapine has significant side effects that limit its use to patients who do not respond to other medications, evidence suggests

that it may be the most effective antipsychotic available today (McEvoy et al., 2006). Other post-clozapine atypical antipsychotic medications, introduced in 1994 or later (risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole), have nearly replaced the typical antipsychotic medications in general clinical practice because they are considered to be at least equally effective and, as a group, do not cause neurologic side effects as frequently as the typical antipsychotics. Whether the atypical antipsychotics other than clozapine are better for reducing symptoms of schizophrenia than the older typicals is not clear (Lieberman et al., 2005; McEvoy et al., 2006) (although it is clear that many of these medications, including clozapine, are associated with weight gain, diabetes, and elevated cholesterol and triglycerides). However, there is a growing body of opinion and evidence suggesting that at least some of these atypical antipsychotics may be more helpful than typical antipsychotics in patients with schizophrenia and co-occurring substance use disorder. In the following section, we will discuss the evidence for the use of these medications in this co-occurring population.

3.4 Clozapine

Clozapine was introduced to treat patients who did not respond well to other medications (treatment-resistant patients). Although less than 5% of American patients with schizophrenia are treated with clozapine currently, research suggests that this medication, despite its potential toxicity, is more effective than other atypical antipsychotic medications (McEvoy et al., 2006), and is indicated for patients with schizophrenia who experience ongoing psychotic symptoms, suicidality (Meltzer et al., 2003) and aggression (Chengappa et al., 2002; Krakowski, Czobor, Citrome, Bark, & Cooper, 2006; Volavka, Zito, Vitrai, & Czobar, 1993).

Clozapine can cause a variety of serious side effects, including suppression of white blood cells, that, if uninterrupted, can lead to death. Fortunately, a frequent white blood cell monitoring protocol has dramatically decreased low white blood cell-related fatalities to almost zero. However, other side effects of concern include rare instances of cardiomyopathy, seizures, and more frequent problems with weight gain, diabetes, and elevated cholesterol and triglycerides.

A series of case reports and case series reports, beginning in the mid-1990s, suggested that this medication was effective in patients with co-occurring disorders and that it appeared to limit substance use. These reports involved patients who used alcohol, cocaine, and multiple substances (Albanese, Khantzian, Murphy, & Green, 1994; Marcus & Snyder, 1995; Yovell & Opler, 1994) as well as nicotine (George, Sernyak, Ziedonis, & Woods, 1995; McEvoy, Freudenreich, Levin, & Rose, 1995; McEvoy, Freudenreich, & Wilson, 1999).

The data from these initial reports were then bolstered by a number of other studies. A report by Buckley and colleagues (1999) of a 12 week open-label study of clozapine in 55 patients with schizophrenia, some of whom had co-occurring substance use disorder, indicated that the response to clozapine did not differ depending on substance use disorder status. Moreover, among the patients with a co-occurring disorder who remained on clozapine for the full 12-week period, 70% had a reduction in or abstinence from substance use. Lee and colleagues (1998) also reported on an open label study of 35 patients, also indicating that clozapine was associated with decreased substance use.

Drake and colleagues (2000) reported on 151 patients with schizophrenia or schizoaffective disorder and substance use disorder who were prospectively followed within dual disorder treatment programs. Among the 36 patients who received clozapine treatment for schizophrenia symptoms, remission rates for alcohol and cannabis use disorders were 67-79%, compared to 34% among the 115 patients taking typical antipsychotics. Moreover, in a 10-year follow-up report from this same study group, patients in remission who were treated with clozapine were less likely to relapse over the subsequent year (8%) than those who were treated

with other antipsychotics (40%) (Brunette, Drake, Xie, McHugo, & Green, 2006). Zimmet and colleagues also reported on a retrospective survey of patients with schizophrenia or schizoaffective disorder and substance use disorder treated with clozapine. Among 36 patients who were active substance users at time of clozapine initiation, 85-93% decreased use of alcohol, marijuana or cocaine over the course of clozapine treatment, with 72-80% achieving abstinence (Zimmet, Strous, Burgess, Kohnstamm, & Green, 2000).

Despite these intriguing and highly consistent data, however, it must be noted that to this point there are no randomized prospective studies of the effects of clozapine in patients with schizophrenia and co-occurring substance use disorder. Thus, the evidence suggesting that clozapine can decrease substance use remains preliminary.

3.5 Other atypical antipsychotics

A number of atypical antipsychotics have been introduced in the years following the approval of clozapine. As a group, these medications appear to be safer than clozapine, produce fewer extrapyramidal (neurologic) side effects than typical antipsychotics, and may also decrease at least some negative symptoms in patients with schizophrenia (Corrigan, Reinke, Landsberger, Charate, & Toombs, 2003). As previously mentioned, however, some of these medications are associated with significantly more risk than typical antipsychotics for the development of obesity, diabetes, elevated cholesterol and triglycerides and the metabolic syndrome. In general, recent guidelines tend to recommend the use of these medications in the dually diagnosed population, instead of the older typical antipsychotics (Ziedonis et al., 2005). We review here the data regarding each of these atypical agents in the population of patients with co-occurring schizophrenia and substance use disorders.

3.5.1 Risperidone—After case reports suggested that risperidone may be helpful in controlling substance use in patients with co-occurring schizophrenia and substance use disorders, Smelson and colleagues (2002) studied 18 recently withdrawn inpatients with schizophrenia and cocaine dependence who demonstrated craving while watching cocaine use on videotape. Patients assigned to 6 weeks of risperidone reported reduction in 2 components of cocaine craving (intensity and depression) relative to patients remaining on conventional antipsychotics, and demonstrated a lower rate of relapse to cocaine use at study completion. However, Green and colleagues reported on a 1-year retrospective study among 41 patients with schizophrenia or schizoaffective disorder and comorbid alcohol or cannabis use disorder who were treated with either risperidone (n=8) or clozapine (n=33) (Green, Burgess, Dawson, Zimmet, & Strous, 2003). Only 12% of patients treated with risperidone became abstinent within one year of treatment, as compared to 54% of patients treated with clozapine. Moreover, a larger retrospective chart review study of 249 Veterans Administration patients with schizophrenia and co-occurring substance use disorders showed that, after controlling for confounding factors, atypical antipsychotic treatment (mostly risperidone or olanzapine) was not associated with greater improvements on clinical Addiction Severity Index scores of substance use compared to treatment with typical antipsychotics (Petrakis, Leslie, Finney, & Rosenheck, 2006). Recently, Rubio and colleagues (2006) reported that the new, long-acting, injectable form of risperidone was more effective in improving substance abuse than a depot form of the typical agent, zuclopenthixol (that is not available in the U.S.), but the difference was small and potentially not clinically significant. Further research is required to fully assess the effects of risperidone treatment, including the potential value of the long-acting injectable risperidone (Risperdal Consta) on substance use in this population.

3.5.2. Olanzapine—Olanzapine, the second atypical antipsychotic introduced after clozapine, is quite effective in the treatment of psychosis (Lieberman et al., 2005; Lieberman et al., 2003), but is also associated with higher rates of significant metabolic syndrome side

effects (including weight gain and elevated blood sugar, cholesterol and triglycerides) than risperidone, aripiprazole, ziprasidone, and the typical antipsychotics. This medication has been used for many patients with co-occurring disorders. An initial study reported by Conley and colleagues (1998) suggested that, like clozapine but unlike typical antipsychotics, olanzapine is efficacious for the treatment of symptoms in patients with schizophrenia whether or not they have co-occurring substance use disorder. Moreover, Littrell and colleagues (2001) reported an uncontrolled 12-month open label trial of olanzapine plus psychoeducation and self-help referral in 30 patients with schizophrenia or schizoaffective disorder and co-occurring substance use disorders. Seventy percent of patients achieved early full remission and the remainder achieved partial remission from substance use disorders with olanzapine treatment, and 100% achieved sustained abstinence from cocaine use. Other studies, however, have not supported an advantage for the use of olanzapine compared to typical antipsychotic medications in this population. For example, Noordsy and colleagues reported on a naturalistic follow-up of 105 patients (87% of whom had schizophrenia or schizoaffective disorder and co-occurring substance use disorder) who were switched to olanzapine, and compared them to 49 patients remaining on conventional antipsychotics (Noordsy, O'Keefe, Mueser, & Xie, 2001a, 2001b). While they noted that those patients switched to olanzapine demonstrated significant improvements in alcohol and drug abuse at 6, 12, and 48 months relative to their own baseline, these improvements in the level of abuse did not differ from those who remained on a typical antipsychotic. Moreover, the previously mentioned Veterans Administration study of 249 patients with schizophrenia and co-occurring substance use disorder showed that, after controlling for confounding factors, atypical antipsychotic treatment (mostly risperidone or olanzapine) was not associated with greater improvements on clinical Addiction Severity Index scores of substance use compared to treatment with typical antipsychotics (Petrakis, Leslie, Finney, & Rosenheck, 2006).

Lastly, two more rigorous prospective studies of olanzapine also provide conflicting results. Smelson and colleagues (2006) presented a 6-week double-blind, randomized trial of olanzapine vs. haloperidol among 31 patients with schizophrenia and co-occurring cocaine dependence. Weekly ratings of cocaine craving in response to videotape images of cocaine use were administered. Patients assigned to olanzapine reported significantly lower scores on several dimensions of craving, and 13% of completers had positive urine drug screens at endpoint vs. 40% in the haloperidol group, but the difference between the groups was not statistically significant. Moreover, Sayers and colleagues (2005), conducted a more lengthy 26-week, double-blind, randomized trial of olanzapine compared to haloperidol in 24 patients with schizophrenia and cocaine abuse. There were no differences in cocaine-positive urines, and craving was actually greater in the olanzapine-treated group compared to the haloperidol-treated group. Further randomized trials are necessary to establish the effect of olanzapine in this population.

3.5.3. Quetiapine—Preliminary data also suggest that quetiapine may be helpful in reducing substance abuse in patients with co-occurring disorders. One case report showed reduced polysubstance abuse in a patient with schizophrenia (Cruz, 2001), and Potvin and colleagues (2004) reported on 4 patients with co-occurring schizophrenia and 4 with bipolar disorder and cannabis use disorder who reduced cannabis consumption by 97% for an average of 6 months following treatment with quetiapine. In addition, in an open trial of 24 patients with schizophrenia spectrum disorders and a co-occurring substance use disorder, severity of substance abuse improved over the 12-week study (Potvin, Stip et al., 2006). Lastly, Brown and colleagues (2001) presented data on 29 patients with major depression, schizophrenia, schizoaffective or bipolar disorders who were receiving chronic treatment with a conventional antipsychotic and had co-occurring cocaine or amphetamine use disorders. Patients were randomly assigned to continue (N=17), or to discontinue conventional antipsychotic treatment (N=12). The discontinuation group was switched to quetiapine if psychotic symptoms were

present (N=8, mean dose 394 mg/day), or to no antipsychotic (N=4). The entire discontinuation group and the quetiapine treated subgroup had significantly lower psychiatric symptom and cocaine craving scores than those remaining on conventional antipsychotics.

3.5.4. Ziprasidone and aripiprazole—There are no data on ziprasidone and few data regarding aripiprazole in this population; these two medications are the newest atypical antipsychotics available in the U.S.. One case report showed reduced alcohol use with aripiprazole (Warsi, Sattar, Bhatia, & Petty, 2005), and an open label trial of aripiprazole given to 10 patients with schizophrenia and co-occurring cocaine use disorders indicated that the use of this atypical antipsychotic was associated with decreased cocaine use (Beresford et al., 2005). Lastly, another open label study of aripiprazole (Brown, Jeffress, Liggin, Garza, & Beard, 2005) in patients with schizophrenia/schizoaffective disorder and alcohol abuse (N = 17) or cocaine abuse (N = 9) noted decreased alcohol craving and dollars spent on alcohol, as well as decreased cocaine craving. There was no effect on cocaine use.

3.5.5. Atypical antipsychotics and nicotine use—Three prospective studies (Evins et al., 2005; George et al., 2002; George et al., 2000) have suggested that treatment with atypical antipsychotics may augment smoking cessation interventions. In a 10-week study of nicotine patch plus group therapy among 45 patients with schizophrenia, 56% of patients on atypical antipsychotics vs. 22% of patients on typical antipsychotics achieved abstinence (George et al., 2000). Moreover, in two placebo-controlled trials of bupropion for smoking cessation (one in 53 patients (Evins et al., 2005) and the other in 32 patients with schizophrenia (George et al., 2002)), researchers found that treatment with atypical antipsychotics significantly enhanced bupropion's effect. Lastly, McEvoy reported that 2 prospectively studied groups of patients (N=12 and N=55) who switched from typical antipsychotics to clozapine spontaneously reduced cigarette smoking (McEvoy, Freudenreich, Levin, & Rose, 1995; McEvoy, Freudenreich, & Wilson, 1999).

3.5.6 Atypical antipsychotics summary—Preliminary research has been conducted in patients with schizophrenia and co-occurring substance use disorders and has suggested possible benefit for all the atypical agents studied thus far. The only one with no reports is ziprasidone. The type of study conducted, the target substance of abuse, the diagnosis of substance abuse or dependence, and the study measures utilized vary widely, making direct comparison of the impact of any one atypical compared to another or to typicals as a whole rather difficult. It would seem fair to say the following at this junction: 1) The data on the beneficial effect of clozapine are consistently positive, although the lack of prospective randomized trials limits the conclusions that can be drawn. 2) Data regarding quetiapine and aripiprazole are also consistent, but less substantial, with only 2 small, prospective studies without controls having been conducted with each of these medications. 3) While data from small randomized trials suggesting beneficial effects for olanzapine and risperidone have been reported, evidence from other studies is conflicting. Thus, while initial or preliminary research suggests that a number of the atypical antipsychotics may be helpful in this population, all of these medications require further study with randomized, controlled trials to fully define their impact on substance abuse in patients with schizophrenia and co-occurring substance use disorders.

4.0 Other medications for substance disorders

4.1 Naltrexone and acamprosate

In recent years, two new medications have been introduced for the treatment of alcoholism -- naltrexone and acamprosate. To our knowledge, only naltrexone has been studied in patients with schizophrenia. An open trial in 17 patients with schizophrenia and alcohol dependence

suggested a positive effect (Batki et al., 2002). Two later reports from Petrakis and colleagues (Petrakis et al., 2004; Petrakis, Nich, & Ralevski, 2006) both of which were randomized placebo-controlled double-blind trials in Veterans Administration patients, the first in 31 patients with schizophrenia and the second in 66 patients with psychotic illness, suggest that naltrexone may be helpful in decreasing alcohol use in patients with schizophrenia or other psychotic-spectrum disorders and co-occurring alcohol dependence. The new long-acting depot form of naltrexone has not yet been studied in this population.

4.2 Disulfiram

Disulfiram has been used as a treatment for alcoholism for decades. It has also been used for patients with schizophrenia and co-occurring alcohol use disorder (Kofoed, Kania, Walsh, & Atkinson, 1986) although its use has not been widespread, perhaps due to concerns about its potential ability to stimulate psychosis (Kingsbury & Salzman, 1990), its potential liver toxicity (Iber, Lee, Lacoursiere, & Fuller, 1987) and the need for monitoring. Nonetheless, a retrospective study in 33 patients with severe mental illness and alcohol use disorder suggested beneficial effects for the use of disulfiram in over 60% of the patients with no evidence of increased psychosis (Mueser, Noordsy, Drake, & Fox, 2003). In addition, a randomized trial reported by Petrakis and colleagues (Petrakis, Nich, & Ralevski, 2006) suggested that disulfiram was as effective as naltrexone in reducing alcohol use in a group of 66 patients with alcohol dependence and psychotic-spectrum disorders.

4.3 Antiepileptic/Mood stabilizers

Although a few studies (Brady, Sonne, Anton, & Ballenger, 1995; Salloum et al., 2005) have suggested that valproic acid may reduce alcohol use in patients with bipolar disorder and alcohol dependence, it has not been studied in patients with schizophrenia. One study suggested that the anti-seizure medication topiramate may reduce alcohol use in patients with alcoholism (Johnson et al., 2003), but the only evidence for the potential value of this medication in patients with schizophrenia and co-occurring alcohol use disorder is two case reports of 1 patient (Huguelet & Morand-Collomb, 2005) and 3 patients (Kalyoncu et al., 2005) documenting reduced alcohol use in patients with schizophrenia given this medication. Further studies are appropriate and will need to assess the potential side effects when using topiramate in patients with schizophrenia and alcohol use disorder.

4.4 Other adjunctive agents

Patients with schizophrenia can benefit from opiate replacement therapy (Miotto, Preti, & Frezza, 2001). However, while the partial opioid antagonist buprenorphine has been approved for use in the treatment of opioid addiction, we know of no studies of this agent in patients with schizophrenia. The antidepressant bupropion, used in smoking cessation programs, has shown some beneficial effects as well in patients with schizophrenia, as noted above (George et al., 2002). Lastly, two small studies from the early 1990s suggested that tricyclic antidepressants may be useful in patients with schizophrenia and co-occurring substance use disorder (Siris, Mason, Bermanzohn, Shuwall, & Aseniero, 1993; Ziedonis, Richardson, Lee, Petrakis, & Kosten, 1992).

5.0 Discussion

5.1 A possible neurobiological basis for the effects of clozapine in patients with schizophrenia and co-occurring substance use disorder

As noted above, several authors (Green, Zimmet, Strous, & Schildkraut, 1999; Chambers, Krystal, & Self, 2001; Roth, Brunette, & Green, 2005) have proposed that a brain reward circuit dysfunction may underlie substance use disorders in patients with schizophrenia. The reward

deficiency formulation of the basis of substance use in patients with schizophrenia proposes that people with schizophrenia have a dysfunction in their dopamine-mediated brain reward pathways in the mesocorticolimbic tracts, which underlies their alcohol and substance use. It further proposes that the use of alcohol or substances may produce a transient amelioration of this reward dysfunction, thus allowing people with schizophrenia to experience feelings of pleasure and satisfaction.

This neurobiologic formulation also describes the possible basis of the apparent effect of clozapine on limiting substance abuse in patients with schizophrenia (Green, Zimmet, Strous, & Schildkraut, 1999). Based on data from animal studies (Svensson et al., 1995), Green and colleagues (1999) have proposed: that typical antipsychotics do not decrease alcohol/substance use in this population largely because they do not restore the normal function of the brain reward circuits (in part because of their potent dopamine-2 receptor (D2) blockade); but that clozapine, through its varied actions on multiple neurotransmitter systems, particularly through its potent blockade of alpha 2 noradrenergic receptors, its striking increase in norepinephrine levels, as well as its weak blockade of dopamine D2 receptors, may tend to have a normalizing effect on the signal-detection capability of this dysfunctional mesocorticolimbic brain reward circuit.

What this formulation suggests about the other atypical antipsychotics is not clear. To the degree that other agents can mimic clozapine's putative facilitative effects on brain reward circuitry, they could potentially confer similar benefit. Whether quetiapine, which produces a relatively weak D2 blockade, or aripiprazole, which is a partial dopamine agonist (Kane et al., 2002), will decrease substance abuse in these patients as clozapine seems to do remains to be determined. Moreover, how the apparent effect of naltrexone (a medication that, in essence, blocks reward circuitry in the brain) relates to this neurobiological formulation is not clear at this time (Roth, Brunette, & Green, 2005).

5.2 Treatment Recommendations

Patients with schizophrenia and co-occurring substance use disorders benefit from comprehensive treatment that includes psychosocial and medication treatment of both disorders in an integrated fashion. Medication treatment to reduce psychosis is a key component of treatment. Many clinicians consider treatment with an atypical antipsychotic primary, when feasible and acceptable to the patient (Krystal, D'Souza, Madonick, & Petrakis, 1999; Mueser, Noordsy, Drake, & Fox, 2003; Ziedonis et al., 2005), and they have a lower threshold for recommending a trial of clozapine than in patients without a substance use disorder (Ziedonis et al., 2005). Although the potential side effects of weight gain and metabolic abnormalities that can occur in patients treated with atypical antipsychotics need to be considered, the risks associated with uncontrolled substance abuse, including suicide (Meltzer, 2002), violence and aggression (Soyka, 2000; Swanson et al., 2006), and blood-borne infections (Cournos & McKinnon, 1997; Rosenberg, Trumbetta et al., 2001) should also be taken into account. Importantly, clozapine treatment has been shown to be associated with decreased suicidality (Meltzer et al., 2003) and decreased aggression (Chengappa et al., 2002; Krakowski, Czobor, Citrome, Bark, & Cooper, 2006; Volavka, Zito, Vitrai, & Czobar, 1993) among people with schizophrenia. In many cases, the risks of side effects may be outweighed by the potential benefits of treatment with clozapine or other atypical agents.

Although of real concern, dangerous interactions between antipsychotic medications and substances of abuse seem to be rare (Mueser, Noordsy, Drake, & Fox, 2003). The atypical antipsychotic medications may pose fewer acute risks, although some of them can be significantly sedating, which can be problematic in combination with sedating substances of abuse, and clozapine's side effect profile can be problematic. Combining clozapine with high-dose sedatives (e.g., benzodiazepines) can lead to respiratory depression, and there was one

reported case of near-syncope when clozapine and cocaine were given to a cocaine addict (Farren et al., 2000), suggesting that clozapine should be avoided in patients with cocaine disorders.

As noted above, medications for alcohol abuse, such as naltrexone and acamprosate are not contraindicated in schizophrenia, and naltrexone has been shown to have beneficial effects in these patients (Petrakis, Nich, & Ralevski, 2006; Petrakis et al., 2004). Disulfiram has also been shown to be effective and has seemed to be generally well tolerated in these patients (Mueser et al., 2005). Nonetheless, close monitoring for exacerbation of psychotic symptoms and liver toxicity after initiating disulfiram treatment or after a dose escalation is warranted (Iber, Lee, Lacoursiere, & Fuller, 1987; Kingsbury & Salzman, 1990).

Whatever the potential (and possibly crucial) role that pharmacological strategies may have in the treatment of patients with schizophrenia and comorbid substance use disorder, it is unlikely that the substance abuse will remit with medication treatment alone. Rather, pharmacologic treatment for patients with co-occurring disorders should be delivered in a context of integrated care for both disorders provided simultaneously by the same clinical care team following evidence-based practice guidelines (Drake et al., 2001). Within the framework of integrated care, a shared decision-making approach to selection of medication may be useful (Noordsy et al., 2000).

5.3 Conclusion and Future Directions

Medications are an important component of comprehensive, integrated treatment for patients with schizophrenia and co-occurring substance use disorders. Research specifically testing the effects of medications on substance use outcomes in this group of patients remains in its infancy. Despite numerous suggestive reports, the questions of whether and to what degree antipsychotic medications and other medications for substance use disorders are effective in reducing substance use among people with co-occurring disorders are not yet answered. Further research, including prospective randomized controlled trials, will be needed to provide clarity in this area and to allow for the establishment of a solid evidence base for clinical practice.

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