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The Potential Role of Long-acting Injectable Antipsychotics in People with Schizophrenia and Comorbid Substance Use

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Abstract

Objective—Treatment of schizophrenia in patients with comorbid substance use (alcohol/illicit drug use, abuse or dependence) presents challenges for public health systems. Substance use in people with schizophrenia is up to four times greater than the general population and is associated with medication nonadherence and poor outcomes. Therefore, continuous antipsychotic treatment in this population may pose more of a challenge than for those with schizophrenia alone. Many clinical trials and treatment recommendations in schizophrenia do not take into consideration substance use as people with comorbid substance use have typically been excluded from most antipsychotic trials. Nonetheless, antipsychotic treatment appears to be as efficacious in this population, although treatment discontinuation remains high. The objective of this review was to highlight the importance and utility of considering long-acting injectable antipsychotics for patients with schizophrenia and comorbid substance use.

Methods—We did a literature search using PubMed with key words schizophrenia and substance use/abuse/dependence, nonadherence, antipsychotics, long acting injectables, relapse, and psychosocial interventions. We limited our search to human studies published in English and 4,971 articles were identified. We focused on clinical trials, case reports, case series, reviews and meta-analyses resulting in 125 articles from 1975-2011.

Results—Our review suggests the potential role of long-acting injectables for people with comorbid substance use and schizophrenia in leading to improvements in psychopathology, relapse prevention, fewer rehospitalizations, and better outcomes.

Conclusions—While more research is needed, long-acting antipsychotics should be considered an important option in the management of people with schizophrenia and comorbid substance use.

Keywords

substance use; nonadherence; long-acting antipsychotics; relapse; drug abuse

Co-occurrence of substance use, abuse and dependence is common in people with schizophrenia and is associated with poor long-term outcomes. Despite this common co-occurrence and its negative impact on the course of schizophrenia, there have been very few studies assessing optimal therapeutic strategies for these patients. Because of the cognitive,

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affective, and social impairments in schizophrenia (Morrison, Bellack, & Mueser, 1988; Nuechterlein and Dawson, 1984), the treatment of people with comorbid substance use and schizophrenia presents a formidable challenge to both clinicians and the mental health system. There is a clinically unmet need for more effective therapeutic interventions to improve the outcome of people with comorbid schizophrenia and drug use. However, pharmacotherapy treatment guidelines for persons with schizophrenia having comorbid drug use are still in their infancy. In the absence of specific pharmacotherapy interventions, these individuals are prone to poor quality of life, housing instability, and repeated relapses and rehospitalizations, and these outcomes are associated with substantial costs to society.

Magnitude of the Problem

The prevalence of substance use in people with schizophrenia is higher than substance use in the general population, with estimates of the prevalence of lifetime substance use *disorders* in people with schizophrenia ranging from as low as 10% to over 65% (Bowers and Swigar, 1983; Ananth *et al.*, 1989; Mueser *et al.*, 1990). One large-scale community-based comorbidity study conducted by the National Institute of Mental Health (NIMH) Epidemiological Catchment Area program (Regier *et al.*, 1990), evaluated substance abuse and other psychiatric disorders using structured clinical interviews with over 20,000 individuals and found the lifetime risk of substance use in schizophrenia to be 4.6 times higher than in the general population and also higher than in other psychiatric disorders. Despite the wide range of prevalence reports, most studies demonstrate that nearly 50% of people with schizophrenia have a lifetime history of a substance use disorder (Schneier and Siris, 1987; Hambrecht and Hafner, 1996; Fowler *et al.*, 1998; Dixon, 1999; Green *et al.*, 1999; Mueser *et al.*, 2000; Cantor-Graee *et al.*, 2001; Swadi and Bobier, 2003; Van Mastrigt *et al.*, 2004). More recently, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project examined the baseline correlates of substance use in people with schizophrenia or schizoaffective disorder. Although 60% of the sample reported using illicit drugs and alcohol, only 37% had a diagnosis of abuse or dependence. Male sex, lower education level, recent period of homelessness, childhood conduct problems, history of major depression, illness exacerbation, and lower negative and higher positive symptom ratings have been linked with higher rates of substance misuse in individuals with schizophrenia (Swartz *et al.*, 2006).

Methods of Literature Search and Selection

In order to examine the utility and role of long-acting injectable antipsychotics in schizophrenia and particularly for use with comorbid substance use, we conducted a literature search using PubMed with key words schizophrenia and substance use/abuse/dependence, nonadherence, antipsychotics, long-acting injectables and relapse, and psychosocial interventions. We limited our literature search to human studies published in English and 4,971 articles were identified. We focused on clinical trials, case reports, case series, reviews and meta-analyses which resulted in 125 articles published from 1975 through 2011 which were included in the paper.

Substances of Abuse in Schizophrenia

Alcohol, cannabis, and to a lesser extent, cocaine and amphetamines are the most frequently abused substances in people with schizophrenia, though regional variation influences use patterns (Siris *et al.*, 1988; Mueser *et al.*, 1990; Drake *et al.*, 1996; Kavanagh *et al.*, 2000; Cantor-Graee *et al.*, 2001; Wobrock *et al.*, 2005). The rate of alcohol abuse in people with schizophrenia ranges from 20% to 60%, cannabis abuse ranges from 12% to 42%, cocaine abuse ranges from 15% to 50% (Chambers *et al.*, 2001) and amphetamine use ranges from

10% to 25% (Siris *et al.*, 1988; Mueser *et al.*, 1990; Littrell *et al.*, 2001). A polyvalent pattern (more than two drugs at the same time) of use is also common (Soyka *et al.*, 1993). Other drugs of abuse in this population include heroin and hallucinogens, but these are less often the drugs of choice by psychiatric patients (Margoless *et al.*, 2004). A UK study reported that prevalence rates of co-occurring schizophrenia and substance abuse are increasing by about 10% per year, while the average age of people with both disorders has decreased from 38 years to 34 years (Frisher *et al.*, 2004).

Impact of Substance Use on Health and Illness Course

In general, having comorbid substance use is also deleterious to physical health. On average, people with alcohol or drug use have approximately 30% more physical diagnoses per case than non-substance users (Adrian and Barry, 2003). Regular and modest use of alcohol and drugs is associated with an increased potential for comorbidities such as human immunodeficiency virus (HIV) and Hepatitis B and C infections, as well as other infectious diseases (Drake and Wallach, 1993; Tsuang and Fong, 2004). Dickey *et al.* (2002) reported that the odds ratios for having diabetes, heart disease, asthma, skin infections, cancer, respiratory disorders and gastrointestinal disorders were higher in patients with co-occurring mental illness and substance abuse compared to patients with severe mental illness and no substance abuse diagnosis. Other serious consequences of substance use include victimization, trauma and accidents (Hiday *et al.*, 1999; Goodman *et al.*, 2001), homelessness (Dixon 1999), increased relapse and hospitalizations (Drake *et al.*, 1990; Cleghorn *et al.*, 1991; Gupta *et al.*, 1996; Dixon, 1999; Gerding *et al.*, 1999; Hunt *et al.*, 2002) and increased service utilization and costs of care (Dickey and Azeni, 1996; Hoff and Rosenheck, 1999).

In addition to medical and psychosocial issues, substance use complicates the course of schizophrenia and its treatment. Substance abuse in schizophrenia has been associated with a more severe course of the disorder, including an earlier age of illness onset and more severe symptomatology (Mueser *et al.*, 1990). In an 18-month longitudinal study of 100 people with schizophrenia, those with comorbid substance use had a greater deterioration of function over time than those with schizophrenia who did not use illicit drugs and alcohol (Chouljian *et al.*, 1995). Moreover, comorbid substance use may complicate the establishment of a diagnosis early in the course of schizophrenia and may delay effective treatment (Norman and Malla, 2002; Green *et al.*, 2004). Finally, evidence suggests that early substance use, particularly cannabis, may accelerate the onset of schizophrenia (Green *et al.*, 2004; Green, 2005).

Prospective studies investigating the impact of comorbid substance use in psychosis have shown an increased risk of relapse of positive symptoms (Wade *et al.*, 2006), treatment dropout, poor remission rates and worse outcomes at 18 months (Lambert *et al.*, 2005). Individuals with comorbid substance use have longer admissions (Swofford *et al.*, 2000), more violent episodes (Miles *et al.*, 2003) and suicides (Potvin *et al.*, 2003).

Dixon and colleagues examined symptoms, functioning and alcohol and drug abuse or dependence in 83 inpatients with schizophrenia (N=68), schizoaffective (N=12) and schizophreniform disorders (N=3) at admission and discharge. It is interesting to note that people with comorbid substance use were no different from people without comorbid substance use at the time of admission. People with comorbid substance use (N=40) had less overall psychopathology than people without comorbid substance use at the time of discharge, although lengths of hospital stay and dose of antipsychotics were the same. The authors hypothesized that this interesting finding could possibly be due to people with comorbid substance use responding more quickly or completely to treatment in addition to

the drug and alcohol effect wearing off. However, despite the fact that people with comorbid substance use had lower symptomatology at the time of discharge, they did not have better functioning as assessed by the global assessment scale (Dixon et al., 1991).

Nonadherence in People with Comorbid Substance Use

Among all the deleterious effects of substance use in schizophrenia, nonadherence is one of the most problematic. People with comorbid substance use are at an increased risk of nonadherence compared to those who do not use alcohol and illicit drugs (Drake *et al.*, 1989; Owen *et al.*, 1996; Swofford *et al.*, 1996; Fenton *et al.*, 1997; Olfson *et al.*, 2000; Soyka, 2000a; Soyka, 2000b; Lacro *et al.*, 2002; Margolese *et al.*, 2004). In a longitudinal outcome study of 135 people with schizophrenia, people with current substance use were eight times more likely to report medication nonadherence than those without substance use (Owen *et al.*, 1996). Approximately one-third (35.6%) of people with schizophrenia who were nonadherent with their antipsychotic in this study had comorbid substance use (Wilk *et al.*, 2006). Substance use disorder was a significant predictor of medication nonadherence in a large (N=2,138) VA database (Kreyenbuhl *et al.*, 2011). There is evidence that patients discontinue antipsychotics during phases of active substance abuse because of concerns about medication-drug interactions (Pristach and Smith, 1990). Prescribers may also be less likely to use certain antipsychotic medications in this population. For example, prescribers are sometimes reluctant to use clozapine in comorbid patients because of the need for regular blood testing to monitor for agranulocytosis, and the concern that comorbid substance use patients may be less likely to show up regularly for the blood draws (Kavanagh *et al.*, 2002). Nonadherence, rather than lack of efficacy, is likely one of the greatest threats to effective care. Therefore, prescribing considerations should include patient preferences, limitations of side effects and a focus on ways to improve medication adherence.

Oral Antipsychotic Treatment in People with Comorbid Substance Use

Clinical trials have largely excluded patients with comorbid substance use and few published studies have examined the effectiveness of oral antipsychotics in this population. Thus, existing data reporting the effectiveness of antipsychotics in people with comorbid substance use are mostly based on open-label studies or case series. Wobrock and Soyka (2008) in a comprehensive review of 51 articles suggest that second generation antipsychotics may have superior efficacy to first generation antipsychotics in people who have comorbid substance use with regard to improvement in psychopathological symptoms, reduced drug and alcohol craving, and greater reduction of substance use. This review is based on a variety of controlled, open-label, meta-analysis and case series studies. Other reports have been published touting the efficacy of most currently marketed second generation antipsychotics in patients with comorbid substance use, although the majority of data consists of case reports and case series, and non-controlled studies. These include studies of aripiprazole (Beresford *et al.*, 2005; Brown *et al.*, 2005), clozapine (Zimmet *et al.*, 2000; Kelly *et al.*, 2003), olanzapine (Conley *et al.*, 1998; Littrell *et al.*, 2001; Longo, 2002; Tsuang *et al.*, 2002), quetiapine (Brown *et al.*, 2003; Potvin *et al.*, 2006) and risperidone (Smelson *et al.*, 2002; Rubio *et al.*, 2006). Finally, in a 16-week clinical trial olanzapine (n=28) and risperidone (n=21) were compared in first-episode schizophrenia subjects with cannabis use disorder. Both olanzapine and risperidone had similar efficacy on psychotic symptoms and substance use. In fact, for patients taking either medication, cannabis use was higher in patients who used cannabis in the first three months post-admission (Sevy *et al.*, 2011).

There is a fair amount of literature supporting the deleterious effects of first generation antipsychotic use in those with comorbid substance use. The results of some studies suggest that treatment with first generation antipsychotics may even worsen substance abuse (Brady *et al.*, 1990; Dixon *et al.*, 1991; McEvoy *et al.*, 1995). First generation antipsychotics are associated with a high incidence of extrapyramidal side effects in patients with comorbid substance use, which may contribute to increased use of drugs and alcohol to self medicate (Siris, 1990; Green *et al.*, 2004). Likewise, people with comorbid substance use may be at a higher risk for experiencing extrapyramidal side effects and tardive dyskinesia (Olivera *et al.*, 1990), potentially making self-medication more likely.

It remains unclear if specific antipsychotics worsen or can improve drug craving in schizophrenia. Limited evidence suggests that specific agents may lead to higher drug use and craving (McEvoy *et al.*, 1995), such as the first generation agents. There is some evidence that clozapine and aripiprazole may be associated with less craving (Zimmet *et al.*, 2000; Brown *et al.*, 2005), while other reports suggest that risperidone, olanzapine and quetiapine are associated with less craving than first generation medications. Although the direct effects of antipsychotics on illicit drug craving remain unclear, regular follow ups, symptom improvement and better medication adherence may have secondary effects on decreasing drug use.

While second generation antipsychotics appear to be effective for symptoms of psychosis in those with comorbid substance use, discontinuation is common. Perkins *et al.* (2008) reported that in first episode patients, substance use was a predictor of discontinuation of second generation antipsychotics against medical advice. Long-acting antipsychotics may offer a treatment alternative for patients with dual disorders who are at particular risk for having antipsychotic nonadherence and treatment discontinuation.

Long-Acting Injectable Antipsychotics

Studies suggest that 25% to 60% of people with schizophrenia may not take their antipsychotic medication as prescribed (Gilmer *et al.*, 2004; Becker *et al.*, 2007; Velligan *et al.*, 2007). Since many patients have problems with nonadherence, using a depot or a long-acting injection as a mechanism where the treatment delivery is assured may be especially beneficial. In fact, the main advantage of this dosing formulation is to ensure continuous delivery of antipsychotic medications. However, one could argue that the real advantage of a long-acting injectable is that it eliminates covert nonadherence, continuous medication delivery is only assured if the patient returns for the next injection. Another advantage of long-acting injectables is that nonadherence is detected early and the treatment team can intervene by calling the patient, treatment guardian or the assertive community treatment program, so that the patient receives the long-acting injectable on a timely basis. Long-acting injectables also have slow clearance, so that antipsychotic serum levels do not drop rapidly following nonadherence.

Long-acting formulations of antipsychotics are an important treatment option, particularly for patients who have difficulties remaining adherent to medications (Weiden *et al.*, 1995; Perkins *et al.*, 2002; Valenstein *et al.*, 2006; Byerly *et al.*, 2007). Depot antipsychotics provide a strategy to help patients to overcome the challenges of consistent and perhaps, life-long medication-taking in the face of a complex illness that often results in poor insight and impaired cognitive functioning (Adams *et al.*, 2001; Haddad *et al.*, 2009).

The use of long-acting injectable antipsychotics continues to be less popular in the United States as compared to many other countries. However, the increasing availability of second generation antipsychotic long-acting injectables (Fleischhacker *et al.*, 2009) in combination

with ever increasing needs to control the costs associated with relapse leading to rehospitalization might impact utilization rates.

First Generation Long-acting Injectable Antipsychotics (Depot Antipsychotics)

First generation long-acting injectables have been available in the US since 1967. These dosage forms have been found to offer advantages over oral antipsychotic treatment. In a meta-analysis from the Cochrane Database, Adams et al. (2001) found a statistically significant advantage for first generation long-acting injectables compared to oral haloperidol and fluphenazine for global improvement in symptoms. However, this meta-analysis compared different antipsychotics in the oral and long-acting injectable formulations. This could be a major bias because of different D2 affinities and pharmacokinetics. A meta-analysis published by Schooler (2003) reported that the 1-year relapse rate for patients treated with depot antipsychotics was 27% compared with 42% for patients who received oral medication. In a 4-arm study, fluphenazine decanoate in combination with psychosocial treatment was associated with fewer relapses than depot alone, oral antipsychotic treatment alone or the combination of oral antipsychotic and psychosocial treatment. In this study, anxiety and depression scores were significantly higher in the long-acting group than the oral group (Hogarty et al., 1979). In another study comparing fluphenazine decanoate with oral fluphenazine, 35% (N=8) of patients taking decanoate were removed from the study because of severe akinesia as opposed to only two patients being terminated from the oral group (Rifkin et al., 1977). Because these agents are oil-based, there could be delayed normalization of D2 receptor availability after discontinuation of long-acting injectables. This may lead to persistent plasma levels or slow decline of the drug and prolactin levels after discontinuation of chronic treatment with long-acting injectables (Wistedt et al., 1981; Gitlin et al., 1988; Nyberg et al. 1997). Patients treated with fluphenazine enanthate had significantly fewer rehospitalizations than patients who were on oral fluphenazine. It is important to note that a nurse was available to study participants on a 24-hour basis by telephone, did home visits to give patients the indicated injection and was available for patients in both fluphenazine enanthate and oral fluphenazine groups. The nurse doing home visits guaranteed the delivery of fluphenazine enanthate. (del Guidice et al., 1975). This eliminated the possibility of not showing up for the long-acting injectable.

Risperidone Microspheres Long-acting Injectable

Risperidone long-acting injectable was the first long-acting second generation antipsychotic available in the United States and was marketed in 2003. Several studies have demonstrated its efficacy in the treatment of people with schizophrenia. For example, a 12-week, double-blind, placebo-controlled randomized study of 400 patients with schizophrenia receiving either 25-, 50- or 75 mg biweekly intramuscular injections of placebo or long-acting risperidone found significant improvement on the positive and negative syndrome scale (PANSS) scores for long-acting risperidone relative to placebo (Kane *et al.*, 2003). In another randomized, double-blind 52-week study with risperidone long-acting injectable 25 mg or 50 mg every 2 weeks (N=324), risperidone long-acting injectable 50 mg had a lower rate of relapse and also significant improvements in psychosocial functioning (Simpson *et al.*, 2006).

Paliperidone Palmitate Long-acting Injectable

Paliperidone palmitate is the active metabolite (9-OH risperidone) of the parent compound risperidone, bound to a palmitate molecule. It was marketed in 2006 and has several advantages over long-acting risperidone in that it does not require refrigeration or

reconstitution, has other injection site options, allows use of a smaller needle size, and does not require oral treatment coverage upon initiation. In a randomized, double-blind, placebo-controlled study in people with schizophrenia (N=312), paliperidone palmitate significantly ($p<0.0001$) delayed time-to-relapse compared with placebo (Hough *et al.*, 2010). Paliperidone palmitate was well tolerated in the short-term efficacy studies, with low drop out rates due to adverse effects that were generally lower than for placebo. In another three-arm, randomized double-blind study comparing doses of 50 mg and 100 mg monthly with placebo, both doses significantly separated from placebo on improvement of the PANSS total score and CGI severity ratings (Kramer *et al.*, 2009).

Olanzapine Pamoate Long-acting Injectable

Olanzapine pamoate is the newest second generation antipsychotic long-acting injectable marketed in the US. In an 8-week, double-blind placebo-controlled study (N=404) in people with schizophrenia, olanzapine long-acting injectable 210 mg, 300 mg and 405 mg were found to be superior to placebo on reduction of the PANSS total score. There was no statistically significant difference between the three dose groups (Lauriello *et al.*, 2008). In another study recently published, olanzapine long-acting injectable “low” (150 mg every 2 weeks; N=140), “medium” (405 mg every 4 weeks; N=318), or “high” (300 mg every 2 weeks; N=141) doses were found to be efficacious and tolerable in a randomized, 24-week, double-blind trial compared to various injection doses as mentioned above. The majority of the patients on all of the olanzapine long-acting injectable doses remained exacerbation free (Kane *et al.*, 2010). This medication carries the risk of post injection sedation and delirium, and patients must be observed for a period of 3 hours post injection (Lindenmayer, 2010).

Long-acting Injectables and Relapse

In a recently published (Leucht *et al.*, 2011) systematic review and meta-analysis of ten randomized long-term (more than one year) clinical trials (N=1700), long-acting antipsychotics significantly reduced relapse rates, with relative and absolute risk reductions of 30% and 10% respectively ($p=0.0009$) compared with oral antipsychotics. Eight of the ten studies reported that long-acting injectable antipsychotics and depot antipsychotics had a risk ratio of less than one and an overall risk ratio of 0.7 for those studies included in the meta-analysis. Among the ten trials included in this analysis, six were with long-acting fluphenazine, two with risperidone and one with haloperidol and zuclopenthixol. With the exception of long-acting haloperidol, which is administered every four weeks, all the other studies administered the medication every two (eight studies) to three weeks (one study). Although long-acting injectable was administered to provide continuous antipsychotic treatment, none of the studies clearly documented whether long-acting injectable actually improved adherence. Also, in this meta-analysis, different antipsychotics were used in the oral and long-acting injectable formulations. The comparison of antipsychotics with differing D2 affinities and pharmacokinetics could introduce major bias. Finally, it is important to note that no studies have specifically focused on enrolling patients with nonadherence.

At the same time, there are many clinical trials that have compared the same antipsychotic in oral and long-acting injectables forms. In these studies, long-acting injectables were not more effective than their oral counterpart (Rifkin *et al.*, 1977; Schooler *et al.*, 1980; Arango *et al.*, 2006; Kane *et al.*, 2010). This may be because of the same D2 affinities and pharmacokinetics.

In a recently published study, Rosenheck and colleagues did not find that risperidone long-acting injectable was superior in preventing rehospitalization compared to psychiatrists' choice of an oral antipsychotic in 369 veterans with schizophrenia or schizoaffective

disorder who were followed for two years. Risperidone long-acting injectable was associated with more local injection-site reactions and extrapyramidal symptoms. However, alcohol use, measured by the Addiction Severity Index, was significantly higher in the oral group than the long-acting injectable group ($p=0.04$), and there was no difference in illicit drug use between two groups (Rosenheck et al., 2011). In another recently published study, the risk of rehospitalization and antipsychotic discontinuation in 2,588 consecutive patients hospitalized for the first time with a diagnosis of schizophrenia between 2000 and 2007 in Finland was examined. Of 2,588 patients, only 1,507 (58%) collected a prescription for an antipsychotic during the first 30 days after hospital discharge, and only 1,182 (46%) continued their initial treatment for 30 days or longer. The risk of rehospitalization for patients who received long-acting injectables was about one-third of that for patients who received their equivalent oral formulations (Tiihonen et al., 2011).

In the recently published Schizophrenia Patient Outcomes Research Team (PORT) pharmacologic review, the authors recommend that long-acting injectable antipsychotics may be offered as an alternative to oral antipsychotics for the maintenance treatment of people with schizophrenia. Buchanan and colleagues argued that the long-acting injectables provide a convenient alternative to taking multiple daily oral doses of antipsychotics. They concluded, however, that at the time of the publication, there was insufficient evidence to recommend a specific long-acting injectable antipsychotic over another (Buchanan *et al.*, 2010).

In summary, the long-acting injectable antipsychotics may be used as evidence-based treatment for relapse prevention in people with schizophrenia. There is accumulating evidence that long-acting injectable antipsychotics may have better effectiveness in some domains, however, this point still remains controversial.

Long-acting Injectable Antipsychotics in Schizophrenia and Comorbid Substance Use

As reviewed above, people with schizophrenia who use illicit drugs and alcohol may be a population of patients for whom long-acting injectable antipsychotics are an important consideration. In fact, a few studies utilizing long-acting injectables have been conducted among people with dual diagnosis. Table 1 lists the studies that have been published on schizophrenia and comorbid substance use population and each study is briefly reviewed below.

Levin and colleagues (1998) examined the effectiveness of flupenthixol decanoate for people with schizophrenia or schizoaffective disorder and cocaine abuse, dependence, or recent use ($N=8$) in an open-label study, which had a 4-week inpatient and a 6-week outpatient phase. The aims of the study were to assess the tolerability of flupenthixol, to determine whether a standard dose of flupenthixol would effectively control positive and negative symptoms, and to examine whether flupenthixol would be a promising medication for cocaine use in people with comorbid substance use. During the second week after admission, flupenthixol decanoate was started at 20 mg and the dose was gradually increased. Patients received injections approximately seven days apart. Patients received flupenthixol decanoate 40 mg every two weeks for six weeks during the 6-week outpatient phase. Substantial improvement in psychiatric symptoms was noted as measured on the PANSS, and depressive symptoms as measured by the Beck Depression Inventory (BDI). On the PANSS, positive and negative scores decreased by 31% and 29% respectively ($p<0.05$), whereas BDI scores decreased by 57%. Cocaine-positive urines decreased by an average of 28%, although a majority of the patients (5 of 8) had a reduction of >75%. Although the reduction in cocaine craving did not reach statistical significance, small sample

size may have limited the ability to detect differences. In addition, missed clinic visits decreased by 26%. Finally, flupenthixol was well-tolerated with no exacerbation of side effects including extrapyramidal side effects (Levin *et al.*, 1998).

In an open-label, 6-month clinical trial, Soyka and colleagues aimed to examine whether flupenthixol decanoate would decrease alcohol use in 27 people with schizophrenia and International Classification of Diseases (ICD)-10 criteria for moderate to severe alcohol dependence for at least two years. This study population of 14 completers experienced improvements in PANSS global, positive, and negative symptoms, as well as social functioning assessed using the 8-item self-report social functioning questionnaire (SFQ). There was an improvement of 30% in SFQ scores. Six out of 14 (43%) patients remained completely abstinent from alcohol throughout the study and eight patients were abstinent at the end of the study. Alcohol consumption in standard drinks/day as measured by the timeline follow-back interview (TFLB) decreased significantly over time. Further, the mean number of relapses to heavy alcohol consumption and the number of drinks per relapse decreased after initiation of treatment. In patients who relapsed, the mean number of drinks per relapse decreased from 7.7 (5.8) drinks to 4.4 (3.2) drinks during the initial study phase and remained reduced throughout the study. The percentage of abstinent days during treatment also increased significantly during treatment. Craving scores decreased significantly between visits one and two, and continuously remained on a reduced level throughout treatment. Out of the 27 subjects who received at least one flupenthixol injection, nine subjects (33%) reported at least one adverse event. Nineteen percent each reported akathisia and nervousness and 12% experienced extrapyramidal side effects. Two subjects were prematurely terminated from the study for the abovementioned side effects; one had severe akathisia (Soyka *et al.*, 2003).

There has only been one published study examining the use of a second generation antipsychotic long-acting injectable in people with comorbid substance use. In the open-label, rater blinded, randomized controlled trial, Rubio and colleagues (2006) compared the effectiveness of long-acting injectable risperidone and zuclopenthixol in people with schizophrenia and alcohol and/or drug abuse or dependence. In a large sample of 115 people who were considered dually diagnosed, risperidone microspheres 47 mg/2weeks (n=57) and zuclopenthixol decanoate 200 mg/3 weeks (n=58) were administered for 6 months (Rubio *et al.*, 2006). There was significantly less positive urine drug tests ($p=0.005$), longer time until relapse to illicit drug use, and a greater improvement of positive, negative, general and total symptom measures on the PANSS ($p<0.0001$) in the long-acting injectable risperidone group as compared to long-acting injectable zuclopenthixol. In addition, long-acting injectable zuclopenthixol was associated with more extrapyramidal side effects ($p<0.04$) and a greater use of antiparkinsonian medications as compared to long-acting injectable risperidone ($p<0.01$). During the follow-up period, nine out of 115 subjects dropped out of the study, 6 out of 58 (10%) from the zuclopenthixol long-acting group and 3 out of 57 (5%) from the long-acting injectable risperidone group. This study is limited by its open-label design, however, it is important to note that it was randomized and rater blinded, enrolled a large number of patients with comorbid substance use, compared a first generation antipsychotic to a second generation antipsychotic long-acting injectable, and employed a six-month design. This study included subjects with family support, which may partially explain the high adherence and follow-up rates.

In addition to these three studies, a few case reports have touted the benefits of long-acting injectables in people with schizophrenia and comorbid substance use (Soyka and Sand, 1995).

Thus, these findings suggest that long-acting injectable antipsychotics may provide some benefits in people with comorbid substance use. The most rigorous was the recent prospective study (Rubio *et al.*, 2006) that found the second generation antipsychotic long-acting to be superior to the first generation antipsychotic long-acting in regards to psychopathology, substance use and side effects. It is important to note, however, that this area of research is lacking in depth and quality. There are no double blind randomized trials among people with comorbid substance use, and there are no studies that specifically target nonadherence as an inclusion criterion, despite a clear theoretical basis for including such participants. These studies generally utilize uncontrolled designs, are of short duration, and have small sample sizes. Finally, long-acting risperidone is the only second generation antipsychotic with published data in patients with comorbid substance use. There are many issues regarding the use of long-acting injectable antipsychotics in people with comorbid substance use.

Other Treatment Considerations in People with Comorbid Substance Use

Although long-acting injectable antipsychotics are intended to improve adherence, it is noteworthy that this is not clearly documented in the literature. It may be argued that the studies published to date with long-acting injectables may be reporting on a somewhat skewed population, enrolling those with minimal nonadherence and a desire to participate in clinical trials. People with schizophrenia who are prescribed a long-acting injectable antipsychotic medication in the real-world may be more diverse. One of the advantages of a long-acting injectable is that nonadherence is detected at the time of a missed injection. Ensuring medication delivery through a continuous delivery system will not completely solve adherence problems in this population, however, missed injections can alert the health care team to address the issue of adherence. Other strategies for addressing nonadherence in this population must be considered to improve overall patient outcomes. Initiating a reminder system for injection appointments may be a worthwhile strategy as forgetfulness has been reported as a significant factor in nonadherence (Tegeler and Lehmann, 1981).

Other strategies available for persons with comorbid substance use may include Assertive Community Treatment (ACT) teams, which may play a role in supporting and monitoring medication adherence in areas where ACT teams are available (Bush *et al.*, 1990; Stein *et al.*, 1980). People with comorbid substance use may benefit from psychosocial interventions like supported employment and assertive community treatment (Ziedonis, 2004), but these services have minimal impact on substance use *per se* (Drake *et al.*, 2008). The most effective integrated interventions for people with dual diagnosis include group counseling with cognitive behavioral and motivational enhancement therapy (Bellack *et al.*, 2006; Weiss *et al.*, 2007), contingency management (Haddock *et al.*, 2003; Ries *et al.*, 2004; Drebing *et al.*, 2005, Kelly *et al.*, 2012), and for people who do not respond to less intensive interventions, long-term residential programs (Brunette *et al.*, 2004). Other evidence-based approaches include social skills training and psychoeducation (Lieberman *et al.*, 1984), development of substance refusal skills (Bellack *et al.*, 1990), family interventions (McFarlane *et al.*, 2003), and 12-step facilitation and addiction recovery programs (Ziedonis, 2004). There is little evidence demonstrating the superiority of any one particular program. Therefore, the intervention may be tailored based on an individual patient's needs. The authors of the PORT psychosocial treatment recommendations (Dixon *et al.*, 2010) suggest that motivational enhancement and behavioral strategies will be effective in those with comorbid substance use. In particular, those interventions that focus on engagement in treatment, coping skills training, relapse prevention training, and delivery in a service model that is integrated with mental health care for people with comorbid substance use may be most beneficial.

Finally, the PORT pharmacologic treatment guidelines (Buchanan *et al.*, 2010) recognize the significant problem of comorbid substance use but do not recommend any pharmacologic agents specifically for the treatment of illicit drug and alcohol use in schizophrenia beyond those agents known to treat substance use in the general population.

Future Directions

There is sparse evidence with few well-designed, randomized controlled clinical trials addressing pharmacotherapy for people with dual disorders. Oral second generation agents offer benefits in this population; however, nonadherence continues to be a problem. We reviewed the potential utility of long-acting injectables and suggest that this drug delivery system may be advantageous over oral treatment. Future studies are warranted with long-acting injectable antipsychotics, including randomized head to head comparisons of second generation antipsychotic long-acting injectables versus first generation antipsychotic long-acting injectables, and oral antipsychotic medications. Further evidence is needed to evaluate integrated treatment with long-acting injectables combined with psychosocial interventions and other medications aimed at fostering adherence and decreasing substance use. Integrated strategies may have a better chance for maximizing positive outcomes for both psychiatric symptoms and substance use.

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Table 1
Summary of Studies of Long-acting Injectables in People with Schizophrenia and Comorbid Substance Use

Article	Medication(s)	Study Design	Sample	Duration	Key Measures	Results
Levin et al., 1998	flupenthixol (FGA)	Open Label	N=8 Schizophrenia and cocaine dependence, abuse, or recent use	10 weeks	PANSS, BDI, drug urine screens	Improved psychiatric symptoms Improved depressive symptoms Decreased positive urine screens
Soyka et al., 2003	flupenthixol (FGA)	Open Label	N=27 Schizophrenia and alcohol dependence	6 months	PANSS, SFQ, TFLB, OCDS	Improved psychiatric symptoms Improved social functioning Significant reduction in alcohol use Significant reduction in craving
Rubio et al., 2006	risperidone (SGA) vs. zuclopenthixol (FGA)	Open Label Blinded raters RCT	N=115 Schizophrenia and substance abuse or dependence risperidone (n=57) zuclopenthixol (n=58)	6 months	PANSS, drug urine screens, ESRs	Risperidone associated with: Lower illicit drug use Longer time to drug use relapse Greater improvement on psychiatric sxss Fewer extrapyramidal side effects Lower use of antiparkinsonian medications

Note: FGA = first generation antipsychotic; SGA = second generation antipsychotic; RCT = randomized controlled trial; dx = diagnosis; PANSS = Positive and Negative Syndrome Scale; BDI = Beck Depression Inventory; sxss = symptoms; SFQ = Social Functioning Questionnaire; TFLB = timeline follow-back interview; OCDS = Obsessive Compulsive Drinking Scale; ESRs = Extrapyramidal Symptom Rating Scale.