Pharmacotherapy for co-occurring schizophrenia and substance use disorder

AUTHORS: E Cabrina Campbell, MD, Stanley N Caroff, MD, Stephan C Mann, MD, DLFAPA
SECTION EDITORS: Andrew J Saxon, MD, Stephen Marder, MD
DEPUTY EDITOR: Michael Friedman, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Oct 2023.**
This topic last updated: **Sep 29, 2020.**

INTRODUCTION

Schizophrenia and addiction are both chronic disorders with serious complications, consequences, and costs for individuals and society. Both conditions are associated with poor adherence to treatment and poorer outcomes when the co-occurring disorder is present.

Some of the symptoms of schizophrenia overlap with symptoms of intoxication, chronic substance use, or withdrawal from alcohol or other drugs. Family history and the temporal relationship of symptoms can help to distinguish patients with a substance use disorder (SUD) alone from co-occurring schizophrenia and SUD.

Pharmacotherapy of co-occurring schizophrenia and SUD are described here. The epidemiology, pathogenesis, clinical manifestations, course, assessment, diagnosis, and psychosocial interventions for co-occurring schizophrenia and SUD are described separately. The epidemiology, pathogenesis, clinical manifestations, course, assessment, diagnosis, and treatment of schizophrenia or SUD individually (not co-occurring) are also discussed separately.

- (See "Co-occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis".)
- (See "Co-occurring schizophrenia and substance use disorder: Psychosocial interventions".)

- (See "Schizophrenia in adults: Epidemiology and pathogenesis".)
- (See "Schizophrenia in adults: Maintenance therapy and side effect management".)
- (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)
- (See "Schizophrenia in adults: Psychosocial management".)
- (See "Opioid use disorder: Epidemiology, clinical features, health consequences, screening, and assessment".)
- (See "Cannabis use disorder: Clinical features, screening, diagnosis, and treatment".)
- (See "Risky drinking and alcohol use disorder: Epidemiology, clinical features, adverse consequences, screening, and assessment".)
- (See "Cocaine use disorder: Epidemiology, clinical features, and diagnosis".)
- (See "Stimulant use disorder: Psychosocial management".)
- (See "Stimulant use disorder: Treatment overview".)

CLINICAL GOALS AND PRINCIPLES

The primary long-term goals of treatment for co-occurring schizophrenia and substance use disorder (SUD) are reduced symptoms of schizophrenia, improved role functioning, reduced substance use, and improved quality of life.

Both SUD and schizophrenia are associated with poor adherence to treatment and poorer outcomes when the co-occurring disorder is present. Nonadherence is the foremost cause of acute psychotic relapse in this population. Relapses should be anticipated. Clinicians should seek to maintain treatment despite periods of active substance use [1].

The individual treatments and overall complexity of the treatment plan for schizophrenia and SUD must be weighed against the patient's cognitive and self-care capacities, willingness to participate in treatment, capacity for adherence, education, and resources. More intensive protocols may require external support from family, friends, social service agencies, case managers, or other professional caregivers, especially given the fact that patients with schizophrenia are found often among disadvantaged and lower socioeconomic groups [2,3], which are associated with higher rates of and greater resistance to treatments for substance

use [4,5]. (See "Assertive community treatment for patients with severe mental illness" and "Substance use disorders: Determining appropriate level of care for treatment".)

Integrated treatment — We suggest integrated care rather than parallel or sequential care for patients with co-occurring schizophrenia and SUD. Components of integrated treatment include [6]:

- Treatment of both disorders (schizophrenia and SUD) by the same clinician or clinical team.
- Multimodal care generally includes pharmacotherapy and one or more psychosocial interventions. (See "Co-occurring schizophrenia and substance use disorder: Psychosocial interventions".)
- Collaborative goal setting.
- Respectful and empathic treatment of both conditions – Less confrontational than some SUD treatments, we believe that this approach can help foster a strong therapeutic alliance.

The availability of integrated care varies widely. Separate systems of care have traditionally provided mental health care versus SUD treatment in the United States and other countries; this continues to be the case in some areas. The availability of integrated treatment can also vary by level of care, such as inpatient, residential, and outpatient settings.

Clinical trials comparing integrated and parallel treatment for substance use disorders and schizophrenia in patients with both disorders have shown mixed results [7,8]; however, a broad consensus among researchers and clinicians with expertise in the area supports integrated treatment of co-occurring disorders [9,10]. Treatment of mental disorders and SUD in separate health systems and by separate clinical teams had been associated with poor communication and poor coordination of care.

When integrated treatment is not available, clinicians treating each disorder separately should coordinate care by:

- Agreeing on a common treatment plan
- Communicating regularly to share information about the patient's clinical status, treatment compliance, substance use, and risk status
- Monitoring the clinical status and treatment response of both conditions

SCHIZOPHRENIA

Patients with schizophrenia and a co-occurring substance use disorder (SUD) should be stabilized with an antipsychotic medication at the outset of treatment. Sequential treatment of the addiction first and followed later by treatment of schizophrenia is not recommended.

Antipsychotic drugs — Available evidence and our clinical experience support the efficacy of antipsychotic drugs for schizophrenia in patients with co-occurring SUD [11-16]; antipsychotic drugs are first-line treatment for schizophrenia with SUD as they are for schizophrenia without SUD. (See "Schizophrenia in adults: Maintenance therapy and side effect management".)

Efficacy — Large, well designed clinical trials of antipsychotic drugs have found little difference in efficacy between schizophrenia patients with substance use/SUD versus those without substance use/SUD. Some differences were seen in subgroup analyses and smaller trials.

- The Clinical Antipsychotics Trial of Intervention Effectiveness (CATIE) in the United States, randomly assigned 1432 patients with chronic schizophrenia to one of five first- or second-generation antipsychotic medications. Little difference was seen in symptom improvement, time to treatment discontinuation, or neurologic or metabolic side effects between patients who were concurrently using illicit drugs (55.1 percent) compared with those who were not (44.9 percent) [17,18]. A secondary analysis found that patients with moderate or severe drug use had poorer outcomes in symptoms of psychosis, depression, and quality of life compared with patients with no use or mild use [16].

- The European First Episode Schizophrenia Trial (EUFEST) randomly assigned, without blinding, 498 first-episode schizophrenia patients to one of five first- or second-generation antipsychotic medications. After six months, no difference in psychopathology, overall neurocognitive functioning, or extrapyramidal symptoms (EPS) was found between patients with or without a concurrent SUD [19]. In subgroup analyses, patients with continuing, active substance use during treatment had a greater severity of positive symptoms compared with inactive and nonusers [20].

Early, small trials of antipsychotic drug treatment between schizophrenia patients with and without SUD largely found poorer results for patients with the co-occurring disorders across a wide range of outcomes, including general and cognitive functioning, adherence, relapse rates, unemployment, incarceration, homelessness, suicidality, violence, and rehospitalization [16,21]. More recent trials with smaller sample sizes have shown mixed results [20,22].

Secondary analysis of data from the EUFEST and CATIE antipsychotic trials found that substance use correlated significantly with nonadherence and discontinuation of antipsychotic treatment [23].

Drug selection — There is insufficient evidence to conclude that any one antipsychotic drug offers an advantage over others in controlling psychotic symptoms in schizophrenia patients with co-occurring SUD [24]. In the EUFEST and CATIE studies, no difference was found in effectiveness among numerous first- or second-generation antipsychotics in patients with schizophrenia and substance use [17,18,20].

Three smaller trials reported mixed results with clozapine compared with other antipsychotics in this population:

- A trial of 61 patients with schizophrenia and alcohol use disorder found that clozapine was more likely to reduce hospitalization rates compared with risperidone [25].
- A trial of 30 patients with schizophrenia and cannabis use found that clozapine led to a greater reduction of positive symptoms compared with ziprasidone, but also produced more side effects and poorer compliance [26].
- A study of 31 patients with schizophrenia and cannabis use found no differences in symptoms or outcomes when patients were either switched to clozapine or remained on their baseline antipsychotic [27].

In our clinical experience, long-acting, injectable antipsychotics can contribute to improved adherence and clinical outcomes in patients with schizophrenia and a co-occurring SUD [24]. They have shown mixed results in clinical trials [28,29]; however, these drugs are difficult to study in the unstable population that most needs them.

Antipsychotic-substance interactions — Interactions between abused substances and medications need consideration in the selection and dosing of antipsychotics in patients with schizophrenia and SUD. Smoking tobacco (rather than nicotine intake more broadly) has been found to lower plasma levels of antipsychotic drugs [30,31]. The polycyclic aromatic hydrocarbons inhaled when smoking induce hepatic cytochrome P450 isoenzymes CYP1A1, 1A2, and 2E1, which effectively reduce plasma antipsychotic levels. Olanzapine and clozapine are most affected among second-generation antipsychotics; chlorpromazine, fluphenazine, perphenazine, and haloperidol among first-generation antipsychotics [32,33]. This effect has been linked to compensatory administration of increasing doses of antipsychotics [33].

When their smoking status changes, careful monitoring of schizophrenia patients' antipsychotic side effects and psychotic symptoms is warranted; antipsychotic dose adjustments may be needed. Alcohol use in patients with schizophrenia is associated with reduced antipsychotic plasma levels; however, these patients generally do not require antipsychotic dose adjustments [30].

Side effects — Analyses of data from observation studies and clinical trials of antipsychotic drug treatment have found mixed results in comparisons of rates of tardive dyskinesia (TD) and other EPS between schizophrenia with and without an SUD [17,19,21,34-37]. All patients receiving antipsychotics drugs should be closely monitored for TD and EPS. (See "Tardive dyskinesia: Prevention, treatment, and prognosis" and "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Side effect management'.)

SUBSTANCE USE DISORDER

Substance use disorder (SUD) is commonly a chronic, relapsing condition requiring open ended, frequently life-long, continuous treatment. Continuing care for SUD is described in detail separately. (See "Continuing care for addiction: Components and efficacy" and "Continuing care for addiction: Implementation".)

Based on research studies and our clinical experience, the presence of co-occurring schizophrenia can influence the choice of medications to treat the SUD, as described below. Pharmacotherapies for SUDs in patients **without** schizophrenia, including dosing and adverse effects not addressed here, are discussed separately. (See "Pharmacotherapy for smoking cessation in adults" and "Cannabis use disorder: Clinical features, screening, diagnosis, and treatment" and "Stimulant use disorder: Treatment overview" and "Opioid use disorder: Pharmacologic management" and "Alcohol use disorder: Treatment overview".)

Antipsychotic drugs and SUDs — While some clinical trials and secondary data analyses have found antipsychotic drugs to reduce substance use in schizophrenia patients with SUD, the findings (below) have been mixed, the studies have been methodologically limited, and the evidence is insufficient to recommend changes to antipsychotic drug prescribing in these patients [24,38].

Some of these studies suggest that clozapine may have a greater effect on substance use compared with other antipsychotics. Properties unique to clozapine have been hypothesized to explain its possible superiority in reducing substance use [39]:

- Weak and rapidly dissociated blockade of dopamine receptors.

- Alpha adrenergic blocking, which has been associated with substance use reduction [40,41].

- Amelioration of the mesocorticolimbic brain reward circuit deficiency that contributes to substance use disorder in patients with schizophrenia.

- Clozapine may increase dopamine release in the prefrontal cortex and improve signal-detection capacity of the mesocorticolimbic dopamine-mediated circuitry.

Research on the influence of antipsychotic medications on substance use are described below in samples of schizophrenia patients with a specific SUD or a mix of SUDs:

- **Mixed SUDs** – Evidence for substance use reduction in samples of patients with mixed SUDs is mixed:

  - The Clinical Antipsychotics Trial of Intervention Effectiveness (CATIE) study, described above, did not find differences in substance use reduction among four second-generation antipsychotic and a first-generation antipsychotic drugs [42]. (See 'Antipsychotic drugs' above.)

  - An open trial of patients with schizophrenia and SUD treated with various antipsychotics suggested that clozapine may be superior to other antipsychotics in reducing substance use. The study followed 223 schizophrenia patients from their initial six-month remission of substance use forward for 10 years [43]. Patients on clozapine at one year were much less likely to experience a relapse of the SUD compared with patients treated with other antipsychotics (8 versus 40 percent).

  - An open trial of 1049 individuals with schizophrenia or schizoaffective disorder compared 257 participants taking clozapine with 792 patients taking other antipsychotic medications [44]. Patients taking clozapine had lower odds of current alcohol (70.3 versus 82.4 percent), cannabis (19.7 versus 37.8 percent), and other drug use (7.1 versus 16.9 percent) despite similar lifetime odds.

- **Tobacco smoking** – It is not clear whether antipsychotic drugs reduce tobacco smoking in patients with schizophrenia. Secondary analyses of data from the CATIE study, described above, found antipsychotic drug treatment to be associated with reduced smoking [42]. Results from clozapine trials were mixed [45-48]. As an example, in a clinical trial of 70 patients with treatment-refractory schizophrenia, the transition of 55 smokers from their baseline first-generation antipsychotic medication to clozapine was associated with reductions in cigarette smoking compared with prebaseline antipsychotic treatment [46].

- **Alcohol use** – There have been no clinical trials that directly test whether antipsychotic drugs reduce alcohol use in schizophrenia patients. Several uncontrolled trials and secondary analyses of clinical trial data have found associations between antipsychotics and reduced alcohol use in this population:

  - In an analysis of data from CATIE, an 18-month clinical effectiveness trial described above, first- or second-generation antipsychotic treatment was associated with reduced alcohol use in 501 schizophrenia patients who used alcohol [42].

  - Earlier secondary analyses and uncontrolled trials with small samples reported that second-generation antipsychotics were associated with decreased alcohol use in schizophrenia patients [49-51].

  - A secondary analysis of data from a three-year, uncontrolled study of 105 patients with schizophrenia or schizoaffective disorder and co-occurring SUD found clozapine treatment to be associated with reduced alcohol use [52]. Nineteen schizophrenia patients treated with clozapine experienced decreases in alcohol abuse severity scores and in days of alcohol use (12.5 versus 54.1 drinking days) during periods on clozapine compared with periods off clozapine. At the end of the study, a greater proportion of patients on clozapine were in remission from alcohol use disorder for six months or longer compared with patients not taking clozapine (79 versus 33.7 percent).

- **Cannabis use** – Small clinical trials found that patients treated with clozapine did not reduce cannabis use compared with patients remaining on their current antipsychotic drug or treated with ziprasidone [26,27]. As an example, a clinical trial randomly assigned 31 antipsychotic-treated patients with schizophrenia and co-occurring cannabis use disorder to switch to clozapine or to stay on their current antipsychotic medication and be followed weekly for 12 weeks [27]. After 12 weeks, a statistically nonsignificant difference was seen between groups with patients receiving clozapine using less cannabis compared with the control group (mean of 11 versus 15.5 joints per week), suggesting that a well-powered trial is needed.

  A small study suggested clozapine may decrease craving for cannabis compared with risperidone. 38 patients with schizophrenia (30 with and 8 without co-occurring cannabis use disorder) and 20 healthy controls were randomized to antipsychotic treatment with clozapine or risperidone [53]. Brain response to cannabis-related images in areas implicated in substance-related cue reactivity such as the amygdala were measured using functional magnetic resonance imaging. Subjective craving was assessed using a self-report questionnaire. At baseline, patients with comorbid cannabis use disorder evinced

greater subjective craving and greater activation in response to cannabis-related images compared with patients without comorbid cannabis use and healthy controls. Clozapine-treated patients with co-occurring cannabis use disorder reported a greater reduction in craving and showed a larger decrease in amygdala activation during cannabis-related images compared with risperidone-treated patients with cannabis use disorder.

- **Cocaine use** – There are no clinical trials comparing the efficacy of antipsychotic drugs with placebo in reducing cocaine use. Small clinical trials found mixed results in comparing the efficacy of first-generation versus second-generation antipsychotics in reducing cocaine use [11,12,54]. As an example, a clinical trial compared olanzapine with haloperidol in 24 patients with schizophrenia and cocaine abuse, finding no difference in positive drug screens. Craving for cocaine was rated as lower by patients receiving haloperidol [12].

Tobacco use disorder — For schizophrenia patients attempting to stop smoking tobacco, we suggest first-line treatment with nicotine replacement therapy (NRT) in combination with behaviorally oriented psychosocial treatment rather than other medications. Bupropion and varenicline are reasonable alternatives to NRT in patients without suicidal ideation or a history of suicidal behavior. Pharmacotherapy appears to play a more critical role for smokers with schizophrenia than in other smokers, increasing the odds of quitting by a factor of four- to fivefold, likely because of the low quit rate with behavioral treatment alone [55]. Maintenance pharmacotherapy also appears to differentially improve relapse rates for smokers with schizophrenia.

Reports submitted to the US Food and Drug Administration (FDA) suggesting an association between the latter drugs and neuropsychiatric adverse events have not been borne out in subsequent research. There are no controlled trial data in smokers with psychiatric illness in general or with schizophrenia that have shown increased neuropsychiatric adverse events with varenicline or bupropion compared with placebo or NRT [55]. (See 'Safety' below.)

Schizophrenia patients attempting to stop smoking, whether treated with smoking cessation medications or not, should be closely monitored for emerging depression, suicidality, or exacerbation of existing psychiatric and extrapyramidal symptoms. Patients should be advised to stop taking medications if changes in thinking or behavior develop. Some clinicians take a more conservative approach with varenicline, not prescribing the drug to patients with unstable or prominent depressive symptoms or those at risk for suicidal behavior.

Efficacy

Comparative and combination smoking cessation medication studies — Systematic reviews and meta-analyses have found that the smoking cessation medications varenicline and bupropion are effective in patients with serious mental illness including schizophrenia [56,57]. There were no differences between groups in tolerability. No trials were found that compared nicotine replacement therapies with placebo. As an example, a 2017 26-week trial randomly assigned 42 patients with DSM-IV diagnoses of schizophrenia and tobacco use disorder to either treatment as usual or combined treatment initiated with bupropion (150 mg twice daily), nicotine patch (21 mg), nicotine lozenges (2 and 4 mg), weekly group cognitive-behavioral therapy (CBT), and in some cases biweekly home visits. Combined medication and CBT resulted in a greater reduction in cigarettes smoked and a greater seven-day point prevalence rate of abstinence compared with treatment as usual [58].

Varenicline — Clinical trials have found varenicline, a nicotinic receptor partial agonist, to increase smoking cessation rates in schizophrenia patients (below); reports of increased suicidal ideation and attempts associated with the drug have not been borne out in meta-analyses of available data or a large, rigorous trial [59-62]. As an example, a 2013 meta-analysis of two clinical trials with a total of 137 patients with schizophrenia found an increased smoking cessation rate with varenicline compared with placebo (risk ratio = 4.74, 95% CI 1.34-16.71) [45]. Improved cessation rates with varenicline have been found in patients with and without severe mental illness.

Bupropion — Bupropion, which modulates dopamine and noradrenergic tone and may inhibit nicotinic acetylcholine receptors [59,63], appears to be efficacious for smoking cessation in patients with schizophrenia. A systematic review and meta-analysis of seven clinical trials with a total of 340 schizophrenia patients found higher cessation rates in patients receiving bupropion compared with patients receiving placebo at the end of treatment (risk ratio = 3.03; 95% CI 1.69-5.42) and at six months [45].

Nicotine replacement therapy — The efficacy of nicotine replacement therapy (NRT) for smoking cessation in the general population is well established and has been reported in patients with schizophrenia [59], but available research is insufficient to draw conclusions about its efficacy for smoking cessation in patients with schizophrenia [45]. In our clinical experience, these agents are effective in reducing symptoms of nicotine withdrawal in schizophrenia, with consistency across delivery systems (transdermal patch, gum, lozenges, nasal spray, and inhalation).

Nicotinic agents may have positive effects on concentration and cognition in schizophrenia, having been implicated in studies of mechanisms underlying improvements [45,64]. NRT does not affect antipsychotic drug levels; the effect of smoking tobacco on plasma levels is described

above [30,31]. (See 'Antipsychotic-substance interactions' above and "Pharmacotherapy for smoking cessation in adults", section on 'Nicotine replacement therapy'.)

Safety — Preliminary studies of the effects of nicotine and smoking cessation agents on antipsychotic-induced extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) have yielded conflicting findings. Studies of tobacco smoking and smoking cessation in schizophrenia patients receiving antipsychotics have found both increased and decreased risk and severity of EPS and TD. Apart from direct effects on nicotinic receptors, smoking can induce metabolism and lower plasma levels of antipsychotic drugs [65-69]. Patients should be advised of possible effects and monitored for changes in involuntary movements when altering smoking habits or initiating smoking cessation treatment.

Early reports of newly emergent psychiatric symptoms raised questions about the safety of varenicline and bupropion for smoking cessation in patients with mental disorders, but subsequent research has supported their use in patients whose disorders are stable.

A 2009 review of adverse events submitted to the FDA raised concerns about a possible association between the medications and the emergence of depression, suicidal ideation, and/or suicidal behavior [70,71]. Subsequent reviews and meta-analyses of clinical trials comparing these drugs to placebo did not find associations between the smoking-cessation medications and emergence or exacerbation of psychiatric symptoms or suicidal/self-injurious behavior [45,60,72,73]. As an example, a 2015 meta-analysis of 39 randomized trials comparing varenicline with placebo in over 10,000 participants [74]. (See "Pharmacotherapy for smoking cessation in adults", section on 'Varenicline' and "Pharmacotherapy for smoking cessation in adults", section on 'Bupropion'.)

A subsequent, large clinical trial found that the rate of psychiatric adverse events in smokers receiving varenicline or bupropion did not exceed the rate in patients receiving placebo by a statistically significant extent [59]. The trial randomly assigned 8144 motivated adult smokers, approximately half with clinically stable mental disorders (10 percent with schizophrenia or schizoaffective disorder), to receive varenicline, bupropion, transdermal nicotine, or placebo for 12 weeks. All patients received brief cessation counseling. Patients with mental disorders were more likely to experience neuropsychiatric adverse events (including moderate-to-severe anxiety, depression, agitation, or hostility) during the treatment period compared with patients without mental disorders (5.8 versus 2.1 percent), but among patients with mental disorders, the rate of events did not differ for patients assigned to varenicline (risk difference = 1.59, 95% CI -0.42 to 3.59) or bupropion (1.78, 95% CI -0.24 to 3.81) rather than placebo. Rates of smoking abstinence were higher with all three drugs compared with placebo, and with varenicline compared with bupropion and transdermal nicotine, in both patients with and without mental

disorders. The trial supports the use of varenicline and bupropion in smokers with stable mental disorders.

To separate the adverse nicotine withdrawal effects of smoking cessation itself from adverse reactions to pharmacotherapy, some authors have suggested using the flexible quit approach outlined in the FDA approved labeling for varenicline [55]. This requires separating initiation of cessation pharmacotherapy from the target quit date by four weeks, thus allowing assessment and adjustment of tolerability to treatment apart from smoking/nicotine withdrawal effects.

Alcohol use disorder

- Naltrexone – Based on our clinical experience, evidence from open trials, and randomized controlled studies involving diverse psychiatric populations [75], naltrexone appears to be effective and safe in inpatients with co-occurring schizophrenia and alcohol use disorder [76,77]. As an example, a 12-week randomized controlled trial of 31 patients with co-occurring schizophrenia and alcohol dependence found that patients treated with naltrexone experienced fewer alcohol cravings, drinking days, and heavy drinking days compared with patients treated with placebo [78]. (See "Alcohol use disorder: Treatment overview".)

  Clinical studies are insufficient to draw conclusions on the efficacy and safety of other medications for alcohol use disorder in this population:

- Disulfiram – A retrospective study of disulfiram for alcohol abuse/dependence in 33 patients with a severe mental illness (70 percent with schizophrenia) found that 64 percent attained remission of at least one year [79]. Seventy-six percent of the sample reported drinking while taking the medication; 28 percent reported experiencing negative reactions to alcohol. The drug was mostly well tolerated at doses of 250 mg/day; 21 percent of patients reported side effects, consisting mainly of upset stomach and skin rash. Higher doses, eg, 1000 mg/day, have been associated with agitation and exacerbation of psychotic symptoms.

  Disulfiram inhibits dopamine beta-hydroxylase, the rate limiting enzyme in the conversion of dopamine to norepinephrine, and may increase dopamine levels in the brain [76]. Patients with schizophrenia who are treated with disulfiram should be screened for their capacity to abstain from alcohol, and should be monitored closely for drug reactions, SUD treatment response, and exacerbation of psychosis.

- Acamprosate – Randomized clinical trials have had mixed findings on the influence of acamprosate on alcohol use among patients with schizophrenia and DSM-IV alcohol

dependence:

- A randomized clinical trial of 23 recently abstinent patients with alcohol dependence and comorbid schizophrenia, schizoaffective disorder, or psychosis not otherwise specified compared acamprosate with placebo [80]. Participants in both groups decreased their drinking during medication treatment; no difference in alcohol use was found between the two groups. The medication was well tolerated.

- A randomized clinical trial divided 36 patients with schizophrenia and alcohol use disorder into three groups: acamprosate 999 mg daily, naltrexone 50 mg daily, and counseling focused on addictive behavior [81]. Over the 24-week treatment period, although both naltrexone and acamprosate had significant effects on maintenance of abstinence, acamprosate produced a larger effect, adding an additional 23.6 days sober.

- Baclofen – An uncontrolled trial of baclofen in 10 patients found mixed results [82].

Use of medications in the treatment of alcohol use disorder, including dosing and adverse effects, is discussed in detail separately. (See "Alcohol use disorder: Treatment overview".)

Cannabis use disorder — There are no medications with demonstrated efficacy in patients with cannabis use disorder and schizophrenia. A meta-analysis concluded that existing trials are limited and inconclusive due to their small number and size [83].

Clinical trials of medications for noncomorbid cannabis use disorder are discussed separately. (See "Cannabis use disorder: Clinical features, screening, diagnosis, and treatment".)

Cocaine use disorder — Two reports found treatment with tricyclic antidepressants to be associated with reduced cocaine use in small samples [84,85]. As an example, a nonrandomized, unblinded trial of patients with schizophrenia and DSM-IV cocaine abuse compared 12 patients who were treated with antipsychotics and desipramine with 25 patients treated with antipsychotics and placebo, finding that patients treated with desipramine had fewer urinalyses positive for cocaine during the last six weeks of the trial compared with placebo (20 versus 50 percent) [84]. Clinical trials of medications for noncomorbid cocaine use disorder are discussed separately. (See "Stimulant use disorder: Treatment overview".)

Opioid use disorder

Opioid agonists — Methadone and buprenorphine, which provide effective maintenance treatment of opioid use disorder [38,86,87], have not been studied for opioid use disorder in patients with schizophrenia. In our clinical experience, however, the medications have been

used safely and effectively in patients with the dual disorders. Medication treatment of noncomorbid opioid use disorder is discussed in detail separately. (See "Opioid use disorder: Pharmacologic management".)

Opioid antagonists — Naltrexone has received little study in the treatment of opioid use disorder in patients with schizophrenia; it has been used safely and effectively in patients with noncomorbid opioid use disorder and to treat alcohol use disorder in patients with schizophrenia. (See 'Alcohol use disorder' above and "Opioid use disorder: Pharmacologic management", section on 'Naltrexone: Opioid antagonist'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Opioid use disorder and withdrawal" and "Society guideline links: Benzodiazepine use disorder and withdrawal" and "Society guideline links: Alcohol use disorders and withdrawal" and "Society guideline links: Stimulant use disorder and withdrawal" and "Society guideline links: Cannabis use disorder and withdrawal".)

SUMMARY AND RECOMMENDATIONS

- We suggest multimodal, integrated care for patients with co-occurring schizophrenia and substance use disorder (SUD) rather than separate care for each disorder or sequential care (**Grade 2C**). Multimodal care generally includes pharmacotherapy and one or more psychosocial interventions. In integrated care, the same clinician or team treats both conditions, while in parallel care the mental disorder and SUD are treated by different clinicians. When integrated treatment is not available, clinicians treating the co-occurring disorders should closely coordinate care. (See 'Integrated treatment' above and "Co-occurring schizophrenia and substance use disorder: Psychosocial interventions".)

- SUDs can exacerbate psychotic symptoms directly through the psychoactive effects of substances, or indirectly by pharmacokinetically lowering antipsychotic plasma levels or by contributing to poor patient adherence to treatment. (See 'Schizophrenia' above.)

- We recommend treatment of schizophrenia symptoms, including SUD-induced exacerbations, with an antipsychotic medication rather than other primary medications (**Grade 1A**). (See 'Schizophrenia' above and "Schizophrenia in adults: Maintenance therapy and side effect management" and "First-generation antipsychotic medications:

Pharmacology, administration, and comparative side effects" and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

- We suggest treatment of schizophrenia in patients with SUD who are nonadherent to antipsychotic medication with a long-acting injectable antipsychotic rather than a daily antipsychotic taken orally (**Grade 2C**). (See 'Antipsychotic drugs' above and "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication".)

- Tobacco smoking has been found to lower antipsychotic plasma levels in schizophrenia patients. Careful monitoring of patients' antipsychotic side effects and psychotic symptoms is warranted when their smoking status changes; antipsychotic dose adjustments may be needed. Alcohol use in patients with schizophrenia is also associated with reduced antipsychotic plasma levels; however, these patients generally do not require antipsychotic dose adjustments. (See 'Antipsychotic-substance interactions' above.)

- While some clinical trials and secondary data analyses have found antipsychotic drugs to reduce substance use in schizophrenia patients with SUD, the findings have been mixed, the studies have been methodologically limited, and the evidence is insufficient to recommend changes to antipsychotic drug prescribing in these patients. (See 'Antipsychotic drugs and SUDs' above.)

- For schizophrenia patients attempting to stop smoking tobacco, we suggest first-line treatment with nicotine replacement therapy (NRT) in combination with behaviorally oriented psychosocial treatment rather than other medications (**Grade 2C**). Bupropion and varenicline are reasonable alternative to NRT in stable patients without suicidal ideation or a history of suicidal behavior.

  Schizophrenia patients attempting to stop smoking and those treated with smoking cessation medication should be closely monitored for emerging depression, suicidality, or exacerbation of existing psychiatric or extrapyramidal symptoms. Some clinicians take a more conservative approach with varenicline, not prescribing the drug to patients with prominent depressive symptoms. (See 'Tobacco use disorder' above and "Pharmacotherapy for smoking cessation in adults".)

- Although research is limited, in our clinical experience, the following agents can be used safely and effectively for the corresponding SUD in patients with co-occurring schizophrenia.

  - Naltrexone in alcohol use disorder. (See 'Alcohol use disorder' above and "Alcohol use disorder: Treatment overview".)

- Methadone, buprenorphine, or naltrexone in opioid use disorder. (See 'Opioid use disorder' above and "Opioid use disorder: Pharmacologic management".)

Topic 106146 Version 15.0

→