Schizophrenia and Suicide: Treatment Optimization

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Opinion statement

In the aftermath of a serious suicide attempt, 25–50 % of patients with schizophrenia or schizoaffective disorder will make another attempt within 2 years; within 10 years, 3 % will have completed suicide, which represents about 60 % of all patients with these diagnoses who complete suicide. When treating such high suicide risk patients, initiating or continuing treatment with clozapine must always be the initial consideration. Clozapine is the only treatment approved to reduce suicide risk in this (or any other) population. Its efficacy for this purpose is supported by the highest quality evidence, including a prospective, randomized controlled trial, InterSePT. A trial of clozapine should be strongly considered even for first-episode patients and those whose psychotic symptoms have responded to other antipsychotics, as amelioration of psychotic symptoms may be insufficient to reduce suicide risk. When recommending a trial of clozapine, thorough psychoeducation for the patient and his or her support system is necessary. This should include informing patients that indefinite treatment with clozapine may be needed because of the elevated risks of suicide and relapse to psychosis upon drug discontinuation. Discussion of the anticipated side effects and the providers' commitment to help minimize side effects are needed to make the trial of clozapine more attractive. If a trial of clozapine is unacceptable or impossible, alternative antipsychotic medications should be used and adherence monitored. A long-acting injectable atypical antipsychotic drug is preferable to oral medication, and certainly, to no antipsychotic treatment. The clinician should regularly inquire about suicidal thoughts and hopelessness and limit patients' access to means of self-harm. In addition, one should identify the symptoms, behaviors and social factors that contribute to each patient's suicide risk, and provide a combination of pharmacotherapy, psychosocial rehabilitation modalities, and psychotherapeutic interventions to address these factors.

Introduction

4.9 % of individuals with schizophrenia will eventually complete suicide [1]. In 2010, 38,364 people died by suicide in the United States and approximately 7–12 % of these are estimated to be suicides in individuals with schizophrenia, making suicide prevention in this population a major public health concern [2–4]. Those who complete suicide are disproportionately young adults, and suicide plays a major role in reduced longevity in schizophrenia. The mean age of those who commit suicide is just 33 years, and schizophrenia increases suicide risk 30-fold and 140-fold, respectively, for men and women under 35 years of age [5, 6]. Many risk factors for suicide in patients with schizophrenia are those found in the general population, and include being young, male, white, never married, socially isolated, having prior suicide attempts, recent loss or rejection, and substance use disorder. Disease-specific risk factors include early phase of illness, with two-thirds of suicides occurring within 3 years of onset of illness, recent hospitalization, fear of mental deterioration, treatment non-adherence, and high pre-morbid functioning and awareness of impairments, which in conjunction may lead to demoralization and hopelessness [7, 8]. Awareness of these risk factors can help clinicians identify those patients at high risk for suicide who should be offered targeted interventions to address this risk.

Clozapine stands alone as the only treatment that has been demonstrated to decrease suicide deaths in patients with schizophrenia. Consequently, it is the only medication with a United States Food and Drug Administration indication for reducing suicide risk in this population. In fact, clozapine is the only intervention that has consistently been shown to reduce mortality in patients with schizophrenia due to all-causes, including suicide. Tiihonen et al. demonstrated that clozapine's benefit over other antipsychotics in improving all-cause mortality is due, in large part but not exclusively, to its statistically significant superiority over other drugs in reducing suicide deaths. In this study, the adjusted risk for death from suicide on clozapine was just 0.34, compared to 1.0 for perphenazine and 1.58 for quetiapine [9]. Remark-

ably, it is estimated that if 10,000 patients with schizophrenia were treated with clozapine instead of standard treatment, 1,000 to 1,300 suicides would be prevented [10–12]. In addition, clozapine reduces suicide in high-risk patients with schizophrenia by approximately 80 % compared to standard treatment [13, 12]. Clozapine's superiority in diminishing suicidal behavior appears to be independent from its efficacy in treating positive, negative, or depressive symptoms, which suggests that perhaps suicidality should be viewed as a distinct dimension of the schizophrenia to be targeted individually [14]. Despite this clear benefit, clozapine is strikingly underutilized and efforts need to be made at the regulatory, educational, and quality improvement level to organize structures to increase its use [15]. In addition, we will briefly discuss management of the potentially serious side effects of clozapine (See Table 1 below), which may help increase its utilization, though it should be noted that clinicians may overestimate the burden of side effects and inconvenience that patients experience with clozapine [16]. The only other biological intervention recommended to address acute suicidality in schizophrenia is electroconvulsive therapy, though the evidence for this intervention in schizophrenia is inconsistent and may be best reserved in cases when used to augment clozapine [17–19].

Intuitively, it seems that another way to reduce suicide risk in schizophrenia should be to address modifiable risk factors; namely, treatment non-adherence, substance misuse, and depressive symptoms. However, there have been strikingly few studies investigating whether interventions targeting these risk factors actually change suicide-related outcomes in schizophrenia. In this article, we will review the current evidence base for treatments to address these modifiable suicide risk factors in schizophrenia, with a particular emphasis on biological interventions, but it should be noted that there is a clear and pressing need for further investigation to directly link these interventions to a reduction in suicide in schizophrenia. These interventions could then be incorporated into the algorithm for the approach to the suicidal patient with schizophrenia and schizoaffective disorder suggested by Meltzer et al. [20].

Table 1. Potential serious side effects and management [26, 27]

Side Effect	Management Options	Re-Challenge Potential
Agranulocytosis	Discontinue Drug, Possible Hospital Admission, Granulocyte Colony Stimulating Factors, Lithium	No
Myocarditis/ Cardiomyopathy	Discontinue Drug, Possible Hospital Admission	No
Ileus/Constipation	Prophylactic Laxatives, Diet modification	Yes
Weight Gain	Metformin, Exercise/Diet, Topiramate	Yes
Sedation	Stimulants, Dosing Strategies, modafinil	Yes
Seizures	Lower dose, Divide dose, Valproic Acid, Lamotrigine	Yes
Sialorrhea	Clonidine, Anticholinergics, Sugarless Rock Candy	Yes
Orthostatic Hypotension	Slow Titration, Compression Stockings, Increase Fluids, Fludrocortisone	Yes

Treatment

Pharmacologic treatment

Treatment of suicidal behavior in schizophrenia and for treatment resistant schizophrenia

Clozapine

The gold standard study supporting the FDA indication for clozapine in suicidal patients is called the InterSept Study. This 2-year, prospective, international, multicenter, randomized study of 980 patients with schizophrenia at high risk for suicide showed a 26 % reduction in the risk of suicide attempts in clozapine-treated patients compared to those using olanzapine. The NNT was just 12 for clozapine [21, Class I]. In addition to demonstrating this anti-suicide effect, this study also refuted the argument that this reduction is due to the increased provider contact needed for the administration of clozapine. It also showed that clozapine's reduction of suicide risk was seen in both treatment-resistant and treatment-responsive patients, which emphasized that the drug should be used to address suicidality in all patients with schizophrenia, not just the treatment resistant patients it is sometimes reserved for. Another study that controlled for clinical contact was published by Modestin et al. They used a mirror-image, retrospective design with hospitalized patients and found an 88 % decrease in the suicides and a 12-fold decrease in suicidal behaviors during the period of continuous clozapine treatment. In patients who discontinued clozapine, the rate of suicidal behavior increased to the baseline rate [22].

Further epidemiological studies and meta-analyses have added support to the evidence for clozapine in suicidal patients with schizophrenia. Walker et al undertook a large-scale retrospective epidemiologic study of

mortality and morbidity in 67,072 current and past clozapine users obtained from the US Clozaril National Registry. Deaths occurring in this cohort of patients were ascertained using the Social Security Administration Death Master Files and The National Death Index. An 83 % reduction in death by suicide was observed in current clozapine users compared with past users [23]. John Hennen et al.'s random-effects meta-analysis indicated a substantially lower overall risk of suicidal behaviors with clozapine vs. other treatments (risk-ratio 3.3; 95 % confidence interval [CI] 1.7–6.3; $p=0.0001$). For completed suicides, the risk ratio (RR) was 2.9 ([CI 1.5–5.7]; $p=0.002$) [24]. Kiviniemi et al published a nationwide, register-based, 5-year follow-up study of all patients presenting with first-onset of schizophrenia between 1998 and 2003. Use of clozapine reduced the likelihood of suicides (OR 0.29; $P=0.002$) in patients with schizophrenia, supporting the conclusion that clozapine is effective in suicide reduction in all patients with schizophrenia: treatment resistant, treatment responsive, and even first-break patients [25•, Class 2]

Standard dosage	300–900 mg per day in divided doses. Doses greater than 600 mg increase risk of seizures. Gradual titration is recommended.
Contraindications	Agranulocytosis, chemotherapy, coma, ileus, leukopenia, neutropenia, seizure disorder.
Main drug interactions	Smoking, concurrent use of strong CYP3A4 inducers is not recommended, Dosage reduction of clozapine is necessary during concurrent use of strong CYP1A2 inhibitors.
Main serious side effects and management options	
special points	Separated from olanzapine at 3 months for suicide protection, so remember suicidal protective effects are delayed, plasma levels of clozapine (≥ 350 ng/ml) may be more effective, avoid abrupt discontinuation as may result in increased risk of rebound violent behavior, close monitoring of patients with Arab/African descent for WBC in 2,500–3,500 range, attempt to avoid antipsychotic polypharmacy, particularly with first generation antipsychotics as they may decrease efficacy of clozapine
Cost/cost-effectiveness	Generic, Inexpensive

*Antipsychotics: typical/FGA antipsychotics
and atypical/SGA antipsychotics excluding clozapine*

While clozapine is clearly superior and unique among antipsychotics in preventing suicides, for those patients unable or unwilling to take clozapine, antipsychotic treatment in general does seem to be useful in reducing suicide risk. Tiihonen et al. studied 2,230 adult patients with schizophrenia or schizoaffective disorder following initial admission and found that mortality was 12 times higher in patients not taking antipsychotics, and the risk of suicide in these patients was elevated 37.4 times [28]. Haukka et al. reported on 1,611 patients with a mean follow-up of 4.3 years and found that current antipsychotic use was associated with decreased mortality due to suicide (HR 0.52, 95 % CI 0.34–0.81, $p=0.004$) [29]. When comparing the data for the use of first generation

antipsychotics (FGA) versus second generation antipsychotics (SGA) excluding clozapine, there is little high quality evidence that supports the use of FGA for suicide reduction [30]. There is some better general data on the use of SGA for the reduction of suicide, including a 5-year, retrospective, case control study that showed a decreased rate of suicide in patients using atypical antipsychotics (odds ratio=3.54, 95 % confidence interval=2.4 to 5.3) [31, 32]. However, direct, prospective high quality studies of individual SGA are lacking, and there does not seem to be any evidence that other agents possess the anti-suicide properties of clozapine.

Treatment of nonadherence in schizophrenia: long-acting injectables

Several review studies have directly linked nonadherence to an increase in suicide in schizophrenia. Leucht and Heres found that non-adherent patients were at four times greater risk of suicide than adherent patients (relative risk adjusted for age and gender 4.2, 95 % CI 1.7–10.1) [33]. Lloca et al. found an even greater effect, as non-adherent patients were at seven times greater risk for suicide [34]. Herings and Erkens found that an increased suicide attempt rate was observed when comparing uninterrupted and interrupted drug use (20.0/1,000 person-years vs. 72.1/1,000 person years, respectively) [35]. The reasons for non-adherence are complex and many, but recent years have seen the development of additional long-acting injectable (LAI) formulations of second generation antipsychotics (SGA) to add to the previous armamentarium of first generation antipsychotic (FGA) LAI. The hope has been that these formulations can help with this issue of nonadherence, which could indirectly help with the issue of suicide in schizophrenia. However, recent meta-analyses of randomized controlled trials (RCTs) regarding LAI and adherence were disappointing. Kishimoto et al.'s review of 21 RCT studying a total of 4,950 patients showed that LAIs were similar to oral antipsychotics (OAP) for relapse prevention at the longest time point of relative risk [RR]=0.93, 95 % confidence interval [CI]: 0.80–1.08, $P=0.35$. Regarding nonadherence directly, pooled LAIs did not separate from OAPs (studies=10, $n=2018$, $RR=0.77$, 95 % CI: 0.49–1.22, $P=0.22$. [36, Class I]. Kane et al. wrote a commentary that highlighted some of the methodological issues that may cause randomized controlled trials to underestimate the effectiveness of LAIs compared to OAPs. These include RCT patients being less ill and more adherent than real-world patients and current RCT procedures leading to an improvement in adherence. All of these issues would help to decrease any difference between OAP compared to LAI, as they would help the OAP adherence issue disproportionately [37]. In response to this, Kishimoto et al. ran a meta-analysis of 25 mirror-image studies from 28 countries that followed 5,940 patients with schizophrenia for ≥ 12 months (≥ 6 months each on oral antipsychotic and LAI treatment). The results showed strong superiority over oral antipsychotics in preventing hospitalization (16 studies, $N=4,066$; risk ratio=0.43; 95 % CI, 0.35–0.53; $P<0.001$) and in decreasing the number of hospitalizations (15 studies, 6,342 person-years; rate ra-

tio=0.38; 95 % CI, 0.28–0.51; $P<0.001$) [38•, Class I]. While multiple limitations of mirror image studies exist, it is likely that this methodology is best at accurately assessing comparative efficacy of LAI in the naturalistic settings that most examiners practice. There is insufficient data to compare the different formulations of LAI regarding adherence, but Table 2 lists the newer and most frequently used LAI and summarizes some of the features that clinicians consider when choosing a particular LAI for their patients.

Antidepressants

There has been a surprising lack of quality studies investigating the impact of antidepressant use on depressive symptoms, suicidal ideation, and suicidal behavior in schizophrenia. [7, 39, 40]. In 2008, a Finnish registry-based prospective cohort study of 1,611 high-risk patients with schizophrenia and at least one prior suicide attempt found that current antidepressant use was not significantly associated with decreased risk of completed suicide (HR 0.66, 95 % CI 0.41–1.08, $p=0.099$) [29]. However, in more detailed analysis, citalopram use was associated with significantly lower risk of death by suicide (HR 0.26; 95 % CI 0.10–0.65) [29, Class II]. In the entire high-risk cohort, antidepressant use was actually associated with an increased likelihood of suicide attempts; however, this association was not found in patients who were concurrently receiving antipsychotic medications [29]. A second registry-based cohort study followed 2,588 patients for a mean of 4.2 years after initial hospitalization for schizophrenia, and found that current antidepressant use compared with no use was associated with significantly lower risk of completed suicide (HR 0.15, 95 % CI 0.03–0.77) [41•, Class II]. However, a 2013 Swedish registry-based study of examined 84 matched case-control pairs of patients with schizophrenia or schizoaffective disorder, and found no significant association between completed suicide and lifetime history of either antidepressant use, or more specifically, selective serotonin reuptake

Table 2. LAI (in order of release to market, newest to oldest)

LAI	Frequency of Dosing	Need for Concomitant Oral Dosing (based in part on clinical experience)	Special Points	Cost
Abilify Maintenna	Monthly	2 weeks		Very Expensive
Zyprexa Relprevv	2–4 weeks (depending on dosing desired)	None	Post-Injection Delirium/Sedation Syndrome	Very Expensive
Invega Sustenna	Monthly	0–1 week		Very Expensive
Risperdal Consta	Every 2 weeks	3–4 Weeks		Expensive
Haldol Decanoate	Every 4 weeks	1–2 Weeks	Conversion from Oral to Decanoate is 10–20X Oral dose	Inexpensive
Prolixin Decanoate	Every 3–4 weeks	1 Week	Conversion from Oral to Decanoate is 1.2–1.4X Oral Dose	Inexpensive

inhibitor (SSRI) use [42, Class III]. A possible explanation for these conflicting findings could be that the smaller Swedish study was underpowered to detect this difference, as this study also failed to find a statistically significant association between clozapine use and suicide [42]. Additionally, as its authors note, the Swedish study only examined lifetime history of receiving an antidepressant prescription, and patients at higher risk of suicide from comorbid depression might have been more likely to have been prescribed antidepressants [42].

Only a handful of randomized placebo-controlled trials have investigated the question of whether antidepressants improve depressive symptoms or suicidal ideation in schizophrenia. In a 2002 meta-analysis, authors found that the overall poor quality of these studies left them unable to recommend or advise against the use of antidepressants in patients with schizophrenia. However, in 2009 and 2010, the largest to date randomized, double-blind, placebo-controlled trial of an SSRI in this population, demonstrated that citalopram improved depressive symptoms and suicidal ideation in this population [43, 44, Class I]. This study included 198 middle aged and older adult outpatients with a diagnosis of schizophrenia or schizoaffective disorder and sub-syndromal depressive symptoms [43, 44]. The initial finding was that augmentation with citalopram (10–40 mg/day) led to statistically significant decrease in depressive symptoms and improvement in quality of life [43]. Subsequent analysis demonstrated that among patients who endorsed baseline suicidal ideation, those who received citalopram were significantly more likely than those who received placebo to deny suicidal ideation at study endpoint (28.6 % vs. 66.7 %; $P < 0.05$) [44]. Of note, there were no suicidal behaviors during the course of this trial, so actual impact of citalopram on completed suicide or attempts could not be determined.

Citalopram

Standard dosage	10 to 40 mg per day.
Contraindications	Concurrent monoamine oxidase inhibitor (MAOI) use. Citalopram causes dose-dependent QT prolongation, and is not recommended in patients already receiving medications that prolong QT or in patients with acute myocardial infarction, uncontrolled heart failure, bradycardia, hypokalemia, hypomagnesemia, or congenital long QT syndrome.
Main drug interactions	There is a risk of serotonin syndrome when combined with other serotonergic medications.
Main side effects	Drowsiness, insomnia, nausea, diarrhea, hyperhidrosis, decreased libido, erectile dysfunction
Cost/cost-effectiveness	Inexpensive, as low as \$4 per month

Treatment to reduce substance use

50 % of patients with schizophrenia will develop comorbid substance use disorders, and the increased risk of suicide in these patients is likely related to the potential for substance misuse to increase impulsivity and violence, reduce overall functional status, promote social isolation, and reduce treatment adherence [7, 11, 45–48]. For patients with comorbid schizophrenia

and substance use disorder, the most effective treatment strategy appears to be an integrated approach that combines aggressive management of both disorders with a combination of pharmacotherapy and psychosocial interventions [45, 49].

There is evidence that choice of antipsychotic can impact substance use patterns in patients with schizophrenia, with clozapine having the best evidence supporting its use [45, 54, 55]. In a 3-year retrospective study of 58 current and former clozapine patients with co-occurring diagnoses of schizophrenia or schizoaffective disorder and substance use disorder, current clozapine use was associated with a marked reduction in substance use (85 % of those actively using substances at time of initiation of clozapine decreased their use, and 72 % achieved abstinence) [56, Class II]. Additionally, an observational study of 66 patients with schizophrenia or schizoaffective disorder and comorbid alcohol use disorder, suggested that clozapine patients were more than twice as likely to have achieved substance use remission than patients taking typical antipsychotics [57, Class II]. In 2003, another retrospective study examined substance use patterns in 68 patients with schizophrenia or schizoaffective disorder and alcohol or marijuana abuse, who were prescribed either risperidone or clozapine, and found that patients taking clozapine were significantly more likely to abstain from substances [58, Class II]. In a 2006 prospective study of 75 patients with diagnoses of substance use disorder in early remission and either schizophrenia or schizoaffective disorder, clozapine users were significantly less likely to relapse than patients prescribed other antipsychotics [59, Class II].

There have been few studies investigating the use of medications to address specific substance use in patients with schizophrenia. Two small randomized placebo-controlled studies demonstrated that naltrexone (compared to placebo) reduced alcohol consumption in patients with comorbid primary psychotic disorder and alcohol use disorder [60–62, Class II]. There is very little evidence on methadone replacement and buprenorphine use in patients with schizophrenia and opiate use disorders: one small case series suggests potential benefit from methadone, and one uncontrolled study suggested that patients with comorbid schizophrenia and opiate use disorder benefitted less from buprenorphine than patients with other psychiatric disorders [63, 64].

Naltrexone

Standard dosage	50 mg once daily with food; some patients may require up to 100 mg. Alternatively, patients who demonstrate the ability abstain from alcohol use in an outpatient setting may receive 380 mg IM every 4 weeks.
Contraindications	Absolute contraindications are hypersensitivity, concurrent use of opiate analgesics and acute opiate withdrawal.
Main drug interactions	Opiate agonists, mixed opiate agonists/antagonists, nilotinib (tyrosine kinase inhibitor). May have additive hepatotoxic effect when combined with disulfuram.
Main side effects	Dizziness or syncope, anxiety, insomnia, headache, nausea, injection site reactions (with injectable form), liver toxicity, may increase suicidal thoughts.

Special points	Only start naltrexone if there is no reasonable possibility within of short-acting opiate use in the past 7–10 days or long-acting opiate use in the past 2 weeks. If there is any suspicion of opiate use, naloxone challenge should be tried prior to naltrexone initiation.
Cost/Cost-effectiveness	Oral: \$50–150 per month, injectable Vivitrol \$1,050 per month

Interventional procedures

Electroconvulsive therapy (ECT) is recommended for acutely suicidal patients with schizophrenia, primarily because of its potential to produce rapid improvement in symptoms compared to pharmacologic treatments [17, 65–67]. However, the empirical evidence supporting the use of ECT for reducing suicide risk in schizophrenia is scant and inconsistent [17]. In the 1940s, two case-control studies of patients with affective psychosis suggested that treatment with ECT was associated with a decreased risk of death by suicide [68, 69, Class III]. These findings were not reproduced in two subsequent observational studies in the 1950s, which found no significant association between ECT and suicide risk in patients with diagnoses of involutional psychosis or manic-depressive illness [70, 71]. A 1979 observational study of 74 patients with schizoaffective disorder found significantly decreased overall mortality and death by suicide in those treated with ECT [72]. In contrast, a 1986 an observational study of 1,494 psychiatric inpatients failed to demonstrate any significant decrease in suicide in patients treated with ECT, and this finding remained in subsequent analysis of only patients with schizophrenia [73]. Most recently in 2007, a Danish national registry-based cohort study examined mortality and suicide outcomes in 783 deceased psychiatric inpatients who had received ECT and 5,781 inpatients who had not [74]. Patients who had received ECT had a lower mortality rate from natural causes, but a marginally significant higher suicide rate (RR 1.20, 95 % CI 0.99–1.47), which was more pronounced within 7 days of last ECT treatment (RR. 4.82, 95 % CI 2.12–10.95) [74]. However, authors note that risk was likely due to selection bias, as they were unable to control for pre-existing suicide risk factors, and patients at higher risk of suicide may have received ECT at a higher rate [75]. Thus, while ECT may be useful in preventing imminent self-harm in some patients with schizophrenia, its potential to modify ongoing suicide risk in this population remains unclear.

Standard procedure	A series of treatments in which unilateral or bilateral electrodes are used to deliver an electrical stimulus sufficient to cause a seizure, performed under anesthesia and by a trained specialist.
Contraindications	No absolute contraindications. Certain medical conditions such as structural brain disease, increased intracranial pressure, pulmonary disease and cardiac disease require careful analysis of risks versus benefits and close monitoring.
Complications	Cognitive impairment, anterograde and retrograde amnesia, headache, musculoskeletal pain. Less common but serious complications include ar-

rhythmias, prolonged seizures, and apnea. Mortality is estimated 1:10,000 patients, similar to minor surgery.

Cost/cost-effectiveness Expensive, cost varies depending on medical center.

Psychotherapy and psychosocial interventions

There are remarkably few studies examining the impact of specific psychotherapeutic and psychosocial interventions on suicide risk in patients with schizophrenia [47]. A 2007, randomized controlled trial of cognitive behavioral therapy (CBT) in 90 outpatients with schizophrenia, found that cognitive behavioral therapy led to significant reduction in suicidal ideation compared to "befriending," and that this improvement continued for at least 9 months after completion of therapy intervention [76, Class II]. A 2002 randomized trial comparing CBT to treatment as usual in 422 patients with schizophrenia found that CBT was superior in ameliorating depressive symptoms, with a number needed to treat of nine [77, Class I]. A methodologically rigorous 2008 meta-analysis of CBT for schizophrenia suggested that CBT produces a modest yet significant improvement in mood symptoms (weighted effect size 0.363, 95 % CI 0.079–0.647), but authors found significant heterogeneity in the effect sizes among the 15 different trials that assessed mood [78, Class II]. This meta-analysis did not find any significant impact of CBT on hopelessness, which was measured in only four trials [78].

Additionally, there is some evidence that psychosocial interventions such as assertive community treatment, reality-orientated psychotherapy, family psycho-education, and the use of token economy can improve treatment adherence in patients with schizophrenia [79–81]. Evidence-based psychosocial treatments to reduce substance use in patients with schizophrenia include group therapy that combines CBT and motivational enhancement techniques, contingency management, and residential treatment when outpatient management is insufficient [45, 50–53].

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Herbert Meltzer has received honoraria for consulting, or research contracts within the last 5 years from Alkermes, Astellas, EnVivo, DaiNippon Sumitomo, Forest, Merck, Naurex, Novartis, Otsuka, Sunovion Pharmaceuticals Inc., SureGene, Takeda, and TEVA. Dr. Meltzer was the Principal Investigator of the InterSePT study, funded by Novartis and has prepared an educational program regarding suicide and clozapine sponsored by Teva. He has served as a board member or received payment to lecture at Acadia, Asenapine, BioLine Rx, Boehringer Ingelheim Pharma GmbH & Co. KG, Janssen, Sunovion, SureGene, and Teva. Additionally, Dr. Meltzer owns stock or stock options in Arcadia, SureGene and GlaxoSmithKline.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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