

Clozapine Use and Relapses of Substance Use Disorder Among Patients With Co-occurring Schizophrenia and Substance Use Disorders

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Background: Previous correlational research with schizophrenic patients has suggested that the second-generation antipsychotic medication clozapine helps to induce remissions of substance use disorder in patients with co-occurring psychosis and substance abuse. This research, however, could be biased by selection factors. Studying patients who are currently in substance abuse remission could control for level of motivation to stop using substances and other methodological confounds. **Methods:** To test whether clozapine was associated with prevention of substance abuse relapses, we examined patients with schizophrenia or schizoaffective disorder who were in their first 6-month remission of substance use disorder during a prospective 10-year follow-up study. All patients received yearly multimodal assessments of substance use. Antipsychotic medications were prescribed by community doctors as part of usual clinical care. **Results:** Patients using clozapine at the first 6-month period of substance abuse remission ($n = 25$) were much less likely to relapse over the next year compared with those on other antipsychotic medications ($n = 70$): 8.0% vs 40.0%, $\chi^2 = 8.73$ ($df = 1$), $P = .003$. Although medication assignment was not randomized, several potential confounders were similar between the groups. **Conclusion:** Clozapine should be considered for the treatment of patients with schizophrenia and co-occurring substance use disorder to prevent relapses to substance abuse.

Key words: schizophrenia/substance use disorder/
clozapine/antipsychotic medication/relapse

Introduction

Comorbid substance use disorder (termed “substance abuse” in this report) is common in patients with schizophrenia¹ and is associated with a variety of serious adverse consequences, such as relapse of mental illness,^{2,3} hospitalization,^{4,5} violence,⁶ decreased functioning,⁷ homelessness,⁸ and serious infectious diseases, such as HIV and hepatitis C.^{9,10} Research suggests that integrated dual disorder interventions are effective in reducing substance abuse over several months or years.^{11–13} There is no clear evidence that first-generation antipsychotic medications, per se, decrease substance abuse, and several investigators have in fact argued that first-generation antipsychotic medications may actually precipitate or worsen the abuse of alcohol and other drugs in patients with schizophrenia.^{14,15} One study showed that schizophrenic patients starting a first-generation antipsychotic increased nicotine use.¹⁶

In contrast to concerns that first-generation antipsychotic medications may worsen substance abuse, case reports and correlational studies suggest that the second-generation antipsychotic medication clozapine may decrease the use of nicotine, alcohol, or other drugs of abuse among patients with schizophrenia. Regarding nicotine, retrospective and cross-sectional studies of small groups of patients have found an overall decrease in smoking¹⁷ and less smoking compared with smoking in patients taking first-generation antipsychotics or risperidone.^{18,19} Two prospective studies of patients switching to clozapine found spontaneous reductions in cigarette smoking.^{20,21} Regarding drug use disorders, 2 case reports of clozapine^{22,23} and a small study of 13 patients²⁴ found that patients experienced reduced craving, reduced use of substances, or attainment of abstinence while taking clozapine. Three larger retrospective surveys reported that patients taking clozapine decreased their use of substances compared with patients taking first-generation antipsychotics or risperidone.^{25–27} Buckley and colleagues²⁸ reported that 70% of 16 patients with co-occurring substance use disorder and schizophrenia reduced or stopped using substances during a 12-week prospective trial of clozapine. Drake and colleagues²⁹ previously reported that among 151 schizophrenic patients with current substance use disorder, those placed on clozapine were more than

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twice as likely to attain full remission of substance abuse as those on other antipsychotic medications (79% vs 34%). Randomized, controlled trials are needed to confirm these correlational studies but are difficult to conduct because patients with dual disorders are difficult to engage and retain in trials and because patients, their families, and their clinicians may view clozapine side effects and monitoring as burdensome.

Research on the impact of antipsychotics on substance use disorders in patients with severe mental illness has focused on patients who were actively using substances. The major confounds in these correlational studies are potential between-group differences in motivation to change substance use, to participate in psychosocial treatments, and to adhere to medication. That is, patients who take clozapine for psychotic symptoms, despite high symptom burden and active substance abuse, may be more aware of their mental illness and/or more motivated to manage both their psychotic and substance use disorders. Furthermore, prescribers may select patients for clozapine treatment who are more compliant with medication, who are more reliable participants in treatment, or who have less severe substance use disorders. Similarly, the patients' willingness to attend weekly blood draws that were required at the time of these studies may have ensured a higher level of regular mental health care than that received by similar patients who took other antipsychotic medications that did not require close monitoring for side effects.

In the absence of randomized controlled trials, one method to control for the possible confound of differing levels of motivation to stop using substances is to prospectively assess patients who are in full remission from substance use disorders for rate of relapse, which is high in dual disorder patients.^{30–32} Although this design controls for differences in motivation for sobriety, the amount of treatment received would still need to be assessed and, if nonequivalent, controlled for as a potential confound. The purpose of the present study was, therefore, to identify patients in a 6-month remission (no evidence of abuse or dependence) from substance abuse and to assess the relative rates of substance abuse relapses in relation to antipsychotic medication use, starting at the point of the initial 6-month remissions.

Materials and Methods

The New Hampshire Dual Diagnosis Study is a 15-year, longitudinal, prospective follow-up of patients throughout New Hampshire who were dually diagnosed with severe mental illness and substance use disorder.^{32,33} The study was approved and monitored by the Dartmouth College and New Hampshire State Committees for the Protection of Human Subjects.

Participants

A total of 223 outpatients with co-occurring severe mental and substance use disorders began the longitudinal study between 1989 and 1992. The 223 original participants were predominantly male (74.4%), Caucasian (96.4%), young (average age 34 years), and unmarried (89.3%). Diagnostically, 53.4% were diagnosed with (*Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*) *DSM-III-R* schizophrenia, 22.4% with schizoaffective disorder, and 24.2% with bipolar disorder. All were diagnosed with co-occurring substance use disorders: 74.8% with alcohol use disorder and 41.9% with drug use disorder. Cannabis was the most commonly abused drug followed by cocaine, and other specific drugs were abused by a small number of participants. At baseline, the participants had high rates of recent hospitalization, homelessness, and unemployment, similar to other dually diagnosed patients who received care in the New Hampshire mental health system at that time.¹¹

For the analyses reported here, only the patients with schizophrenia and schizoaffective disorder ($N = 169$) are included because clozapine was not prescribed for patients with bipolar disorder during much of this study. Based on multimodal assessments (described below), 123 schizophrenic and schizoaffective disorder participants (72.8% of the group) experienced a 6-month remission from substance use disorder (defined below in the "Statistical Analyses" section) at some point in time during the 10-year follow-up, and 115 (93.5%) of these were subsequently followed up 1 year later. Of these 115 patients, 95 reported taking one or more antipsychotic medication at the time of the first 6-month remission, and this is the study group for the analyses reported here. Of the study group of 95 patients, 62 took first-generation antipsychotics (16 in a decanoate form), 25 took clozapine, and 8 took other second-generation antipsychotics (4 took risperidone and 4 took olanzapine). Clients who took clozapine were designated as clozapine patients even if they were taking another additional antipsychotic. The 62 patients taking first-generation and the 8 taking other second-generation antipsychotics were then grouped together for analyses for 2 reasons. Firstly, the rate of relapse in this group of 8 patients and the patients on first-generation antipsychotics did not differ, and secondly, little preliminary evidence suggested that risperidone and olanzapine were associated with better substance abuse outcomes than the first-generation antipsychotics.

Medication information was available for the previous year on 89 of the 95 patients: 42.1% of clozapine patients had been on clozapine for more than a year, and 73.8% of patients on other antipsychotics had been on their antipsychotic for more than a year. None of the patients in the other antipsychotic group had been on clozapine at the assessment in the year prior to remission. Clozapine

dose was collected via clinical chart review for 20 of the 25 participants at the time of interview of the first 6-month remission and for all 25 at the interview 1 year after remission. Mean clozapine dose over the 3 months prior to the interview corresponding to first remission was 417 mg (SD = 166). At 1 year after remission, mean clozapine dose was 484 mg (SD = 157). Doses of the other antipsychotic medications were not collected.

Twenty-four patients were taking concomitant mood stabilizers (3 valproate, 5 tegretol, and 16 lithium), 23 were taking antidepressant medications, and 19 were taking benzodiazepines. Nine took a second antipsychotic (3 clozapine patients and 6 first-generation antipsychotic patients). There were no statistically significant differences in concomitant medications between clozapine patients and first-generation antipsychotic patients.

Procedures

Participants with co-occurring disorders were recruited from 7 of New Hampshire's 10 community mental health centers and gave written informed consent at baseline and at yearly follow-ups. At baseline, research psychiatrists diagnosed participants with schizophrenia or schizoaffective disorder and active substance use disorder (alcohol or drug abuse or dependence during the previous 6 months). Participants were subsequently assessed yearly by research interviewers and urine toxicology and were paid for their participation at each assessment. Clinicians (case managers) also rated the participants for substance abuse yearly for the first 3 years.

Measures

The Structured Clinical Interview for DSM-III-R (SCID)³⁴ was used to establish diagnosis. At baseline, the research interview included items from the Uniform Client Data Inventory³⁵ to assess demographic information; the Timeline Follow-Back (TLFB)³⁶ to assess days of alcohol and drug use over the previous 6 months; the medical, legal, and substance use sections from the Addiction Severity Index (ASI)³⁷; detailed chronological assessment of housing history and institutional stays using a self-report calendar supplemented by outpatient records and hospital records³⁸; the Quality of Life Interview³⁹ to assess objective and subjective dimensions of quality of life; the expanded Brief Psychiatric Rating Scale (BPRS)⁴⁰ to assess current psychiatric symptoms; and management information systems data and the Service Utilization Interview⁴¹ to assess service utilization. Medication use was assessed via interview. Clozapine dose was assessed by clinical chart review. In addition, we conducted urine toxicology screens in our laboratory using quantitative enzyme multiplied immunoassay technique (EMIT; Syva-Behring) to assess drugs of abuse. Follow-up interviews contained the same instruments, without reassessing demographic and lifetime informa-

tion. The same 2 masters-level trained interviewers conducted the interviews and collected the urine samples for the entire study, maximizing trust and improving the validity of the self-report measures. While the interviewers were not blind to study medications, no hypotheses existed regarding the impact of clozapine on substance use at the time of the study.

To supplement the research substance abuse assessments, clinicians (case managers) rated patients yearly on 3 rating scales for the first 3 years of the study: the Alcohol Use Scale (AUS), the Drug Use Scale (DUS), and the Substance Abuse Treatment Scale (SATS), which address client status for the prior 6 months. The AUS and DUS are 5-point scales based on *DSM-III-R* criteria for severity of disorder: 1 = abstinence, 2 = use without impairment, 3 = abuse, 4 = dependence, and 5 = severe dependence.⁴² The SATS⁴³ is an 8-point scale that indicates progressive movement toward recovery from a substance use disorder according to the model of treatment and recovery of Osher and Kofoed⁴⁴: eg, 1–2 = early and late stages of engagement, defined as developing a regular treatment relationship and 7–8 = stages of relapse prevention, defined as developing skills and supports to maintain abstinence.

To address the problems with self-report of substance use in persons with severe mental illness (denial, minimization, distortions due to symptoms, and problems with traditional measures for this population),⁴⁵ we supplemented self-report with laboratory measures and clinician ratings to attain more valid assessments.⁴⁶ Additionally, a team of 3 independent raters blind to medication considered all available data at each time point on substance use disorder (from the research interview ASI and TLFB, clinician ratings, and urine drug screens) to establish separate ratings on the 6-month AUS, DUS, and SATS, following procedures validated previously.^{47,48} This blind rating is our primary outcome measure used for the analyses reported here. To determine the interrater reliabilities, researchers independently rated a randomly selected subgroup of 32% of the patients. Intraclass correlation coefficients were high for all 3 scales: 0.94 on the AUS, 0.94 on the DUS, and 0.93 on the SATS.

Data Analysis

The bivariate relationships between clozapine use and relapse were analyzed using chi-square tests. Confounding factors were compared between patients taking clozapine and those taking other antipsychotic medications using *t* tests and chi-square tests. For these analyses, remission was defined as independent, blind rater AUS and DUS less than 3 (indicating abstinence or occasional use with no signs of abuse or dependence for the past 6 months). Relapse was defined as independent, blind rater AUS or DUS returning to 3 or greater (indicating return to substance use with symptoms to diagnose abuse or dependence during the past 6 months).

Table 1. Characteristics of Clozapine Users and Other Antipsychotic Medication Users at the First 6-Month Remission

Variables	Clozapine (<i>n</i> = 25)	Other Medicines (<i>n</i> = 70)	<i>t/χ</i> ²
Demographics and diagnosis			
Sex (female)	4 (16.0%)	24 (34.3%)	2.96
Education (less than high school) at baseline	10 (40.0%)	24 (34.3%)	0.26
Age, y	33.72 (6.82)	35.14 (6.17)	0.80
Marital status (not married at remission)	25 (100%)	63 (90.0%)	2.70
Race (White)	25 (100%)	68 (97.1%)	0.73
Diagnosis (schizophrenia vs schizoaffective disorder)	15 (60.0%)	51 (72.9%)	1.44
Antisocial personality disorder (yes)	4 (16.7%)	10 (15.6%)	0.01
Substance abuse			
AUS (1–5)	1.58 (0.61)	1.81 (0.57)	1.68
DUS (1–5)	1.30 (0.50)	1.50 (0.58)	1.52
Days of alcohol use in past 6 months	2.78 (7.13)	8.42 (14.00)	2.49*
Days of drug use in past 6 months	0.26 (0.75)	3.59 (9.32)	2.88**
SATS (1–8)	5.52 (1.53)	5.40 (1.39)	0.36
Other outcomes			
Global Assessment Scale	44.09 (12.04)	45.15 (12.45)	0.36
BPRS total score	48.35 (13.64)	41.43 (12.13)	2.12*
Days of independent living (80% of time or more)	5 (20.0%)	19 (27.5%)	0.55
Contact with non-substance abuse friends (yes)	6 (25.0%)	23 (33.9%)	0.52
Currently working (yes)	6 (25.0%)	15 (21.4%)	0.13
Outpatient substance abuse treatment (yes)	11 (55.0%)	25 (40.3%)	1.32
General life satisfaction	4.33 (1.53)	4.77 (1.27)	1.38

P* < .05, *P* < .01.

Results

Group Equivalence

Table 1 shows the comparisons between patients taking clozapine and those taking other antipsychotic medications at the time of the first 6-month remissions, according to demographics, diagnoses, type of substance abuse (alcohol, drugs, or both), and functional status. Patients on clozapine had greater total BPRS symptom scores for the 2 weeks prior to evaluation and fewer days of alcohol and drug use in the 6 months prior to evaluation, although there were no differences on independent, blind ratings of alcohol and drug use disorder severity or stage of substance abuse treatment.

Relapse to Substance Use Disorder

Compared with patients taking other antipsychotic medications, patients with comorbid alcohol or drug disorders who were taking clozapine were less likely to experience substance abuse relapse at 1 year following remission: 2 of 25 (8.0%) compared with 28 of 70 (40.0%), $\chi^2 = 8.73$ (*df* = 1), *P* = .003. Among patients taking first-generation antipsychotics, rates of relapse did not differ between those taking decanoates (long-acting injectables; *N* = 16) and those taking oral pills (*N* = 46; 6 of 16 = 37.5% vs 19 of 46 = 41.3%, the Fisher exact test = 1.00). Additionally, the 8 patients taking risperidone or olanzapine experienced similar rates of substance abuse relapse as patients taking conventional antipsychotics (3 of 8 =

37.5% vs 25 of 62 = 40.3%; $\chi^2 = 0.024$, *P* = .88). Table 2 shows that patients who were prescribed clozapine also experienced better 1-year postremission outcomes on other measures of substance use and disorder than patients who were prescribed other antipsychotic medications.

Potential Confounds at 1-Year Follow-Up

At follow-up assessments (1 year after remission), the patients on clozapine were similar to the patients on other antipsychotic medications on all other outcome variables (see table 2). BPRS symptom scores for the clozapine patients improved over the year, becoming similar to scores of the nonclozapine patients, whose scores remained constant. Patients on clozapine and those on other antipsychotic medications used similar amounts of treatment services (case management, psychiatrist visits, and hospital days). Use of concomitant medications was similar between the 2 groups and unrelated to substance abuse outcomes. Too few clozapine patients relapsed to allow us to test for the potential effects of other variables, such as alcohol vs drug use disorder, on relapse.

Two-Year Follow-Up

To assess the stability of remission over time, we attempted to assess patients for remission at 2 and 3 years following remission. At the second year following remission, 64 patients had not switched to a different class of

Table 2. Characteristics of Clozapine Users and Other Antipsychotic Medication Users at 1-Year Follow-Up

Variables	Clozapine (<i>n</i> = 25)	Other Medicines (<i>n</i> = 70)	<i>t</i> / χ^2
Substance abuse			
AUS (1–5)	1.60 (0.75)	2.07 (0.90)	2.34*
DUS (1–5)	1.38 (0.56)	1.70 (0.98)	1.96*
Days of alcohol use in past 6 months	9.17 (25.10)	16.89 (32.7)	1.05
Days of drug use in past 6 months	1.50 (3.84)	11.21 (29.57)	2.61**
SATS (1–8)	6.21 (1.53)	5.23 (1.90)	2.17*
Remain full remission (yes)	23 (92.0%)	42 (60.0%)	8.73**
Other outcomes			
Global Assessment Scale	45.20 (12.23)	48.30 (11.61)	1.03
BPRS total score	45.31 (12.20)	41.20 (11.11)	1.26
Days of independent living (80% of time or more)	5 (20.0%)	22 (31.9%)	1.27
Contact with non-substance abuse friends (yes)	8 (40.0%)	30 (46.9%)	0.29
Currently working (yes)	8 (40.0%)	20 (30.3%)	0.66
Outpatient substance abuse treatment (yes)	7 (36.8%)	34 (54.0%)	1.71
General life satisfaction	4.78 (1.11)	4.53 (1.43)	0.67
Service utilization			
Case management (hours)	132.42 (83.56)	101.26 (98.40)	1.05
Medication visits (hours)	25.33 (27.75)	20.81 (20.35)	0.66
Hospitalization (days)	29.31 (65.94)	24.92 (58.60)	0.23

P* < .05, *P* < .01.

antipsychotic medication and had data available. The clozapine group (*N* = 16) maintained a significantly lower rate of relapse than the patients on other antipsychotic medications (4 of 16 = 25% vs 18 of 48 = 37.5%; χ^2 = 5.82; *P* = .05). Because the majority of patients had switched medications or were missing from the data set at the next assessment point, it was not possible to conduct a valid analysis for the third year following attainment of remission.

Discussion

This study reports that patients in 6-month remissions from their substance use disorder who took clozapine had lower rates of relapse back into substance abuse compared with patients who took other antipsychotic medications, despite equivalent utilization of other treatment services. This advantage was maintained at 2 years after initial remission. Little research has assessed relapse prevention interventions in patients with severe mental illness, despite data indicating that patients in remission continue to be vulnerable to relapse.³² This is the first study of clozapine use among patients with schizophrenia during a significant period of remission from substance abuse, adding to prior studies showing that clozapine was effective for patients with schizophrenia and co-occurring substance use disorders who were trying to stop using substances in the active stage of treatment.

The distinction of patient's stage of treatment is important. Past studies of clozapine have neither assessed nor controlled for level of motivation (or stage of treatment). Previous studies of clozapine, therefore, could have been

confounded by the possibility that clozapine was only prescribed to patients who were more motivated to manage their illnesses and to participate in treatment, resulting in better outcomes for that treatment group. This report directly addresses this problem by documenting substance abuse over time in a group of patients who were all in the same stage of treatment (relapse prevention or remission for substance abuse) and, therefore, more likely to have had the same level of motivation.

Moreover, this study also addresses concerns about other related confounds. Patients prescribed clozapine in this study group did not receive a significantly different amount or intensity of treatment during the period of time after the first 6-month remission (including case management, inpatient treatment, and substance abuse counseling). Additionally, although patients taking clozapine reported fewer days of alcohol and drug use in the 6 months prior to the first remission, patients prescribed clozapine used substances for a similar number of days at study baseline,²⁹ and independent, blind ratings of the severity of substance use disorder were similar between the groups at baseline and in the 6 months prior to initial remission. Additionally, at the time these medications were being prescribed, the reports of clozapine and its possible effect on substance use had not yet been published. Taken together, these data suggest that prescribers were not selecting patients with milder substance use disorders for clozapine prescription in this study group.

Although the research reported here extends previous findings regarding clozapine and substance abuse in schizophrenia, these results must be viewed conservatively

because this group of patients was prescribed clozapine based on clinical judgment rather than random assignment and could have been biased toward prescribing to patients who were more compliant or for some other reason were more likely to respond to concomitant psychosocial interventions or to sustain remission from substance abuse for other reasons. Additionally, we relied on patient self-reports regarding other antipsychotic medications and their doses. Moreover, we were not able to monitor or assess medication adherence. Other caveats include the relatively small size of the group of patients prescribed clozapine, the use of a 6-month interval to assess remission, which could have missed periods of relapse in between the yearly interviews, and the use of participants who were willing to be engaged in treatment at mental health centers in New Hampshire, who could be different from people with dual disorders elsewhere, or who were not willing to be engaged in treatment. Randomized controlled trials of adequate size with continuous assessment of substance use are needed to confirm the results reported here. While clinicians wait for further research to be completed, however, these data, added to other information about the efficacy of clozapine in this population, suggest that clinicians should consider use of clozapine for patients with dual disorders of schizophrenia and co-occurring substance use disorders.

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