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Course of Psychosis in Schizophrenia With Alcohol Use Disorder:

A Post Hoc Analysis of the Clinical Antipsychotic Trials of Intervention Effectiveness in Schizophrenia Phase 1 Study

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ABSTRACT

Objective: Patients with schizophrenia and comorbid alcohol use disorder remain understudied. This post hoc analysis evaluated data from Phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness in Schizophrenia study (January 2001–December 2004).

Methods: Patients without substance abuse (except marijuana use) in the month before study entry were categorized into those with a history of alcohol use disorder (SZ + AUD) within 5 years before study entry and those without alcohol use disorder (SZ-only) per *DSM-IV* criteria. Time to first and recurrent exacerbations and hospitalizations were compared between disease states and between olanzapine and perphenazine, quetiapine, risperidone, and ziprasidone.

Results: A total of 1,338 patients (SZ + AUD = 22.6%; SZ-only = 77.4%) were included. Time to first exacerbation of SZ was significantly shorter in the SZ + AUD versus SZ-only population (median = 5.4 vs 6.4 months; hazard ratio [HR] = 1.20 [95% CI, 1.01–1.42]; $P = .039$). Similar findings were observed for first hospitalization (HR = 1.63 [95% CI, 1.20–2.22]; $P = .002$) and recurrent hospitalizations (HR = 1.60 [95% CI, 1.18–2.15]; $P = .002$). The most common reasons leading to exacerbation in both groups were an increase in symptom severity and lack of efficacy. In patients with SZ + AUD related or unrelated to marijuana, perphenazine, quetiapine, risperidone, and ziprasidone were associated with significantly shorter time to first exacerbation versus olanzapine.

Conclusions: This post hoc analysis confirmed that patients with SZ + AUD had a worse illness course than patients with SZ-only and suggests that olanzapine may be associated with a longer time to first and recurrent exacerbations versus other antipsychotics in this difficult-to-treat population. Further research is needed to identify effective treatments for this important yet understudied patient population.

Trial Registration: ClinicalTrials.gov identifier: NCT00014001

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Alcohol use is notably higher in those with severe psychotic disorders than in the general population.[1] The worldwide prevalence of comorbid alcohol use disorder (AUD) in people with schizophrenia ranges from ~5%–34%.[2–5] In the United States, it is estimated that approximately 1 out of every 3 people with schizophrenia (33.7%) meet criteria for AUD.[5] Patients with schizophrenia and AUD have a complex clinical presentation requiring a tailored treatment strategy involving integrated psychosocial and medical care.[6] Although psychosocial treatments are often used, they are not always followed and relapse rates are high.[7] Schizophrenia has an adverse impact on psychosocial factors, including social isolation, financial difficulties, and functioning.[8] The development of comorbid AUD may contribute to the vulnerabilities associated with schizophrenia[8] and may result in an overall exacerbation of symptoms and poor patient outcomes.[2] Furthermore, patients with schizophrenia report greater euphoria and stimulatory effects from alcohol than healthy controls, while also experiencing increases in the symptoms of psychosis and cognitive impairment.[9]

Despite recognition that AUD can complicate the course of illness in schizophrenia,[10] treatment options for these patients are limited,[11] and it has been difficult to evaluate a link between alcohol drinking and symptom worsening in this unique patient population.[12] Clinical trials conducted for the regulatory approval of pharmacologic treatments in schizophrenia exclude those with comorbid AUD. As a consequence, clinical trial data in this population are sparse,[12–14] and further research is needed to identify effective treatments for this clinically relevant yet understudied population.

In clinical practice, psychosocial therapies, including motivational and behavioral interventions aiming to address both schizophrenia and AUD, offer an important management approach.[6,7,15] However, evidence of the long-term benefit of such interventions is inconclusive,[16] and the risk of substance abuse relapse is high.[17] Because abnormalities in dopaminergic transmission have been hypothesized to contribute to the pathophysiology of AUD,[18–22] antipsychotic agents have been tried for the treatment of AUD.[23] Although results of antipsychotic treatment of primary AUD have been mixed to disappointing,[23] in people with schizophrenia and

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Clinical Points

- Although approximately one-third of patients with schizophrenia are estimated to have alcohol use disorder (AUD), data on optimal treatments for these patients are limited.
- Patients with schizophrenia and AUD have worse outcomes, including more and earlier exacerbations and hospitalizations, than those without AUD.
- Olanzapine may have greater effectiveness versus other antipsychotics in patients with schizophrenia and AUD.

comorbid AUD, effective antipsychotic treatment can be expected to improve outcomes. Reasons include that people with schizophrenia and comorbid AUD are likely to abuse substances more if they are symptomatic, partly as a means of self-medicating and partly related to impaired impulse control and reward-seeking behavior. As AUD has been associated with greater severity of psychosis and with antipsychotic nonadherence,[10,24,25] improved control of schizophrenia symptoms is expected to potentially improve AUD and vice versa.[26] Limited literature exists regarding the efficacy of clozapine,[27] paliperidone palmitate once monthly,[28] or long-acting injectable risperidone[13] in this difficult-to-study population. Olanzapine is considered to be one of the most efficacious first-line antipsychotics available for the treatment of schizophrenia, although its effectiveness in schizophrenia and AUD has not been evaluated.[29–33] Furthermore, no large-scale, randomized trial has directly compared the efficacy of different antipsychotics in schizophrenia patients with comorbid AUD.

The National Institute of Mental Health–funded prospective, multiphase, Clinical Antipsychotic Trials of Intervention Effectiveness in Schizophrenia (CATIE) study was one of the largest and longest comparative effectiveness trials of antipsychotics for the treatment of schizophrenia.[34] Unlike many clinical trials in schizophrenia, the CATIE study did not exclude patients with comorbid conditions, such as substance use (drugs, alcohol, and tobacco). Phase 1 data from CATIE have been the topic of previous secondary analyses, including those focusing on comorbid substance use conditions.[35,36] In one analysis, illicit substance use (excluding AUD) attenuated the reduction in time to all-cause discontinuation associated with olanzapine,[36] whereas in another secondary analysis of people with AUD at baseline, there were no observed differences between any of the evaluated antipsychotics.[35]

Here, we report the results of a post hoc analysis that examined the course of illness in patients with schizophrenia and AUD using data from Phase 1 of the CATIE study (CATIE-1). We assessed time to first exacerbation, time to recurrent exacerbations, and risk of first and of recurrent hospitalization in patients with SZ and a history of AUD within the 5 years prior to study entry (SZ + AUD group) compared with patients with schizophrenia only (SZ-only group). To assess if the advantages of olanzapine observed in the full cohort extended to the subgroup of patients with AUD, we compared treatment outcomes with olanzapine versus other antipsychotics in patients with SZ + AUD and SZ-only. On the basis of prior evidence, we hypothesized that patients with SZ + AUD would have a worse outcome than patients with SZ-only, but that within each subgroup the advantages of olanzapine versus other antipsychotics for exacerbations and hospitalizations in Phase 1 of the CATIE study would be retained.

METHODS

This post hoc analysis evaluated data from CATIE-1 (ClinicalTrials.gov identifier: NCT00014001), which was conducted between January 2001 and December 2004 at 57 clinical sites in the United States.[34] The data used in the preparation of this article were obtained from the limited-access datasets distributed from the National Institutes of Health. CATIE-1 was a double-blind randomized study comparing the typical antipsychotic perphenazine with several atypical antipsychotics (olanzapine, quetiapine, risperidone, and ziprasidone) in 1,493 patients with schizophrenia. The primary effectiveness endpoint was time to all-cause discontinuation. In Phase 1 of the study, patients were followed for 18 months or until treatment was discontinued for any reason. Approval for the CATIE-1 study was obtained from the institutional review board at each site, and written informed consent was obtained from patients or legal guardians. Full methodology for the CATIE-1 study has been published elsewhere.[34]

Patients

For this post hoc analysis, patients with or without AUD (excluding those patients with substance abuse [other than marijuana, which was allowed]) were categorized into SZ + AUD and SZ-only groups. The analysis includes 1,338 patients due to the exclusion of patients with substance abuse other than marijuana in the month prior to study entry. Patients with AUD were identified based on *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria for alcohol dependence or abuse.

Assessments

For the comparison of exacerbations between groups, an exacerbation was defined as an event meeting any of the following criteria during CATIE-1: hospitalization for psychopathology; ≥ 25% or 15-point increase in Positive and Negative Syndrome Scale (PANSS) total score from baseline and/or worsening in P1 (delusions), P2 (conceptual disorganization), P3 (hallucinations), P6 (suspiciousness/persecution), P7 (hostility), and G8 (uncooperativeness) item scores (≥ 5 if baseline score ≤ 3 or ≥ 6 if baseline score was 4); clinically significant aggression or suicidal/homicidal ideations; use of rescue medication; emergency room visit; discontinuation due to lack of efficacy; and arrest or incarceration. The individual PANSS items used for the

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Table 1. Demographic and Baseline Characteristics of Patients With Schizophrenia and Alcohol Use Disorder (SZ + AUD) and Patients With Schizophrenia Only (SZ-Only)[a]

	SZ + AUD[b] (n = 303)	SZ-Only[c] (n = 1,035)	*P* Value[d]
Age, y	38.4 (10.66)	41.3 (11.24)	< .001[e]
Male, n (%)	262 (86.5)	726 (70.1)	< .001[e]
Race, n (%)			
White	188 (62.0)	635 (61.4)	.870
Black	102 (33.7)	348 (33.6)	…
Other	13 (4.3)	52 (5.0)	…
Weight, kg	88.4 (23.84)	89.2 (20.87)	.548
BMI, kg/m^2	28.8 (7.32)	30.2 (6.94)	.001[e]
Years of education	11.8 (2.03)	12.2 (2.35)	.002[e]
Psychiatric history			
PANSS total score	76.5 (16.82)	74.9 (17.79)	.153
CGI-S score	4.0 (0.87)	3.9 (0.97)	.078
Calgary Depression Scale	5.0 (4.32)	4.3 (4.38)	.023[e]
No. of hospitalizations, lifetime	2.9 (1.32)	2.7 (1.48)	.010[e]
No. of hospitalizations, previous year	0.9 (1.12)	0.6 (0.95)	< .001[e]
Age at first emotional/behavioral treatment, y	22.9 (8.82)	24.5 (9.02)	.009

[a]Data shown as mean (SD) unless otherwise specified. Patients from the CATIE-1 study with substance abuse other than marijuana in the month prior to study entry were excluded from this analysis.
[b]SZ + AUD group included 58, 60, 68, 86, and 31 patients randomized to perphenazine, olanzapine, quetiapine, risperidone, and ziprasidone, respectively.
[c]SZ-only group included 174, 247, 242, 233, and 139 patients randomized to perphenazine, olanzapine, quetiapine, risperidone, and ziprasidone, respectively.
[d]*P* values from Student *t* test or χ^2 test.
[e]Potential confounders with $P < .10$ from *t* test or χ^2 test were further analyzed by logistic regression model using backward selection. Significant confounders, defined as $P < .20$ from the logistic regression model, were included in the analysis of outcomes to adjust for the potential baseline imbalance. These were age, male gender, BMI, years of education, number of hospitalizations in lifetime, number of hospitalizations in previous year, and baseline Calgary Depression Scale score.
Abbreviations: BMI = body mass index; CATIE-1 = Clinical Antipsychotic Trials of Intervention Effectiveness in Schizophrenia, Phase 1; CGI-S = Clinical Global Impressions-Severity; PANSS = Positive and Negative Syndrome Scale.

definition of exacerbation are the most commonly used PANSS items for this purpose.[37–39]

Time to first exacerbation, time to first hospitalization, time to recurrent exacerbations, and time to recurrent hospitalizations were compared between patients with SZ + AUD and the SZ-only group. The reasons leading to individual exacerbations in SZ + AUD and SZ-only patients were also evaluated. In the SZ + AUD group, exacerbations and hospitalizations were compared between olanzapine and the other antipsychotics (perphenazine, quetiapine, risperidone, and ziprasidone).

Statistical Analysis

Demographic, illness, and randomized antipsychotic treatment characteristics of the SZ + AUD and SZ-only groups were compared using a Student *t* test or χ^2 test. Cox proportional hazards and Andersen-Gill models were used to compare between groups and to obtain the estimate of the hazard ratio for time to first event and time to recurrent event analysis, respectively. Analysis of time to first exacerbation focused only on the time to the first event, whereas analysis of time to recurrent exacerbation also modeled subsequent events. Kaplan-Meier plots were presented for time to first event analyses. The χ^2 test was also used for between-group comparisons of the proportion of patients in each of the exacerbation event criteria groups.

RESULTS

Patient Baseline Characteristics

Of the 1,338 patients included in the analysis, 303 (22.6%) were identified as SZ + AUD and 1,035 (77.4%) as SZ-only (Table 1). At baseline, patients with SZ + AUD were significantly younger than patients with SZ-only (38.4 vs 41.3 years; $P < .001$), had a lower mean body mass index (BMI, 28.8 vs 30.2; $P = .001$), and were more predominantly male (86.5% vs 70.1%; $P < .001$). Patients with comorbid AUD also had a higher mean number of hospitalizations in the year prior to study entry (0.9 vs 0.6; $P < .001$) compared with patients with SZ-only. Their randomized antipsychotic treatments are described in Table 1. Marijuana use was balanced between the 2 groups, with marijuana use reported in 5.9% (n = 18/303) and 8.2% (n = 85/1,035) of SZ + AUD and SZ-only patients, respectively.

Exacerbations and Hospitalizations

The time to first exacerbation of schizophrenia was significantly shorter in SZ + AUD patients than SZ-only patients (median = 5.4 vs 6.4 months; hazard ratio [HR] = 1.20 [95% CI, 1.01–1.42]; $P = .039$) (Figure 1A). The time to first hospitalization for schizophrenia was also significantly shorter in SZ + AUD patients than SZ-only patients (HR = 1.63 [95% CI, 1.20–2.22]; $P = .002$) (Figure 1B). Similar findings were observed for recurrent hospitalizations (HR = 1.60 [95% CI, 1.18–2.15]; $P = .002$), whereas between-group differences in recurrent exacerbations were not statistically significant (HR = 1.16 [95% CI, 0.99–1.36]; $P = .065$) (Figure 2).

Overall, a higher proportion of patients in the SZ + AUD group (n = 186 [61.4%]) had an exacerbation compared with patients in the SZ-only group (n = 539 [52.1%]; $P = .004$). A significantly higher percentage of patients in the SZ + AUD versus the SZ-only group had an exacerbation resulting in hospitalization for psychopathology ($P < .001$) or due to clinically significant aggression or suicidal/homicidal ideations ($P = .003$) or arrest or incarceration ($P < .001$) (Figure 3). SZ + AUD patients did not differ significantly from SZ-only patients on the following individual predefined exacerbation criteria: increase in symptom severity measured by PANSS score, exacerbation due to lack of efficacy, need for rescue medication, or emergency room visit (Figure 3).

Comparison of Antipsychotic Use in the SZ + AUD Group

The times to first and recurrent exacerbations in patients treated with olanzapine compared with the other studied antipsychotics (perphenazine, quetiapine, risperidone, and ziprasidone) are presented in Figure 4A. Overall, perphenazine (HR = 2.28 [95% CI, 1.38–3.77]), quetiapine

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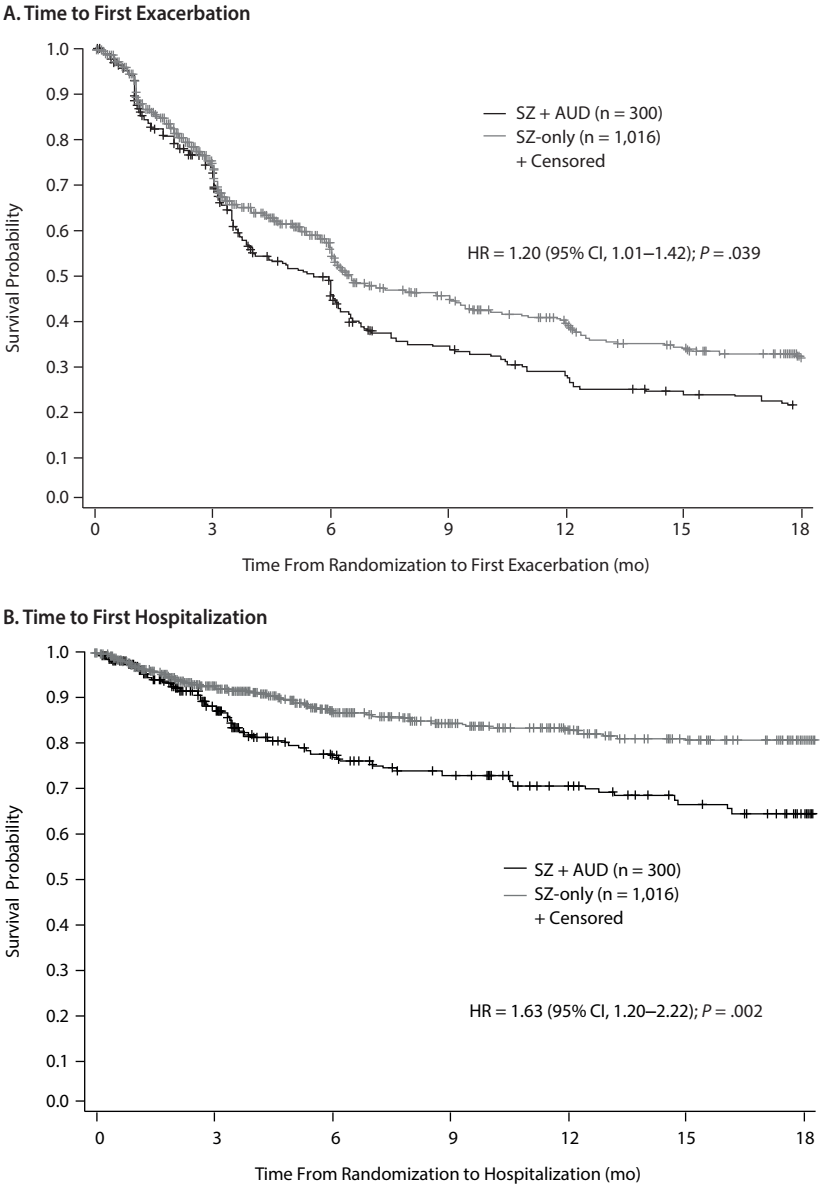
Figure 1. Kaplan-Meier Plots of (A) Time to First Exacerbation and (B) Time to First Hospitalization in Patients With Schizophrenia and Alcohol Use Disorder (SZ + AUD) and Patients With Schizophrenia Only (SZ-Only)



P values are from Cox proportional hazards models adjusting for potential baseline confounders (age, male gender, BMI, years of education, number of hospitalizations [lifetime], number of hospitalizations [previous year], and baseline Calgary Depression Scale score). Twenty-two patients were excluded from the Cox model due to missing values in the confounders.
Abbreviations: BMI = body mass index, CI = confidence interval, HR = hazard ratio.

(HR = 2.09 [95% CI, 1.28–3.43]), risperidone (HR = 1.81 [95% CI, 1.13–2.91]), and ziprasidone (HR = 2.80 [95% CI, 1.58–4.97]) were associated with a significantly shorter time to first exacerbation compared with olanzapine. Findings for recurrent exacerbations followed a similar pattern (Figure 4A). Overall, perphenazine (HR = 1.44 [95% CI, 0.58–3.54]), quetiapine (HR = 2.02 [95% CI, 0.90–4.52]), risperidone (HR = 1.71 [95% CI, 0.78–3.76]), and ziprasidone (HR = 3.77 [95% CI, 1.53–9.30]) had a shorter time to first hospitalization compared with olanzapine, although only the findings for ziprasidone versus olanzapine reached statistical significance. Results for recurrent hospitalizations were similar to those for time to first hospitalization (Figure 4B).

DISCUSSION

Using data from the CATIE-1 study, this post hoc analysis evaluated the course of disease in patients with SZ + AUD compared with SZ-only patients. Findings confirmed our hypothesis that patients with SZ + AUD experienced

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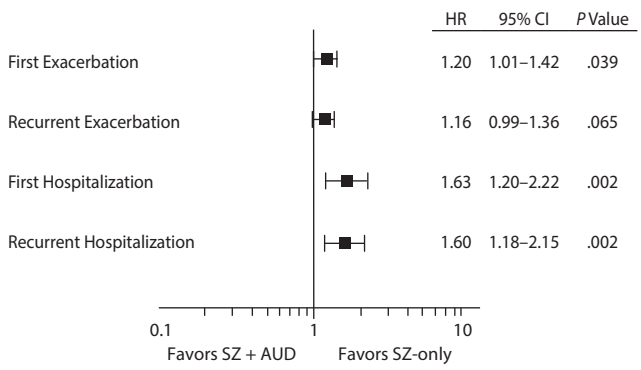
Figure 2. Comparison of Time to First and Time to Recurrent Exacerbations and Hospitalizations Between Patients With Schizophrenia and Alcohol Use Disorder (SZ + AUD) and Patients With Schizophrenia Only (SZ-Only)[a]

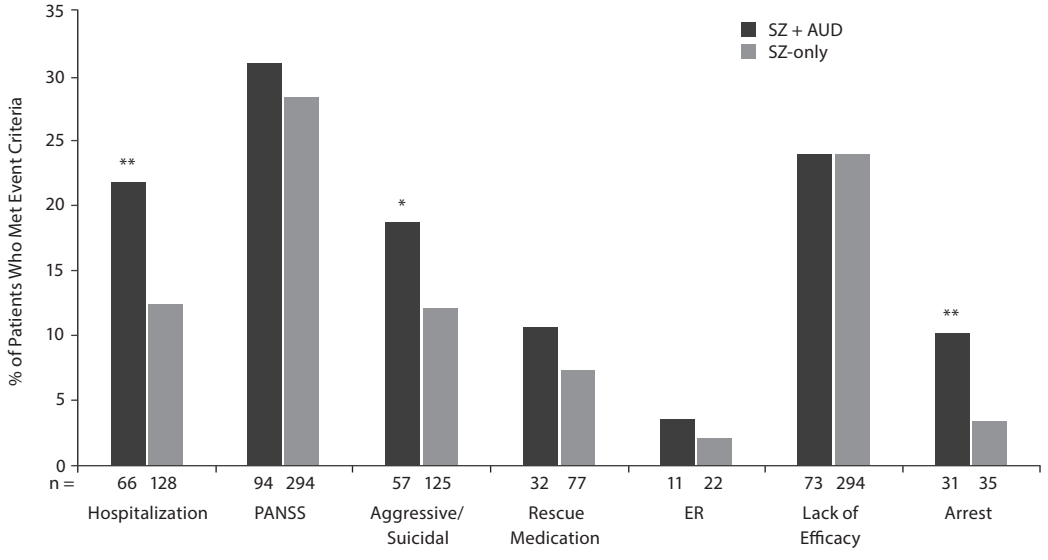


[a]Data from Cox and Andersen-Gill models after adjusting for potential baseline confounders (age, male gender, BMI, years of education, number of hospitalizations [lifetime], number of hospitalizations [previous year], and baseline Calgary Depression Scale score).
Abbreviations: BMI = body mass index, CI = confidence interval, HR = hazard ratio (SZ + AUD vs SZ-only).

a poorer course of illness with higher risk of disease progression, as assessed by time to first exacerbation and time to first hospitalization, compared with schizophrenia patients without comorbid AUD. Compared with SZ-only patients, patients with SZ + AUD experienced significantly more exacerbations resulting in hospitalization for psychopathology or due to clinically significant aggression, suicidal/homicidal ideations, or arrest or incarceration. These results are consistent with prior findings indicating that schizophrenia with alcohol use is more strongly associated with violent behavior, incarceration, depression, suicide, family problems, and housing instability.[10,28,40,41] Interestingly, for patients with SZ + AUD, findings suggest that olanzapine may be associated with longer time to first and recurrent exacerbations compared with the other treatments evaluated (perphenazine, quetiapine, risperidone, and ziprasidone).

There is limited research into the most appropriate management options for patients with schizophrenia and comorbid AUD. This patient group offers unique challenges,[15] such as the difficulties of recruiting sufficient participants to ensure an adequate sample size for statistical analysis.[13] Notably, in the present analysis, patients with SZ + AUD were significantly younger, had a lower mean BMI, and were more predominantly male than patients with SZ-only. These findings reflect previous sample descriptions in that patients with schizophrenia and AUD are more likely male and younger[10] as well as nonadherent with antipsychotics,[24] which may explain the finding of a lower BMI. Furthermore, patients often present with other factors that may impact active engagement in a clinical trial (eg, cognitive impairment and lack of insight) or poor adherence with study procedures.[8] The present data, albeit based on a post hoc analysis of a study not specifically designed to examine the association of AUD with symptom worsening in patients with schizophrenia, offers the opportunity to gain insights into the relationship between AUD and course of disease. In addition, these findings may help to inform the design of future studies in a similar patient population. Indeed, findings from this post hoc analysis point toward a more severe course of disease in those with SZ + AUD, in that patients with SZ + AUD experienced more frequent hospitalizations (both prior to study entry and during

Figure 3. Exacerbation Events Presented According to Predefined Individual Exacerbation Criteria in Patients With Schizophrenia and Alcohol Use Disorder (SZ + AUD) and Patients With Schizophrenia Only (SZ-Only)



*$P < .01$.
**$P < .001$.
Abbreviations: ER = emergency room, PANSS = Positive and Negative Syndrome Scale.

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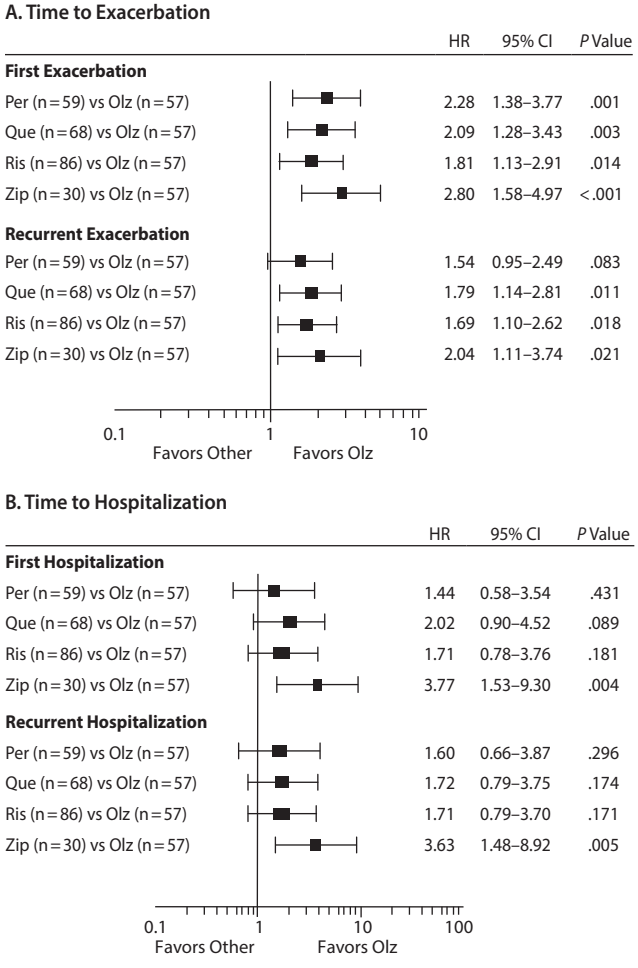
Figure 4. Comparison Between Olanzapine and Other Antipsychotics From CATIE-1 in Patients With Schizophrenia and Alcohol Use Disorder for (A) Time to First and Time to Recurrent Exacerbations and (B) Time to First and Time to Recurrent Hospitalizations[a]



[a]Data from Cox and Andersen-Gill models adjusted for potential confounders (age, male gender, BMI, years of education, number of hospitalizations [lifetime], number of hospitalizations [previous year], and baseline Calgary Depression Scale score).

Abbreviations: BMI = body mass index; CATIE-1 = Clinical Antipsychotic Trials of Intervention Effectiveness in Schizophrenia, Phase 1; CI = confidence interval; HR = hazard ratio (other antipsychotics vs Olz); Olz = olanzapine; Per = perphenazine; Que = quetiapine; Ris = risperidone; Zip = ziprasidone.

the randomized treatment period) and exacerbations of schizophrenia overall compared with SZ-only patients. Nevertheless, there were greater benefits associated with olanzapine treatment in patients with schizophrenia and comorbid AUD compared with the other evaluated antipsychotic treatments (perphenazine, quetiapine, risperidone, and ziprasidone).

Evidence from a meta-analysis[23] of antipsychotics involving 13 double-blind studies and more than 1,500 patients with primary AUD without comorbid schizophrenia suggested that it is unlikely that antipsychotic use alone has a directly beneficial impact on alcohol intake. In that meta-analysis, neither pooled nor individual antipsychotics outperformed placebo regarding alcohol use relapse prevention, and antipsychotics were similar to placebo regarding heavy drinking days, craving, and first alcohol consumption time.[23] However, even though olanzapine may not reduce alcohol use itself,[23] it is possible that it may impact drinking behavior indirectly by enhancing control of psychosis. Although the present analysis provided some insights into the impact of olanzapine use in patients with AUD, it was not possible to explore this hypothesis fully, as changes in alcohol use over time were not captured in detail in CATIE-1.

Substance use disorders (including illicit drugs, alcohol, and tobacco use) are often reported in people with schizophrenia and are known to worsen the outcomes of disease with a negative impact on adherence, hospitalizations, and violence, as well as increased risk of relapse.[42] A previous analysis of the CATIE-1 database evaluated differences between the overall effectiveness of antipsychotics among patients who used or did not use illicit substances (excluding those with AUD only).[36] Prior findings suggested that illicit substance use attenuated any advantage for olanzapine in reducing time to all-cause discontinuation, reinforcing the need for concurrent substance use treatment.[36] In contrast, the current analysis included patients with or without AUD (excluding those patients with substance abuse [other than marijuana]). In another secondary analysis of data from CATIE-1, there were no observed differences between any of the antipsychotics studied on substance use outcomes, including cigarettes smoked in the previous week or clinicians' ratings of alcohol and drug use severity.[35] In that study, alcohol use data were collected using the clinician-rated Alcohol Use Scale, and an exacerbation was defined as having been hospitalized or treated in a crisis center during the previous 3 months.[35] The present study utilized AUD data collected based on *DSM-IV* criteria, and the definition of exacerbation included hospitalization, PANSS total scores, aggression, treatment discontinuation, and arrest. These important differences in patient selection, AUD assessment methodology, and definition of endpoints may explain the diverging findings. While previous studies involving atypical antipsychotics (including quetiapine and aripiprazole) in patients with schizophrenia and comorbid substance use disorder have reported positive results, they have involved small sample sizes and often used uncontrolled study designs.[35,43–45] In this present analysis, the focus was specifically on AUD, with the aim of gaining insights into whether any of the antipsychotics included in CATIE-1 may favorably impact the course of disease in patients with schizophrenia and comorbid AUD.

The results of this analysis should be interpreted within its limitations. While the present analysis reported positive outcomes for patients with schizophrenia and comorbid AUD receiving olanzapine, the generalizability and conclusions drawn are limited by the post hoc nature of the analysis. Because analyses were restricted to the already collected CATIE-1 data set, future studies should use the generated results for power and sample size calculations of subsequent, prospective studies comparing the efficacy and effectiveness

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of different antipsychotics for relapse prevention in patients with schizophrenia and AUD. Furthermore, as the analysis was limited to patients with AUD, these findings cannot be applied to patients with schizophrenia and other substance use disorders. Conversely, because we allowed comorbid marijuana use and because arrest was part of the definition of exacerbation, possession or use of marijuana could have influenced the frequency of exacerbations. However, we were unable to differentiate arrests that were related versus unrelated to marijuana, and marijuana use was low and balanced between the 2 groups in the CATIE-1 sample (SZ + AUD, 5.9%; SZ-only, 8.2%). Moreover, some patients did not have active AUD during the trial, and alcohol use severity was not specifically tracked in CATIE-1. However, to help adjust for baseline imbalances between groups, potential confounders identified from the baseline data were included in the analyses of outcomes. Nevertheless, despite these limitations, our analyses are based on one of the largest randomized samples of patients with schizophrenia and AUD and contribute to the knowledge of this understudied but clinically relevant population.

In summary, findings from this post hoc analysis confirm that patients with SZ + AUD have a worse course of illness than patients with SZ-only and suggest that olanzapine may be associated with longer times to first and recurrent exacerbations compared with other antipsychotics in this understudied population. Clearly, additional large, randomized, controlled trials with greater patient numbers are needed in patients with schizophrenia and a dual diagnosis of comorbid AUD or other substance use disorder.

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Potential conflicts of interest: **Drs Pathak**, **Jiang**, **DiPetrillo**, **Todtenkopf**, and **Liu** are or were employees of Alkermes, Inc, and may own stock/options in the company. **Dr Correll** has been a consultant and/or advisor to or has received honoraria from Alkermes, Allergan, Angelini, Boehringer-Ingelheim, Gerson Lehrman Group, Indivior, Intra-Cellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Merck, Neurocrine, Noven, Otsuka, Pfizer, Rovi, Servier, Sunovion, Sumitomo Dainippon, Supernus, Takeda, and Teva; has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka; served on data safety monitoring boards for Boehringer-Ingelheim, Lundbeck, Rovi, Supernus, and Teva; received royalties from UpToDate and grant support from Janssen and Takeda; and is a shareholder of LB Pharma.

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