Brexpiprazole for the Treatment of Co-occurring Schizophrenia and Substance Use Disorder:

A Multisite, Randomized, Controlled Trial

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Abstract

Objective: This proof-of-concept study examined the effects of brexpiprazole treatment on substance use, psychiatric symptoms, and quality of life in patients with co-occurring schizophrenia and substance use disorder.

Methods: In this 12-week study, patients diagnosed with schizophrenia and substance use disorder using *DSM-5* criteria were randomly assigned to switch from their current antipsychotic medication to brexpiprazole (up to 4 mg/day) or remain on their current antipsychotic treatment (treatment as usual [TAU]). Substance use was assessed by the number of days of substance use and the dollars spent on substance in the past week, and substance craving was assessed using the Visual Analog Scale (VAS). Quality of life was assessed using the Heinrichs-Carpenter Quality of Life Scale (QOL). In addition, psychiatric symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression Scale-Severity of Illness.

Results: Thirty-nine patients were randomized (21 in the brexpiprazole group, 18 in the TAU group). Mixed models for repeated measures showed that, despite the lack of statistical significance, a consistent pattern of decrease in the brexpiprazole group was observed for the number of days of substance use and the dollars spent, as well as substance craving; the brexpiprazole group had a 15.5 points greater decrease in VAS ($P = .157$) and a $33.3 greater decrease in the dollars spent ($P = .108$) from baseline to week 12 compared with the TAU group. The brexpiprazole group did show a statistically significant 8.9 points greater increase in QOL compared with the TAU group ($P = .020$). Even though it was not statistically significant, the brexpiprazole group had a 2.4-point greater decrease in the PANSS General Psychopathology subscale score ($P = .150$) and a 1.9-point greater decrease in the PANSS Negative Symptom subscale score ($P = .126$) compared with the TAU group.

Conclusion: This study suggests that brexpiprazole might be beneficial in reducing substance craving and use in patients with schizophrenia and co-occurring substance use disorder; this potential benefit may help improve quality of life and overall psychiatric symptoms in a difficult-to-treat patient population.

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The lifetime prevalence of substance use disorder (SUD) in patients with schizophrenia has been reported as ranging from 47% to 70%.[1,2] The lifetime prevalence ranges from 21 to 86% for alcohol use,[3] as well as 17% to 83% for cannabis use[4] in patients with schizophrenia. Patients who present with schizophrenia and co-occurring substance use can be difficult to manage in the outpatient setting. The lack of integrated care to address psychotic symptoms, substance problems, and poor treatment compliance are major challenges. Poor treatment compliance is exacerbated by active positive and negative symptoms and ongoing use of substances. Co-occurring substance use is associated with increased relapse and re-hospitalization rates, an increased risk for violence, and poorer global functioning and quality of life.[5,6] Clearly, substance use adds greatly to the financial costs and emotional toll that schizophrenia places on patients, families, and the entire mental health care system.

One of the main hypotheses to explain high prevalence rates of SUD in patients with schizophrenia is related to the brain reward circuitry.[7] Schizophrenia patients tend to experience less reward in response to naturally occurring reinforcement. Therefore, the

Clinical Points

- Available evidence indicates that most antipsychotic agents are of limited value in controlling substance use in patients with schizophrenia and co-occurring substance use disorder.
- This randomized, controlled pilot trial suggests that brexpiprazole, a dopamine D_2 receptor partial agonist, might be beneficial in reducing substance craving and use and improve quality of life in this difficult-to-treat patient population.

rewarding effects of substances are more salient to them, which may make them more sensitive to the rewarding effects of substances and less able to resist the use of substances.[8]

Available evidence indicates that some second-generation antipsychotic agents might be beneficial in controlling substance use in these dual diagnosis patients.[9] Of the second-generation agents, the one most thoroughly studied for use in dual diagnosis patients is clozapine. Studies have suggested that clozapine decreases alcohol and cannabis use in patients with schizophrenia; however, significant side effects associated with clozapine limit its clinical use.[10–12] More recently, a prospective, multicenter, real-world study reported positive effects of lurasidone on substance craving and quality of life in patients with schizophrenia spectrum disorder and co-occurring SUD.[13]

Recent research has suggested that dopamine D_2 receptor partial agonists, such as aripiprazole, decrease drug addiction in several animal models.[14,15] Clinical studies have reported that aripiprazole can reduce substance craving and use in patients with schizophrenia or bipolar disorder.[16] It has been suggested that aripiprazole may lessen substance use, in part through its mechanism of action that helps normalize dysfunctional brain reward circuitry that may underlie the co-occurring alcohol and substance use in patients with schizophrenia.[17]

Brexpiprazole is a newer dopamine D_2 receptor partial agonist approved for schizophrenia treatment. It shows partial agonism with lower intrinsic activity at the D_2 receptor and stronger antagonism at the 5-HT_{2A} receptor than aripiprazole.[18] Similar to aripiprazole, brexpiprazole may also have the potential to decrease substance use in patients with schizophrenia. Potentially, brexpiprazole may be more efficacious than aripiprazole in reducing substance use given its relatively lower association with D_2 partial agonist-mediated activating adverse effects such as restlessness, insomnia, and nausea, which are common substance withdrawal symptoms.[19]

We conducted a 4-site, 12-week, "proof of concept" study of patients who have co-occurring schizophrenia and current SUD. Eligible patients were randomly assigned to switch from their current antipsychotic to brexpiprazole treatment (the brexpiprazole group) or remain on the current antipsychotic treatment (the treatment as usual [TAU] group). The primary aims of this study were to examine the effects of brexpiprazole treatment on the number of days of substance use, the dollars spent on substances in the past week, and substance craving compared with the TAU group. The secondary aims were to examine the effects of brexpiprazole treatment on quality of life and psychiatric symptoms.

METHODS

Participants

Adult outpatients with schizophrenia or schizoaffective disorder and co-occurring SUD of alcohol, cocaine, cannabis, and/or opioids were recruited from 4 university-affiliated mental health clinics (UMass Memorial Health, Massachusetts; Mass General Hospital, Massachusetts; UNC Health, North Carolina; and Augusta University, Georgia). Psychiatric diagnoses were determined using the Mini-International Neuropsychiatric Interview version 7.0.2. Other inclusion criteria included (1) age 18–65 years, (2) used substances on at least 10 of the previous 30 days prior to screening, (3) on stable dose of antipsychotic agent for at least 1 month, (4) well-established compliance with outpatient medications. Exclusion criteria were as follows: (1) inability to provide informed consent; (2) met *DSM-5* criteria for any SUD of substances other than caffeine, tobacco, alcohol, cocaine, cannabis, and opioids; (3) on aripiprazole or cariprazine; (4) on medications to treat substance use (disulfiram, naltrexone, acamprosate, methadone, buprenorphine, varenicline, or bupropion); (5) significant, unstable medical conditions including severe cardiovascular, hepatic, renal, or other medical diseases; (6) history of a seizure disorder; (7) pregnancy or breastfeeding. The study was approved by the institutional review boards of respective study sites. Written informed consent of all participants was obtained prior to study participation.

Procedure

Baseline assessment. After a screening visit to determine eligibility, participants had their baseline assessments. The Timeline Follow-back (TLFB) method was used to collect substance use data and the dollars spent on substances in the past week. TLFB is useful for assessing substance use in people diagnosed with schizophrenia.[20] A urine drug screen was done prior to the TLFB interview; the results were discussed with the participant to encourage truthful reporting in the TLFB. The Visual Analog Scale (VAS) was used to assess substance craving.[21] The VAS is a horizontal

100-mm line, anchored on the right side with "no desire at all" (marked with a "0") and on the left side with "worst imaginable desire" (marked with a "100"). Participants were asked to mark the appropriate point to indicate where their "desire for substance" falls on this line. If a participant was using more than 1 permissible substance, only the primary substance ("the drug of choice") was assessed.

Quality of life was assessed using the Heinrichs-Carpenter Quality of Life Scale (QOL).[22]

Psychiatric symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), which includes the Positive Symptom, Negative Symptom, and General Psychopathology subscales.[23] In addition, the Clinical Global Impression Scale-Severity of Illness (CGI-S) was used.[24]

Follow-up assessment. Participants met with the research team every 2 weeks. The assessments for each visit included vital signs, a urine drug screen, the TLFB, the VAS, and adverse events. During week 6 and week 12 visits, the psychiatric rating scales were repeated.

Intervention. After screening, participants were randomly assigned to either switch their current antipsychotic medication to brexpiprazole or remain on the same treatment, based on a permuted block design with block size of 6. For the brexpiprazole group, an overlap and taper switch method was used. The current antipsychotic medication was tapered and discontinued over a period of 6 weeks. Brexpiprazole was started at 1 mg/day for 4 days, increased to 2 mg/day for 3 days, and then was either titrated by up to 1 mg/day increase every 3 days to reach 4 mg/day, or titrated up as much and as fast as the participant could tolerate. Participants stayed on 4 mg/day or the highest tolerable dose until the end of the study. For patients in the brexpiprazole group, study medication was dispensed during each visit.

All participants received supportive counseling during each study visit, using the NAVIGATE Individual Resiliency Training Manual's substance use section, which provides substance use education specifically for people with schizophrenia. The counseling encouraged a reduction in or abstinence from substance consumption.

Adverse events. Adverse event information was collected and recorded at each study visit, starting on the day the consent was signed until the end of an individual's participation in the study. The assessment began with an open-ended general inquiry and included possible side effects associated with brexpiprazole.

Study site coordination and monitoring. Throughout the study, the lead site (UMass) provided rater training to all study sites to ensure inter-rater reliability. The lead site coordinated with other study sites and conducted site monitoring to ensure overall quality and compliance with protocol by all sites. The monitoring activities were conducted through regular Zoom/telephone calls and emails.

Statistical analysis. Statistical analysis was performed using SPSS (version 29.0, IBM Corp, Armonk, NY, USA). Descriptive statistics were performed to summarize demographic and clinical characteristics of the study sample. Group comparisons were performed using the independent t test for continuous variables and the Fisher exact test or χ^2 test for categorical variables. The normality of continuous variables was verified using the Shapiro-Wilk test. Mixed models for repeated measures were conducted in the intention-to-treat population to estimate the effects of brexpiprazole treatment on the changes in the number of days of substance use and the dollars spent in the past week, substance craving, psychiatric symptoms, and quality of life over 12 weeks. For each outcome measure, the treatment group, time points, and group × time interaction were included as fixed effects with intercepts clustered by participants as random effects. Maximum likelihood estimation modeling was used to handle incomplete data. The baseline score and potential confounding variables were included in the model as covariates. As a supportive analysis, analysis of covariance (ANCOVA) was conducted for study completers to compare changes in outcome measures over week 12 with baseline score and potential confounding variables as covariates. For all analyses, a *P* value less than .05 (2-tailed) was used for statistical significance.

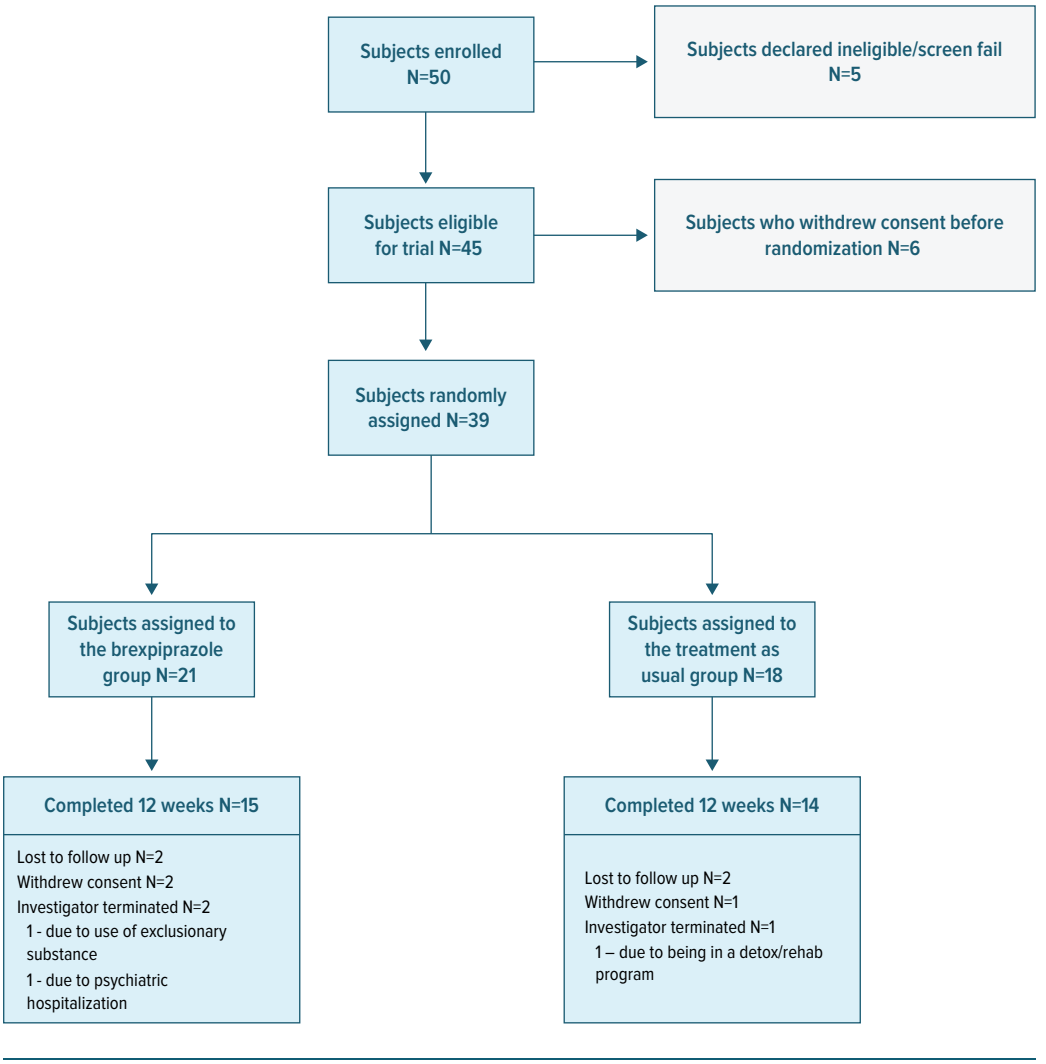
RESULTS

Fifty patients were enrolled. Among those, 45 were eligible for the study, and 39 were randomized (21 in the brexpiprazole group, 18 in the TAU group). Twenty-nine patients completed the study (15 in the brexpiprazole group, 14 in the TAU group) (Figure 1). There were no significant differences between the two groups in age, gender, education level, marital status, diagnosis (schizophrenia or schizoaffective disorder), and age of illness onset (*P* values >.300). However, there was significant between-group difference in the primary substance used ($P = .027$); more patients used marijuana and fewer patients used alcohol in the brexpiprazole group compared with the TAU group. It turned out that the study was not able to recruit patients with current opioid use disorder in either the brexpiprazole group or the TAU group. Furthermore, the brexpiprazole group tended to be more racially diverse ($P = .146$) (Table 1). Within the TAU group, 5 patients were on olanzapine, 2 on lurasidone, 4 on risperidone, 1 on paliperidone, 2 on quetiapine, 1 on iloperidone, 3 on haloperidol, 1 on fluphenazine, 2 on perphenazine, and 1 on chlorpromazine; 4 patients were on more than 1 antipsychotic medication.

Substance Use Measures

Mixed models for repeated measures with baseline score, study site, primary substance used, and race as covariates were conducted for TLFB, VAS, and the

Figure 1.
Flowchart for the Study Sample



dollars spent. Despite the lack of statistical significance, a consistent pattern of decrease in the brexpiprazole group was observed for the number of days of substance use and the dollars spent in the past week, as well as substance craving; in particular, the brexpiprazole group had a 15.5 points greater decrease in VAS ($P = .157$) and a $33.3 greater decrease in the dollars spent in the past week ($P = .108$) from baseline to week 12 compared with the TAU group (Table 2; Figure 2).

Quality of Life and Psychiatric Symptom Measures

The same mixed models for repeated measures were conducted for QOL, the PANSS total score and subscale scores, and CGI-S. The brexpiprazole group had a statistically significant 8.9-point greater increase in QOL from baseline to week 12 compared with the TAU group ($P = .020$). Even though statistically not significant, the brexpiprazole group had a 2.4-point greater decrease in the PANSS General Psychopathology subscale score ($P = .150$) and a 1.9-point greater decrease in the PANSS Negative Symptom subscale score ($P = .126$) from baseline to week 12 compared with the TAU group. Overall, the brexpiprazole group showed some improvement in psychiatric symptoms over 12 weeks as reflected by the changes in the PANSS total score and CGI-S (Table 2; Figure 3).

ANCOVA for Study Completers

For study completers, the brexpiprazole group tended to be younger ($P = .101$) and had a later age of illness onset ($P = .099$) compared with the TAU group; in addition, more patients used marijuana and fewer patients used alcohol in the brexpiprazole group compared with the TAU group ($P = .108$). There were no significant differences between the two completer groups

Table 1.

Baseline Demographic and Clinical Characteristics of the Study Sample[a]

Variable	Brexpiprazole (N = 21)		TAU (N = 18)		*P*
	Mean	SD	Mean	SD	
Age, y	36.1	12.0	39.8	11.2	.323
Education, y	11.7	2.2	11.8	1.3	.915
Age of illness onset, y	22.5	7.2	20.8	9.1	.536
	N	%	N	%	
Gender					1.000
Male	16	76	14	78	
Female	5	24	4	22	
Race					.146
Caucasian	8	38	8	81	
African American	9	43	10	10	
Other	4	19	0	10	
Marital status					.348
Single/separated/divorced/widowed	20	95	18	100	
Married	1	5	0	0	
Diagnosis					.656
Schizophrenia	12	57	9	50	
Schizoaffective disorder	9	43	9	50	
Primary substance used					.027
Alcohol	2	10	8	44	
Marijuana	17	81	10	56	
Cocaine	2	10	0	0	

[a]The total percentages may not equal to 100% because of rounding.
Abbreviation: TAU = treatment as usual.

Table 2.

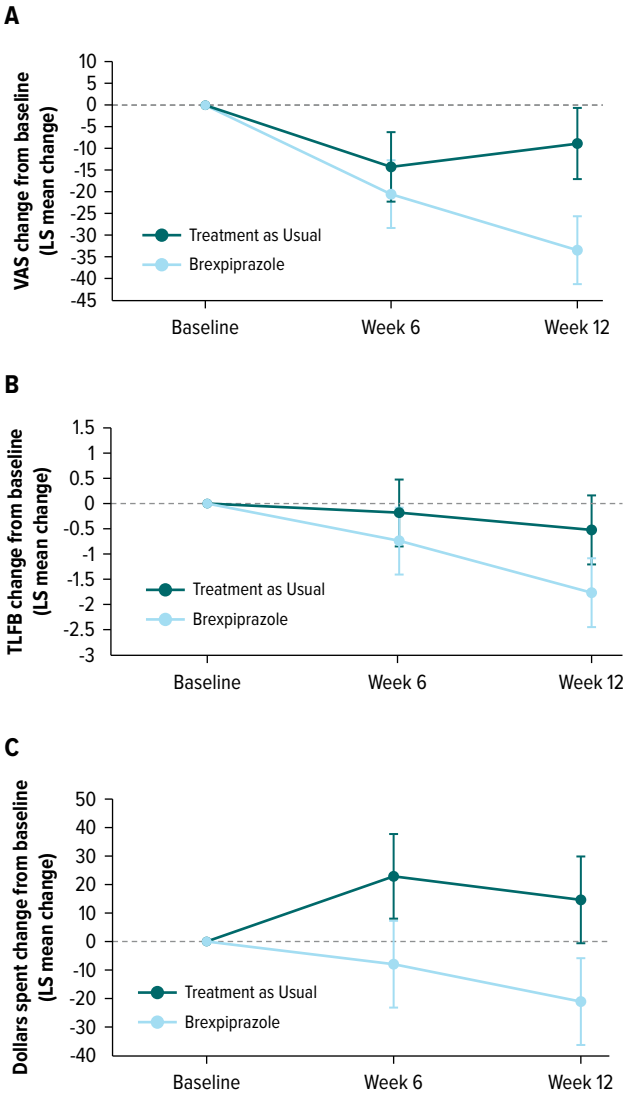
The Effect of 12-Week Brexpiprazole Treatment on Outcome Measures: Mixed Models for Repeated Measures

	Difference[a]	95% CI	*P*
TLFB (days)	−0.9	−2.7 to 0.9	.302
VAS	−15.5	−37.3 to 6.3	.157
Dollar amount spent	−33.3	−74.3 to 7.8	.108
PANSS Total	−3.5	−10.6 to 3.6	.326
PANSS Positive Symptom	0.92	−2.0 to 3.9	.529
PANSS Negative Symptom	−1.9	−4.4 to 0.6	.126
PANSS General Psychopathology	−2.4	−5.8 to 0.9	.150
CGI-S	−0.2	−0.5 to 0.2	.403
QOL	8.9	1.5 to 16.4	.020

[a]The difference in least-squares mean change at week 12 (the brexpiprazole group minus the treatment as usual group) was calculated.
Abbreviations: CGI-S = Clinical Global Impression-Severity of Illness; PANSS = Positive and Negative Syndrome Scale, which includes Positive Symptom, Negative Symptom, and General Psychopathology subscales; QOL = Heinrichs-Carpenter Quality of Life Scale; TLFB = Timeline Follow-back; VAS = Visual Analog Scale.

Figure 2.

Mean Change from Baseline in (A) VAS, (B) TLFB, and (C) Dollars Spent[a]

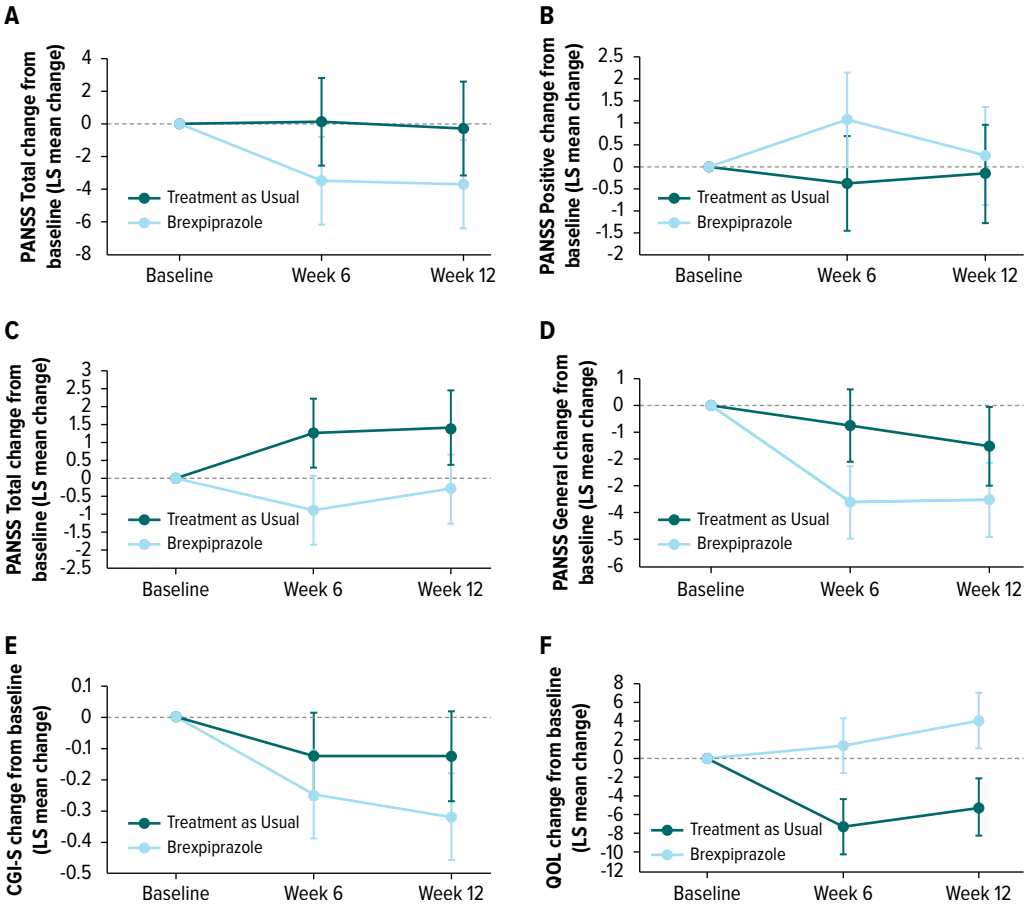


[a]Error bars indicate the standard error of the mean.
Abbreviations: LS = least squares, TLFB = Timeline Follow-back, VAS = Visual Analog Scale.

in other demographic or general clinical characteristics (*P* values >.300) (data not shown). ANCOVA was conducted for all outcome measures, controlling for baseline score, study site, primary substance used, age, and age of illness onset. The results showed a statistically not significant greater decrease in VAS over 12 weeks in the brexpiprazole group compared with the TAU group (mean ± SD: −30.2 ± 40.8 vs −9.3 ± 21.5, *P* = .053). Even though statistically not significant, the brexpiprazole group had a greater decrease in the number of days of substance use and the dollars spent in the past week and showed some improvement in quality of life and psychiatric symptoms over 12 weeks as reflected by the changes in QOL, the PANSS total score, and CGI-S, compared with the TAU group (data not shown). The results from ANCOVA for study completers are consistent with the results from the mixed models for repeated measures.

Figure 3.

Mean Change from Baseline in (A) PANSS Total Score, (B) PANSS Positive Symptoms Subscale, (C) PANSS Negative Symptoms Subscale, (D) PANSS General Psychopathology Subscale, (E) CGI-S, and (F) QOL[a]



[a]Error bars indicate standard error of the mean.
Abbreviations: CGI-S = Clinical Global Impression-Severity of Illness, LS = least squares, PANSS = Positive and Negative Syndrome Scale, QOL = Heinrichs-Carpenter Quality of Life Scale.

Adverse Event Assessment

There were no serious adverse events during the study. For all randomized subjects (N = 39), the adverse events reported in more than 5% of the participants taking brexpiprazole were diarrhea, fatigue/tiredness, dizziness/faintness, cold like symptoms (sore throat, nasal congestion, running nose), trouble sleeping, nausea, and restlessness/irritability. There were no significant differences between the two groups for these adverse events even though the brexpiprazole group tended to have higher rates of fatigue/tiredness and trouble sleeping compared with the TAU group (*P* values >.05).

DISCUSSION

We believe this is the first randomized, controlled, pilot trial to examine the effects of brexpiprazole on substance use, psychiatric symptoms, and quality of life in patients with co-occurring schizophrenia and SUD. The present 12-week, "proof of concept" study suggests that brexpiprazole, in addition to its antipsychotic effect, might also be beneficial in reducing substance craving and use, and improving quality of life in this challenging patient population.

The findings from our study are consistent with the results reported in previous studies. An observational study in patients with schizophrenia with or without SUD showed that brexpiprazole treatment led to significant reductions in substance craving, PANSS total score, and CGI-S in those with SUD over a 6-month follow-up time period.[25] In a more recent prospective, real-world study, Chiappini et al. reported that patients with schizophrenia and co-occurring SUD had significant reductions in craving for substances, PANSS total score, and quality of life as measured by the 36-item

Short Form Health Survey after 1 month of brexpiprazole treatment.[26] While these two studies provided valuable real-world evidence regarding the potential benefit of brexpiprazole in reducing substance craving, a major limitation of both studies is that there was a lack of randomized clinical trial design and comparison groups.

Dopamine partial agonism underlies the mechanism of several atypical antipsychotics including brexpiprazole. Studies have shown that alterations in dopaminergic transmission in the mesolimbic dopamine system not only contribute to the development of psychosis but also are associated with pathological substance-seeking behavior. The use of dopamine partial agonists, such as aripiprazole and brexpiprazole, has been proposed as a potential strategy to restore dopaminergic signaling and the brain reward circuitry and therefore reduce the use of substances.[27,28]

Schizophrenia and SUD are intimately related, yet substance use is often underreported, underrecognized, and undertreated in the schizophrenia patient population. Schizophrenia patients with co-occurring SUD are at an increased risk for treatment nonadherence, emergency room visits, hospitalization, and shortened life expectancy compared with those without SUD.[5,6,29] Improvement in SUD is likely associated with improvement in psychiatric symptoms, psychosocial functioning, and quality of life in patients with mental illness and co-occurring SUD.[30–32]

Integrated treatments for patients with schizophrenia and co-occurring SUD were developed in the 1980s and 1990s. Following this model, schizophrenia and SUD are treated in a single program by a team of clinicians with expertise in both conditions. Treatment components include pharmacologic and psychosocial interventions, case management, and community outreach.[33,34] However, despite the high association between the 2 conditions, there is a surprising paucity of studies that have explored optimal treatment and outcome for this patient population; few controlled trials have been conducted.[34,35] Identifying antipsychotic medications with dual treatment effects for schizophrenia and SUD, especially among those more recently approved by the FDA, has great clinical implications; the "two birds, one stone" approach may simplify the intervention regimen and improve treatment compliance.

The strengths of this study include a randomized clinical trial design with a comparison group, as well as rigorous assessments to evaluate substance use (the number of days of substance use, the dollars spent in the past week, and substance craving), psychopathology, and quality of life. There are several limitations in the present study. In addition to a small sample size, the study did not evaluate schizophrenia patients who were using substances other than alcohol, cocaine, and cannabis. The original study design did include opioid use disorder, but the study was not able to recruit patients with this condition. Therefore, the findings from this study are considered exploratory and may not be generalizable to schizophrenia patients who are on other commonly used substances such as opioids, stimulants, and hallucinogens. Furthermore, the open-label design may introduce confounding factors such as expectation effect.

In conclusion, this study suggests that brexpiprazole might be beneficial in reducing substance craving and use in patients with schizophrenia and co-occurring substance use disorder; this potential benefit may help improve quality of life and overall psychiatric symptoms. Future trials with a double-blind design, a larger sample size, and a longer follow-up time period are needed to better understand the potential benefits of brexpiprazole on substance use, mental health symptoms, and overall functioning in this difficult-to-treat patient population.

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