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Psychiatric symptom differences in people with schizophrenia associated with substantial lifetime substance use but no current substance use disorder

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Contributors

Drs. Kelly and Koola conceived the analysis plan. Drs. Buchanan, Gorelick, and Kelly designed the study. Drs. Buchanan, Kelly, Warren, Ms. Feldman, and Mr. Linthicum were responsible for the conduct of the study. Drs. Kelly, Koola, and McMahon developed the statistical analyses and Ms. Liu performed the statistical analyses. Drs. Buchanan, Gorelick, Huestis, Kelly, Koola, McMahon, Warren, and Wehring were responsible for interpretation of the data. Dr. Koola wrote the first draft of the manuscript. All authors reviewed and approved the final manuscript.

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Conflict of interest

Dr. Kelly has received grant support from Bristol-Myers Squibb and Ameritox, Ltd. Dr. McMahon is a statistical consultant for Amgen Inc. All other authors report no conflict of interest.

People with schizophrenia who have current substance use disorder (SUD) are generally excluded from clinical trials for the following reasons: safety/side effect risk, concern about adherence to the study protocol (Kreyenbuhl et al., 2011) and avoidance of confounds to efficacy evaluations (Buchanan et al., 2010). Patients with a past history of SUD are generally not excluded, but may represent a population with similar potentially unfavorable characteristics. To evaluate the possible consequences of this differential exclusion practice, we examined baseline symptoms of participants with substantial lifetime substance use and compared to participants with no substantial lifetime substance use in a sample of 15 outpatients with schizophrenia or schizoaffective disorder (DSM-IV criteria) enrolled in a controlled clinical trial of an adjunct weight loss medication (Kelly et al., 2011; Boggs et al., 2012). This analysis includes the full sample of patients enrolled in the clinical trial, which was prematurely terminated because of withdrawal of the experimental compound; thus, within-study sample bias did not influence our findings. Participants were 18–55 years old, with stable psychiatric symptoms, treated with a second generation antipsychotic for eight weeks (same dose for four weeks), overweight or obese, with a Calgary Depression Scale (Addington et al., 1992) total score ≥ 7 , no history of hospitalization for depression or suicidal thoughts or behavior in the prior six months, and no substance dependence (DSM-IV criteria) within the prior six months other than caffeine or nicotine and no substance abuse within the prior month. Current drug use status was confirmed by urine and blood tests and self-report.

SUD history was evaluated using the Structured Clinical Interview for DSM-IV Disorders, with more detailed information on alcohol, heroin, methadone, barbiturates, cocaine, amphetamines, cannabis, hallucinogens, inhalants, and nicotine use from the modified Addiction Severity Index (ASI) interview (McLellan et al., 1980). The ASI collects information on use in the prior 30 days and number of years of lifetime use. Substantial lifetime substance use was defined as ≥ 5 years of past use ≥ 4 times per week or with bingeing or problematic use in which normal activities are compromised. Current schizophrenia symptoms were assessed with the Brief Psychiatric Rating Scale and Scale for the Assessment of Negative Symptoms.

There were no significant differences in participants' socio-demographic characteristics. Both patient groups were comparable in demographic characteristics and cigarette smoking. The ten participants with substantial lifetime substance use had more severe current positive symptoms and less severe negative symptoms than the five participants without a substantial history of substance use (Table 1).

This study has several limitations, including very small sample size, which precluded any statistical control for potential confounding factors, and substance use based on retrospective self-report without objective corroboration. Future studies are warranted with larger sample sizes, objective assessments of substance use, and clear distinctions between substance use groups to validate our findings. These findings suggest that more attention be given to past history of substance use in people without a current SUD who enroll in clinical trials. Persisting effects from prior substance use may adversely affect response to treatment, leading clinicians to add or change medications, when a more appropriate action might be evaluation of prior substance use. In addition, prior substance use is a risk factor for relapse

to present substance use or abuse, with potential adverse effects on current treatment response. Therefore, all clinicians should pay attention to lifetime, not just current, co-occurring SUDs. Future research should consider the inclusion of participants with lifetime substance use, even if substantial, in order to improve the external validity of their studies, and account for lifetime substance use in their analysis plan.

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Table 1

Psychiatric characteristics of 15 people with schizophrenia without current substance use disorder and with or without substantial lifetime substance use.

Clinical variables	Substantial lifetime substance use N = 10 mean (SD), median	No substantial lifetime substance use N = 5 mean (SD), median	Statistics
BPRS total	35.0 (5.6), 36.5	32.1 (6.8), 29.7	t = 0.7, df = 1, p = 0.39
Positive symptoms	9.6 (2.5), 10.0	5.7 (2.4), 5.3	t = 5.2, df = 1, p = 0.02
Activation	3.8 (0.8), 3.6	3.9 (0.6), 4.3	t = 0.1, df = 1, p = 0.71
Hostility	4.9 (1.0), 4.5	4.8 (1.3), 4.7	t = 0.06, df = 1, p = 0.81
Anxiety/depression	5.9 (1.8), 5.7	5.4 (2.1), 5.0	t = 0.4, df = 1, p = 0.54
Negative symptoms	4.7 (1.3), 4.3	8.1 (2.3), 8.3	t = 6.3, df = 1, p = 0.01
SANS total	22.9 (7.9), 24.0	36.8 (17.5), 32.8	t = 2.2, df = 1, p = 0.14
Asociality–anhedonia	1.5 (1.0), 1.1	2.2 (0.9), 2.0	t = 1.7, df = 1, p = 0.20
Affective flattening or blunting	0.8 (0.6), 0.8	1.8 (1.2), 1.9	t = 2.5, df = 1, p = 0.11
Alogia	0.3 (0.2), 0.3	1.4 (1.7), 1.1	t = 2.0, df = 1, p = 0.16
Avolition–apathy	2.4 (1.0), 2.3	2.7 (1.3), 3.4	t = 1.3, df = 1, p = 0.71
CDS	2.9 (2.3), 2.2	3.2 (2.1), 3	t = 0.09, df = 1, p = 0.76
RBANS total score	81.2 (10.1), 83.0	82.8 (15.7), 82.5	t = 0.005, df = 1, p = 0.94
CGI-severity	4.2 (0.7), 4.1	4.2 (0.4), 4.0	t = 0.1, df = 1, p = 0.74

BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms; CDS = Calgary Depression Scale; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; CGI = Clinical Global Impression.