Original Investigation

Comorbidity of Severe Psychotic Disorders With Measures of Substance Use

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IMPORTANCE Although early mortality in severe psychiatric illness is linked to smoking and alcohol, to our knowledge, no studies have comprehensively characterized substance use behavior in severe psychotic illness. In particular, recent assessments of substance use in individuals with mental illness are based on population surveys that do not include individuals with severe psychotic illness.

OBJECTIVE To compare substance use in individuals with severe psychotic illness with substance use in the general population.

DESIGN, SETTING, AND PARTICIPANTS We assessed comorbidity between substance use and severe psychotic disorders in the Genomic Psychiatry Cohort. The Genomic Psychiatry Cohort is a clinically assessed, multiethnic sample consisting of 9142 individuals with the diagnosis of schizophrenia, bipolar disorder with psychotic features, or schizoaffective disorder, and 10 195 population control individuals.

MAIN OUTCOMES AND MEASURES Smoking (smoked >100 cigarettes in a lifetime), heavy alcohol use (>4 drinks/day), heavy marijuana use (>21 times of marijuana use/year), and recreational drug use.

RESULTS Relative to the general population, individuals with severe psychotic disorders have increased risks for smoking (odds ratio, 4.6; 95% CI, 4.3-4.9), heavy alcohol use (odds ratio, 4.0; 95% CI, 3.6-4.4), heavy marijuana use (odds ratio, 3.5; 95% CI, 3.2-3.7), and recreational drug use (odds ratio, 4.6; 95% CI, 4.3-5.0). All races/ethnicities (African American, Asian, European American, and Hispanic) and both sexes have greatly elevated risks for smoking and alcohol, marijuana, and drug use. Of specific concern, recent public health efforts that have successfully decreased smoking among individuals younger than age 30 years appear to have been ineffective among individuals with severe psychotic illness (interaction effect between age and severe mental illness on smoking initiation, $P = 4.5 \times 10^5$).

CONCLUSIONS AND RELEVANCE In the largest assessment of substance use among individuals with severe psychotic illness to date, we found the odds of smoking and alcohol and other substance use to be dramatically higher than recent estimates of substance use in mild mental illness.

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ndividuals with severe mental illness die approximately 25 years earlier than the general population, and the cause of this early death is largely owing to medical illness that can be attributed to substance use disorders.[1-3] For example, although suicide and injury are more common among individuals with chronic mental illness, 60% of premature deaths in persons with schizophrenia are due to medical conditions including heart and lung disease and infectious illness caused by modifiable risk factors such as smoking, alcohol consumption, and intravenous drug use.[1] In addition to early mortality, the severity and prognosis of the primary mental illness are worsened in the context of substance dependence.[4,5]

The 2009-2011 National Survey on Drug Use and Health identified adults with mental illness (based on 14 items related to psychological distress and disability) and found that 36% of adults with mental illness are current smokers relative to 21% of adults without mental illness.[6] In addition, it found that adult smokers with mental illness are less likely to quit than adult smokers without mental illness. This discrepancy highlights the public health disparity in the mentally ill, a uniquely vulnerable population.

In addition to increased smoking among individuals with mental illness, alcohol and other substance use disorders have increased prevalence in individuals with mental illness.[7-17] Several large epidemiological surveys have assessed comorbidity of affective and psychotic illness with tobacco, alcohol, and drug use disorders in the general population.[8,9,12,16,18-20] In these studies, alcohol and drug dependence were found to be more than twice as common among individuals with anxiety disorders, affective disorders, and psychotic disorders.[9,10,13,16,21] There is also evidence that associations between substance use/dependence and other psychiatric illness are true for both men and women,[18] and extend to African American[22] and Hispanic individuals.[7]

Despite strong epidemiological studies of the general population showing increased comorbidity of smoking and alcohol and drug use in mental illness, these studies do not address comorbidity of smoking and alcohol and drug use in severe psychotic illness. Not only is severe psychotic illness rare in the general population, but individuals with severe psychotic illness are difficult to contact in general population surveys; therefore, to our knowledge, there is no large-scale survey of substance use among clinically ascertained individuals with severe psychotic illness. Specifically, it is unknown whether the rates of substance use among individuals with mild mental illness, as ascertained in population surveys, apply to individuals with severe psychosis. To address this issue, we assessed substance use in a large, multiethnic sample of individuals with schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features, and corresponding population control individuals. Using this powerful sample, we were able to not only gain insight into substance use among individuals with severe psychosis, but also determine the differences in substance use between sexes and racial/ethnic subgroups.

Methods

The Genomic Psychiatry Cohort (GPC) program is a multi-institutional collaboration.[23] This resource includes a National Institute of Mental Health–managed repository of genomic samples and detailed clinical and demographic data for investigations of schizophrenia and bipolar disorder. All recruitment sites received institutional review board approval (University of Southern California, Cedars Sinai Medical Center, Emory University, Georgia Regents University, New York University, State University of New York Upstate, State University of New York Stony Brook, Wright State University, Texas Tech University, University of California at Los Angeles, and University of North Carolina), and informed consent was obtained from all participants. The current sample consists of 9142 individuals with either the diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features, and 10 195 population control participants. Individuals with bipolar disorder without psychotic features represented a relatively small subgroup (n = 621) and are therefore not included in these analyses.

Psychiatric Diagnoses

Individuals were collected through 12 clinical collaborating sites across the United States. All individuals ascertained to the GPC completed a screening questionnaire eliciting demographic (eg, race, ethnicity, and sex) data, as well as a brief personal and family psychiatric and medical history. Individuals with psychotic illness were ascertained as inpatients in acute care or chronic care facilities and outpatient settings. Control participants were drawn from the same geographic area as cases, either within health care facilities or as community volunteers recruited from Internet advertising or community groups (eg, church congregations and health fair attendees) and screened to ensure absence of schizophrenia or bipolar disorder within themselves and their first-degree relatives.

To confirm the psychiatric diagnoses, case participants were interviewed by trained clinicians using a structured psychiatric interview instrument, the Diagnostic Interview for Psychosis and Affective Disorder. The Diagnostic Interview for Psychosis and Affective Disorder is based on the Diagnostic Interview for Genetic Studies[24] and includes 90 phenomenological symptom items that are used with the Operational Criteria Checklist computer algorithm[25] to arrive at diagnoses using the *DSM*.[26] Clinicians confirmed diagnoses for schizophrenia, schizoaffective disorder, or bipolar disorder with psychosis based on *DSM-IV* criteria.

Substance Use Measurements

As part of the screening questionnaire, a set of questions was asked of all participants regarding the individual's substance use. The questions were adapted from the Diagnostic Interview for Genetic Studies[24] and other validated instruments.[27,28]

1. Do you often have more than 4 drinks in 1 day?
2. Over your lifetime, have you smoked more than 100 cigarettes?

Table 1. Sample Characteristics

Characteristic	Bipolar With Psychosis	Schizoaffective–Bipolar Subtype	Schizoaffective–Depressed Subtype	Schizophrenia	Control	NSDUH Population Survey
No.	1507	1486	552	5586	10 311	18 612
Race/ethnicity, %						
Hispanic	18	19	14	15	34	37.9
African American	18	24	30	35	17	6.2
Asian	2	2	1	2	7	
European American	55	46	49	39	37	40
Mixed race	4	4	2	3	2	
Sex, %						
Female	51	42	45	30	56	49
Male	49	58	55	70	44	51
Age, y						
Average	43	44	44	44	38	38
25th percentile	33	35	35	35	25	28
75th percentile	51	52	52	53	49	47

Abbreviation: NSDUH, National Survey on Drug Use and Health.

3. Have you ever had a period of 1 month or more when you smoked cigarettes every day?
4. Have you ever smoked marijuana more than 21 times in a single year?
5. Have you ever used recreational (street) drugs (other than marijuana) or prescription drugs more than 10 times to feel good or get high?

Epidemiological Sample

To benchmark our sample with epidemiological studies, we looked at items in the National Survey on Drug Use and Health, a population-based epidemiological survey on substance use.[29] Because the control individuals used for this data set were drawn almost exclusively from the Los Angeles area, we restricted the surveyed data to those aged 20 to 55 years from California. We used the following items directly corresponding to the substance use measurements in the GPC:

1. During the past 30 days … on how many days did you have 5 or more drinks on the same occasion? (An answer of >3 [weekly or more] was used to correspond to GPC item 1.)
2. Have you smoked 100 cigarettes in your entire life?
3. Has there ever been a period in your life when you smoked cigarettes every day for at least 30 days?
4. Total number of days used marijuana in the past 12 months. (An answer of >0 was used to correspond to GPC item 4.)
5. Illicit drug use (except marijuana) in the past year.

Statistical Analysis

The goal of this study was to evaluate substance use in individuals with chronic psychotic disorders (cases) compared with population control individuals. We used logistic regression to model the probability of substance use based on case/control status, adjusted for race/ethnicity, sex, age (<30, 30-49, or ≥50 years), and recruitment site. We also evaluated whether there were significant interactions on substance use between case/control status and race/ethnicity, sex, or age. All analyses were performed using SAS version 9.2 for Windows.[30]

Results

Table 1 compares the demographics of the sample across control individuals and the 4 psychiatric diagnoses that constituted our sample of individuals with chronic psychotic disorder: schizophrenia, schizoaffective disorder–depressed subtype, schizoaffective disorder–bipolar subtype, and bipolar disorder with psychotic features. The sample used for this study was multiethnic including African American, Asian, European American, and Hispanic individuals. There were more female participants with bipolar disorder than with schizophrenia ($P < .001$). There was a wide age range among all individuals, although cases were older than the control participants in this sample ($P < .001$). Therefore, further analyses evaluated associations between the severe psychotic disorders and substance use only after adjusting for race/ethnicity, age, and sex.

The prevalence of various measures of substance use was much higher among individuals with schizophrenia, schizoaffective disorder (both depressed and bipolar subtype), and bipolar disorder with psychotic features (**Table 2**). For ease of interpretation, we classified individuals with schizophrenia, schizoaffective disorders, and bipolar disorder with psychotic features as cases with severe psychotic disorder, and we analyzed substance use with respect to case/control status. The prevalence of these measures was uniformly high in individuals with severe psychotic illness relative to the control populations. The odds ratio (OR) of cases vs control individuals for each measure of substance use is given in **Table 3**. Overall, the smoking measures were more strongly associated with case/control status than alcohol or other drugs, with estimated ORs of 4.61 for smoking more than 100 cigarettes ($P < 1.0 \times 10^{-325}$), and 5.11 for daily smoking for more than 1 month ($P < 1.0 \times 10^{-325}$). The estimated ORs for alcohol use (3.96, $P = 1.2 \times 10^{-188}$), marijuana use (3.47, $P = 2.6 \times 10^{-254}$), and rec-

Table 2. Prevalence of Substance Use Measures Across Psychiatric Diagnoses

Variable	Bipolar With Psychosis	Schizophrenia	Schizoaffective– Bipolar Subtype	Schizoaffective– Depressed Subtype	Control	NSDUH Population Survey
No.	1501	5582	1482	555	10 194	18 290
Alcohol: >4 drinks/d, %	26	28	29	30	8	9.5
100 cigarettes in lifetime, %	74	74	80	75	33	34
Daily smoking >1 mo, %	71	72	79	73	29	29
Marijuana >21 times/y, %	52	43	54	49	18	16
Recreational drugs >10 times, %	53	35	54	45	12	10

Abbreviation: NSDUH, National Survey on Drug Use and Health.

reational drug use (4.62, $P < 1.0 \times 10^{-325}$) were also highly clinically and statistically significant.

Although the prevalence of measures of substance use across sex, race/ethnic group, and age group varies, it is markedly higher among individuals with psychotic illness within each group. We tested whether the association between substance measures and case/control status was stronger within each group (ie, whether there was a statistical interaction between case/control status and group). All the items measured showed similar patterns of association. For illustrative purposes, the **Figure** illustrates select associations between substance use and severe psychosis. In groups where the control individuals had lower rates of substance use (Asian and Hispanic relative to European American participants, women relative to men, and individuals younger than age 30 years relative to those aged 30-50 years), the ORs were significantly higher than the reference ORs, leading to statistically significant interaction effects. This suggests that although belonging to certain groups may be protective for substance use in the control population, this protective effect is lost with the development of a severe mental illness. For example, women are at lower risk for using recreational drugs in the general population (7% of women vs 18% of men in the general population have used recreational drugs at least 10 times), but the rates of recreational drug use are much more comparable between men and women among individuals with severe psychosis (37% of women vs 45% of men with severe psychosis have used recreational drugs at least 10 times).

Discussion

Individuals with severe mental illness bear an enormous burden owing to smoking and alcohol and drug use. In a large, multiethnic sample, we found substance use among individuals with severe psychotic disorder to be markedly higher than in population control individuals at a rate that far exceeded previous estimates based on assessments in individuals with mild mental illness.[6] This association extends across substances (alcohol, smoking, and other drugs), across psychiatric diagnosis (bipolar disorder, schizoaffective disorder, and schizophrenia), across race and ethnicity (African American, Hispanic, Asian, and European American), across sexes, and across age groups. To our knowledge, this is the first large-scale study to robustly demonstrate these associations across subgroups. Although substance use among individuals with psychotic disorders has been documented,[12,13,20,31] this study showed that there is a continuing pressing need to target smoking and alcohol, marijuana, and drug use among individuals with severe mental illness.

The most striking finding of this study was the evidence that societal-level protective effects do not extend to individuals with severe mental illness. Specifically, we found that among groups with lower than average rates of substance use (Hispanic and Asian relative to European American individuals and women relative to men), the protective effects of belonging to these groups did not carry over to individuals with severe psychotic disorder: the odds of substance use increased to mitigate the protective effects. For example, relative to non-Hispanic white individuals, those of Hispanic ethnicity had lower rates of heavy alcohol use in control participants (5.7% of 3424 Hispanic and 8.1% of 3748 non-Hispanic European American individuals, $P < .001$). However, individuals of Hispanic descent with severe psychotic illness had higher rates of heavy alcohol use than non-Hispanic European American individuals (28.8% of 1583 Hispanic and 27.3% of 4343 non-Hispanic white individuals, $P = .001$). This highlights the need for targeting substance use specifically

Table 3. Prevalence of Substance Use Measures Compared Between Cases With Chronic Psychotic Illness and Control Individuals

Substance Used	No.	Odds Ratio Estimate (95% CI)[a]	P Value
Alcohol: >4 drinks/d	19 878	3.96 (3.61-4.35)	1.2×10^{-188}
100 cigarettes in lifetime	19 931	4.61 (4.31-4.94)	$<1.0 \times 10^{-325}$
Daily smoking >1 mo	19 882	5.11 (4.78-5.46)	$<1.0 \times 10^{-325}$
Marijuana >21 times/y	19 859	3.47 (3.23-3.72)	2.6×10^{-254}
Recreational drugs >10times	19 864	4.62 (4.27-4.99)	$<1.0 \times 10^{-325}$

[a] Odds ratios are calculated from logistic regression modeling probability of symptom as a function of diagnosis, adjusted for sex, race, age, and data collection site.

Figure. Substance Use Among Subgroups
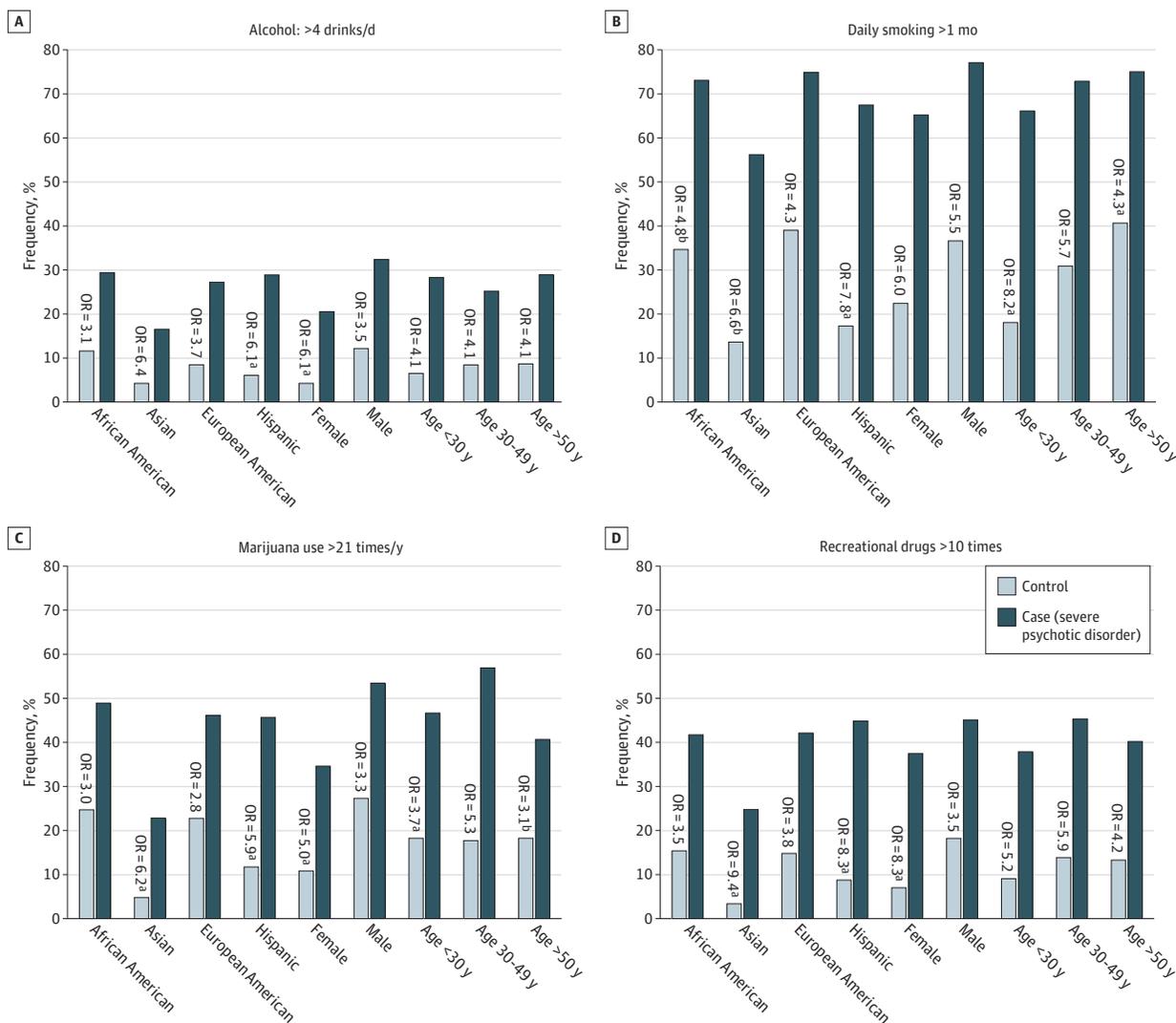
Frequency of alcohol use (A), smoking (B), marijuana use (C), and other drug use (D) contrasted among subgroups. The odds ratios (ORs) correspond to the odds of the prevalence of the symptom among cases with chronic psychotic illness vs control individuals. The ORs are contrasted with one another. The subgroups include African American (n = 4579), Asian (n = 905), European American (n = 8056), and Hispanic (n = 4988) individuals; females (n = 9390);

males (n = 10 501); those aged younger than 30 years (n = 5336); those aged 30 to 49 years (n = 8635); and those aged 50 years and older (n = 5946).
[a] P < .001; OR is statistically different from the reference (European descent for ethnicity, male for sex, and 30-49 years for age group).
[b] P < .05; OR is statistically different from the reference (European descent for ethnicity, male for sex, and 30-49 years for age group).

among individuals with severe psychotic illness because protective influences may not carry over from the general population.

The strongest associations between severe psychotic illness and substance use were seen with cigarette use. This is notable because most of the mortality seen in severe psychiatric illness is due to smoking-related disorders. Also, it appears that recent public health efforts that have successfully decreased smoking in the general population have not been effective in individuals with severe psychotic disorder. Specifically, the decrease in smoking among individuals younger than age 30 years that has been seen among the general population[32] and was present in the control participants in this

data set did not extend to cases: the OR of smoking daily for a month or more was 8.2 among individuals younger than 30 years of age, which is significantly higher than the OR of 5.2 among individuals aged 30 to 49 years and the OR of 3.9 among individuals aged 50 years or older (interaction $P = 4.5 \times 10^{-5}$). Given that (1) early mortality in cases is largely due to cardiovascular and pulmonary disease and (2) many psychotropic medications used to treat psychotic symptoms have severe metabolic adverse effects that increase the risk for diabetes mellitus and cardiovascular disease, it is imperative that we specifically target smoking in these individuals. This is consistent with relatively recent calls for the field of psychiatry to specifically target smoking in severe mental illness.[15]

Although these data illuminate characteristics of substance use in psychotic disorders in a large, multiethnic population, further study is required to better understand the nature of the comorbidity between psychotic disorders and substance dependence. The first step is to specifically evaluate comorbid substance dependence in individuals with severe psychotic illness rather than individual measures of use as assessed in this study. In addition, the validity and reliability of this series of questions has not been established in any population. However, this series of questions was extracted from the Diagnostic Interview for Genetic Studies, a standardized instrument with high test/retest validity and reliability. A further limitation of this study was that it was not a population survey. Because the individuals were not randomly sampled, there may be biases in the data set that limit extrapolation of the rates of substance use to the general populations of both individuals with severe psychotic illness and general populations of both individuals with severe psychotic illness and individuals without a personal or family history of bipolar disorder or schizophrenia. However, the sample was not selected for substance use, therefore, the ORs of substance use for cases vs control individuals should be accurate.

Nicotine, alcohol, and other drugs of abuse target dopaminergic, glutamatergic, and GABAergic transmission, which are also involved in the pathophysiology of severe mental illness. Specifically, nicotine can increase the metabolism of antipsychotics by activation of the cytochrome P450 enzymes[33] and is thus hypothesized to help reduce adverse effects of individuals taking antipsychotics. Conversely, exposure to substances increases the risk for severe mental illness: marijuana use at age 16 years is associated with psychosis at age 19 years,[34] and smoking precedes the onset of symptoms of mental illness.[35,36] Additionally, substance use leads to higher rates of psychiatric emergencies and hospitalizations.[37] This highlights the importance of understanding the biological connection between substance use and severe mental illness.

Conclusions

In summary, the prevalence of substance use in severe psychosis has been underestimated and spans social and cultural strata. To our knowledge, this is the largest study of substance use in individuals with severe psychotic illness to date. The study not only highlights the comorbid pathology of substance use among those with severe psychotic illness, it also suggests that public health efforts to reduce substance use have not been successful in one of our most vulnerable populations, individuals with severe psychotic illness. It is time to use our recent scientific and public health advancements to improve scientific understanding of the comorbidity between substance use and psychotic disorders and improve the treatment of both.

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