Alcohol Use Disorders in Schizophrenia: A National Cohort Study of 12,653 Patients

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Background: Comorbid alcohol use disorders (AUDs) in schizophrenia are associated with increased morbidity, more inpatient treatment, and violent offending. It is of clinical importance to identify those with schizophrenia who may go on to develop an alcohol use disorder; however, the risk factors are not well understood. The aim of this study was to identify risk factors for the development of an AUD in patients after they had been diagnosed with schizophrenia.

Method: We conducted a retrospective case-control study of 12,653 individuals diagnosed with *ICD*-defined schizophrenia in Sweden in 1973–2004, using data from national registers. We tested the associations between individual factors (marital status, immigrant status, and previous violent offending), sociodemographic factors (income and education), and parental risk factors (AUDs, psychosis, and violent offending) *ICD*-defined and AUD development using logistic regression modeling.

Results: Over a median follow-up of 17.3 years, 7.6% of patients had at least 1 hospital diagnosis of AUD. After adjustment for gender and age at diagnosis in a multivariate regression model, previous violent offending (OR = 2.1; 95% CI, 1.8–2.5), low education (OR = 1.3; 95% CI, 1.1–1.5), maternal AUD (OR = 1.9; 95% CI, 1.4–2.7), and paternal AUD (OR = 1.9; 95% CI, 1.5–2.3) remained independently associated with increased risk of patient AUD.

Conclusions: AUDs are a common sequela of schizophrenia. Risk factors that could be identified at the time of first presentation include low educational attainment, previous violent offending, and parental history of AUDs and may inform clinical treatment and follow-up of those most at risk.

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After nicotine, alcohol is the commonest substance abused by people with schizophrenia.[1] The Epidemiologic Catchment Area (ECA) study found that one third of people with schizophrenia have an alcohol use disorder (AUD, which includes alcohol dependence and harmful use),[2] which is 3 times higher than in the general population. Comorbidity with AUD is associated with more positive symptoms,[3,4] greater psychosocial dysfunction,[5] noncompliance with medication,[5] higher rates of hospital admissions,[5,6] chronic physical problems,[7] poor insight,[8] homelessness,[5,9] suicidal behavior,[5] hostile or threatening behavior,[5] and violent offending.[10]

From a clinical perspective, it is important to identify those patients with schizophrenia who are likely to go on to develop an AUD, so that appropriate treatment be focused. Previous studies have found factors associated with comorbid schizophrenia and alcoholism, which include male gender, family history of AUDs, and younger age.[5,11] However, many studies did not differentiate AUDs from misuse of other substances and did not consider the temporal relationship between the two disorders.[2,5,11–18] Hence, risk factors for the development of AUD after schizophrenia may not be the same in those who already have AUD at first presentation with schizophrenia.

We conducted a retrospective case-control study in a 33-year national cohort of people with schizophrenia comprising 12,653 patients. The primary aim was to investigate the role of potential parental and sociodemographic risk factors. This is the largest study to date that investigated comorbid schizophrenia and AUD and, to our knowledge, the only that addresses parental and sociodemographic risk factors for the development of an alcohol disorder in individuals after being diagnosed with schizophrenia.

METHOD

We used data from national population-based registers in Sweden. All citizens in Sweden, including immigrants, receive a 10-digit personal identification number, which is consistent throughout all national registers, making it possible to link them. We obtained data from the Hospital Discharge Registry (HDR; held at the National Board of Health and Welfare), the Cause of Death Register (Statistics Sweden), the National Crime Register (National Council for Crime Prevention), the Migration and Education Registers (Statistics Sweden), and the Multi-Generation Register (MGR; Statistics Sweden). These methods have been published previously.[19]

Data on all individuals admitted to a hospital (including secure or private hospitals) for assessment or treatment in Sweden are recorded in the HDR. Only approximately 1% of hospital discharges have missing personal information.[20] We identified individuals aged 15 years or older who had been discharged between January 1, 1973, and December 31, 2004. We included in this study all individuals who had been given a discharge diagnosis of schizophrenia on at least 2 separate occasions. We included all 12,653 people who met these inclusion criteria.

For Clinical Use

- Alcohol use disorders (AUDs) are common in patients who have been diagnosed with schizophrenia and are associated with significantly increased morbidity.
- The risk of the patient's developing an AUD should be considered at the time of first presentation with schizophrenia to inform appropriate interventions.
- Risk factors for developing an AUD after a patient is diagnosed with schizophrenia are low educational attainment, parental history of AUD, and history of violent offending.

Diagnostic Measures

All diagnoses were made according to the *ICD*-8 (1973–1986, code 295), *ICD-9* (1987–1996, code 295), or *ICD-10* (1997–2004, code F20). Reliability studies indicate good concordance between HDR diagnoses of schizophrenia and OPCRIT[21] record review and interview,[22,23] although specificity is poor to fair,[21] such that some individuals with a true diagnosis of schizophrenia are erroneously diagnosed with another mental illness. A previous longitudinal study of first-episode psychosis found that only 56% of patients who had been abusing substances eventually had schizophrenia, the remainder having drug-induced psychosis.[24] Hence, to increase diagnostic specificity, we included only individuals diagnosed with schizophrenia on 2 separate occasions.

Individuals with any admission with a principal or comorbid diagnosis of alcohol abuse or dependence (*ICD*-8: 303; *ICD-9*: 304, 305.9; *ICD-10*: F10.1-F10.9, except x.5) were classified as having an AUD. We excluded all individuals who had an AUD prior to their second hospital discharge diagnosis of schizophrenia. The agreement of comorbid substance use diagnoses in schizophrenia obtained from the HDR with those obtained during a comprehensive 4-week inpatient forensic psychiatric assessment (n = 1,638) has been tested.[25] The κ was 0.37 (standard error = 0.23, $P < .001$, corresponding to 68% agreement) for HDR diagnoses of comorbid substance abuse in individuals with schizophrenia, indicating fair to moderate agreement.

Individual Factors

We extracted marital status from the 1970 and 1990 censuses. Immigrant status was defined as being born outside Sweden or having at least one parent born outside Sweden. Details of criminal convictions for all case individuals and for their parents were extracted from the National Crime Register. Offenses were categorized as "violent" or "nonviolent." Violent crime was defined as homicide and attempted homicide, aggravated assault (an assault that is life-threatening in nature or causes severe bodily harm), common assault, robbery, arson, any sexual offense (rape, sexual coercion, child molestation, and sexual harassment [including indecent exposure]), illegal threats, or intimidation. We did not include the category of patient nonviolent offenses in our analysis because nonviolent crime may be collinear with AUD (as many of the offenses are directly related to alcohol, such as "drunk and disorderly"). In addition, we did not have information on parental nonviolent crime.

Sociodemographic Factors

Information on income was gathered from the 1970 and 1990 national censuses. We divided income into tertiles for further analysis. Regarding education, we dichotomized the highest level of completed education into compulsory 9-year education and higher.

Parental Factors

We linked data on all individuals with schizophrenia to their parents' records using the MGR. This register connects all individuals born in Sweden since 1933 and living in Sweden since 1960 and immigrants who became Swedish citizens before age 18 years together with one or both parents. We then extracted information regarding parental alcohol or drug use disorders, and diagnosis of a psychotic illness, including schizophrenia and bipolar affective disorder (from the HDR), and criminal convictions (from the National Crime Register).

Analyses

We conducted a case-control study comparing patients with schizophrenia (as reflected in 2 separate inpatient episodes) diagnosed with AUD after the onset of schizophrenia with those that were not. Odds ratios were calculated for the bivariate associations between each potential risk factor and AUD after the onset of schizophrenia. Risk factors with significant associations were entered into a multivariate logistic regression model. All analyses were carried out with Stata 10 (StataCorp LP, College Station, Texas) and SPSS version 16 (SPSS, Inc, Chicago, Illinois).

RESULTS

Of 13,806 people diagnosed with schizophrenia, 1,153 (8.4%) had been diagnosed with an AUD before being diagnosed with schizophrenia and were excluded from further analysis. We therefore followed up 12,653 people diagnosed with schizophrenia, of whom 8,891 (70.3%) were men. The median length of follow-up was 17.3 years, (range, 0–32.0 years). We found that 962 individuals (7.6%) developed a comorbid AUD requiring inpatient care during follow-up (see Table 1). Of these, 719 (74.7%) were male. We found that 44% of those also had a drug use disorder. The median time to an AUD diagnosis was 4.9 years. Individuals who subsequently developed AUD were younger when diagnosed with schizophrenia than those who did not (mean = 27.85 years vs 28.75 years, $t = 3.74$, $P < .001$).

We first tested all risk factors univariately and separately by gender. Since we found no significant differences in the magnitude of associations for men as compared to women (data available upon request), results were not separated by gender. We found that previous violent offending was significantly associated with outcome (OR = 2.5; 95% CI, 2.2–2.9, as was education (OR = 1.5; 95% CI, 1.3–1.7). We tested

Table 1. Prevalence and Associations of Risk Factors With Alcohol Use Disorder (AUD) Among All Individuals With 2 or More Discharge Diagnoses of Schizophrenia in Sweden, 1973–2004

Risk Factor/Covariate	AUD (N = 962), n (%)	No AUD (N = 11,691), n (%)	OR	95% CI	*P*
Individual factors					
Unmarried[a]					
Yes	844 (88.5)	9,786 (86.8)	1.2	1.0–1.4	.14
No	110 (11.5)	1,489 (13.2)			
Immigrant status[b]					
Yes	140 (14.6)	1,804 (15.7)	0.9	0.8–1.1	.40
No	818 (85.4)	9,689 (84.3)			
Previous violent crime					
Yes	260 (27.0)	1,503 (12.9)	2.5	2.2–2.9	<.001
No	702 (73.0)	10,188 (87.1)			
Sociodemographic factors					
Lowest tertile income[c]					
Yes	322 (35.5)	3,812 (36.8)	0.9	0.8–1.1	.43
No	586 (64.5)	6,549 (63.2)			
Low education[d]					
Yes	413 (45.2)	3,858 (35.3)	1.5	1.3–1.7	<.001
No	500 (54.8)	7,056 (64.7)			
Parental factors					
Paternal AUD					
Yes	125 (13.0)	733 (6.3)	2.2	1.8–2.7	<.001
No	837 (87.0)	10,958 (93.7)			
Maternal AUD					
Yes	49 (5.1)	230 (2.0)	2.7	2.0–3.7	<.001
No	913 (94.9)	11,461 (98.0)			
Paternal violent offending					
Yes	58 (6.0)	433 (3.7)	2.2	1.8–2.7	<.001
No	904 (94.0)	11,258 (96.3)			
Maternal violent offending					
Yes	5 (0.5)	71 (0.6)	0.9	0.3–2.1	1.0
No	957 (99.5)	11,620 (99.4)			
Paternal psychosis					
Yes	14 (1.5)	213 (1.8)	0.8	0.5–1.4	.52
No	948 (98.5)	11,478 (98.2)			
Maternal psychosis					
Yes	35 (3.6)	482 (4.1)	0.9	0.6–1.2	.55
No	927 (96.4)	11,209 (95.9)			

[a]Analysis based on 12,229 individuals.
[b]Analysis based on 12,460 individuals.
[c]Analysis based on 11,269 individuals.
[d]Analysis based on 11,827 individuals.

6 parental characteristics (maternal and paternal alcoholism, psychosis, and violent offending, respectively) as risk factors for AUD. Parental AUDs and paternal violent offending were all univariately linked to patient AUD (Table 1). In contrast, we found no link between maternal violent offending or parental psychosis and AUD.

We then entered factors that were univariately significant into a multivariate model and adjusted for gender and age at diagnosis of schizophrenia (Table 2). Due to some missing data, the final model was based on 11,827 individuals. Patient's low education and violent offending as well as paternal and maternal alcoholism were all independently and significantly associated with AUD (adjusted ORs, 1.3–2.1).

DISCUSSION

In a national cohort of 12,653 individuals without a hospital discharge diagnosis of AUD when hospitalized for schizophrenia and followed up for a median of 17 years, we found that 962 (7.6%) were subsequently diagnosed with comorbid AUD. This figure is 11 times higher than that found in a 9-year Swedish general population cohort that used similar inpatient methods.[26] However, some caution is needed when comparing the rate of AUD comorbid with schizophrenia to that for AUD alone. The fact that schizophrenia and AUD both increase the likelihood of getting treatment and being diagnosed with the other disorder inflates the strength of their association.[27] Failure to diagnose preexisting AUD could therefore increase the strength of the association. Nevertheless, the risk of being diagnosed with an AUD in addition to schizophrenia appears several times higher than that reported for the general population.

Table 2. Parsimonious Multivariate Model of Risk Factors for AUD in Schizophrenia, Controlling for Gender and Age at First Diagnosis (n = 11,827)

Variable	Odds Ratio	95% CI	*P*
Patient's low education	1.3	1.1–1.5	<.001
Patient's violent offending	2.1	1.8–2.5	<.001
Paternal AUD	1.9	1.5–2.3	<.001
Paternal violent offending	1.1	0.8–1.5	.43
Maternal AUD	1.9	1.4–2.7	<.001

Abbreviation: AUD = alcohol use disorder.

Alcohol, Schizophrenia, and Violence

Low educational attainment, previous violent offending, and maternal and paternal alcohol use disorder were all independently and significantly associated with comorbid AUD after controlling for potential confounders. We found no association between AUD and parental psychosis.

Violent offending was the strongest predictor of AUD after being diagnosed with schizophrenia. This might be surprising in light of the widely accepted dichotomous taxonomy of AUDs[28] in which type I alcoholism is relatively late onset, less severe, and not associated with criminality and type II alcoholism is early onset, more severe, and associated with criminal offending. Although our primary aim was not to test the validity of the taxonomy in people diagnosed with schizophrenia, it provides a useful framework for comparison, notwithstanding that it was developed for male patients whereas we have included both genders. In addition, we have taken a narrower definition of criminality (specifically, only violent offending) than that used by Cloninger and colleagues.[28]

The patients in our study were on average 35 years old when diagnosed with AUD, which, according to the taxonomy, might suggest a type I pattern. It is known that early-onset offending in schizophrenia is associated with early-onset substance misuse.[29] However, we found that violent offending before a diagnosis of schizophrenia predicted AUD, often many years later. There are several possible explanations for this. First, it is plausible that a proportion of those with early-onset AUD were not diagnosed before being diagnosed with schizophrenia. Second, violent behavior might cause AUD; for example, some people seem to be traumatized by their own violent actions.[30] It is therefore

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possible that individuals who were violent before developing schizophrenia were traumatized in this manner and became more likely to misuse alcohol also after developing psychosis. Third, violence could be a confounder. Violence is associated with chronic and severe psychotic symptoms,[31] hence the psychotic symptoms and associated social adversity associated with a psychotic illness (rather than the violence per se) might result in persistent alcohol misuse. Fourth, it might be that this taxonomy does not apply to people with schizophrenia. The most likely of these possibilities cannot be determined from the present results. However, we speculate that the dichotomous taxonomy of AUD does not apply uniformly to those with schizophrenia, since there might be several mechanisms by which alcohol use, violence, and schizophrenia are associated. Further, the relative importance of such mechanisms might vary both across individuals and within individuals over time. A greater degree of understanding of the relationship between offending and AUD could be achieved if it could be determined whether offenses were planned or carried out impulsively, and the extent to which alcohol was a factor in the commission of each offense, for example, whether the individual was intoxicated at the time, or whether the offense was carried out to procure resources to purchase alcohol. Unfortunately, we do not have this information available in our study.

Whatever the mechanism, the observation that violence predicts AUD in schizophrenia has important clinical implications. Although it is well established that substance misuse predicts violence, our findings suggest recognition that the relationship is reciprocal. Hence, a careful history of previous offending at the time of first presentation of schizophrenia would help the assessment of risk for future violence and of AUD.

The Value of Early Recognition and Treatment of AUD

Among those who have a mental illness and are at risk of developing a substance use disorder, treatment of the mental illness alone may not suffice to prevent the latter.[32] Early identification of those at increased risk of developing AUD could help the delivery of additional preventive interventions. Preventing the progression to severe alcohol abuse or dependence would be important to reduce the risk of alcohol-related physical and social complications and reduce the impact that AUD has on schizophrenia symptoms, medication noncompliance, and hospital readmissions. Brief outpatient interventions to reduce alcohol consumption in those not yet dependent appear to be effective in general population studies[33] and in nonpsychotic psychiatric patients,[34] and further work is necessary to confirm that such benefits also apply to people with schizophrenia.

The Relationship Between Schizophrenia and AUD

Our model accounted for a relatively small proportion of the variance in the risk of developing AUD after schizophrenia, and clearly, other factors, such as individual clinical factors, may well be important. It has been suggested that patients with schizophrenia consume alcohol to reduce psychotic symptoms or to alleviate the adverse effects of prescribed medications, so called "self-medication." There is some support for the notion that alcohol may reduce hallucinations[35,36] and that patients with extrapyramidal side effects drink alcohol excessively.[37] However, other studies have failed to find evidence for self-medication of psychotic symptoms.[12,38] Evidence suggests that people with schizophrenia are motivated to use alcohol and other substances for the same reasons as those without schizophrenia, such as dysphoria or insomnia.[33,39] It is possible, therefore, that people with schizophrenia accumulate risk factors for excessive alcohol consumption as a consequence of the disorder (such as the destruction of social networks, unemployment, lowered self-esteem, and loneliness). Other factors that may be important in people with schizophrenia may include the nature and severity of other positive and negative symptoms, the type of treatment given, and adherence to treatment. Unfortunately, we were not able to investigate these factors in the present study.

Limitations

We were able to include only patients who were diagnosed as having either schizophrenia or an AUD during 2 hospital admissions. The patients in our sample were older when they reached our diagnostic criteria (mean, 28 years) than is typical of the age at onset of schizophrenia; therefore, it is unclear whether our findings generalize well to other populations. However, the mean age of patients in the cohort (mean, 40 years) was similar to those reported in another large study.[40] Patients may have been admitted to hospital primarily due to symptoms of schizophrenia, at which time a comorbid AUD was diagnosed. They may have been admitted primarily due to an AUD at some point after having 2 hospital discharge diagnoses of schizophrenia. We required 2 hospital discharge diagnoses of schizophrenia to improve diagnostic specificity (a method used in a previous study[19]), and some people, for example those who were incorrectly diagnosed as having drug-induced psychosis on one or both occasions rather than schizophrenia, were necessarily excluded by using these criteria. Although 2 separate discharge diagnoses were required for a diagnosis of schizophrenia, we required only 1 hospital diagnosis of AUD. We argue that AUD is less likely to be misdiagnosed than schizophrenia, as schizophrenia may not be easily distinguished from other psychotic disorders at first presentation. We excluded those diagnosed with an AUD before being diagnosed with schizophrenia. Since we required 2 hospital diagnoses of schizophrenia, it is possible that some people developed an AUD between first and second hospital presentations and were thus excluded from the present study. It is also possible that some cases of AUD were not detected before the second diagnosis of schizophrenia. Therefore, our results are bound to underestimate the incidence of AUD in schizophrenia. The advantage of this method, however, was improved specificity both for the diagnosis of schizophrenia and in the ascertainment of cases that developed AUD after schizophrenia.

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CONCLUSION

In summary, alcohol use disorders are a common sequela of schizophrenia, and important risk factors for comorbid AUD possible to identify at the time of the first inpatient schizophrenic episode included patient history of violent offending, low educational attainment, and parental history of AUD.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.
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