Effects of Comorbid Alcohol Use Disorder on the Clinical Outcomes of Schizophrenia: A Nationwide Population-based Study

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Primary research

Keywords: Schizophrenia, alcohol use disorder, comorbidity, drug compliance, hospitalization

DOI: https://doi.org/10.21203/rs.3.rs-322353/v1

Abstract

Background

Alcohol use disorder (AUD) is a common psychiatric comorbidity in schizophrenia, associated with poor clinical outcomes and medication noncompliance. Most previous studies on the effect of alcohol use in patients with schizophrenia had limitations of small sample size and a cross-sectional design. Therefore, this study aimed to use a nationwide population database to investigate the impact of AUD on clinical outcomes of schizophrenia.

Methods

Data from the Health Insurance Review Agency database in South Korea from January 1, 2007 to December 31, 2016 was used. Among 64,442 patients with incident schizophrenia, 1,598 with comorbid AUD were selected based on the diagnostic code F10. We performed between- and within-group analyses to compare the rates of psychiatric admissions and emergency room (ER) visits and medication possession ratio (MPR) with control patients having schizophrenia matched for the onset age, sex, and observation period.

Results

The rates of psychiatric admissions and ER visits decreased after the diagnosis of AUD in both groups; however, the decrease was significantly greater in patients with comorbid AUD compared to the control group. While the case group showed an increase in MPR after the diagnosis of AUD, MPR decreased in the control patients. The rates of psychiatric admissions, ER visits and MPR were worse in the schizophrenia group with comorbid AUD both before and after the diagnosis of AUD.

Conclusions

Clinical outcomes were worse in the comorbid AUD group than in the control group before and after the diagnosis of AUD. Considering that patients with schizophrenia with comorbid AUD had poorer clinical outcomes even before the diagnosis of AUD, schizophrenia with comorbid AUD could be a distinct subtype of schizophrenia.

1. Introduction

Alcohol use disorder (AUD) is a common psychiatric comorbidity in schizophrenia. According to a meta-analysis, the lifetime prevalence of AUD in patients with schizophrenia is 24.3% [1]. Several theories account for the high rate of co-occurring substance use disorder in schizophrenia [2, 3]. The “two-hit” model argues that combined genetic risk and alcohol drinking during adolescence contribute to the development of schizophrenia and AUD. The self-medication theory is that patients with schizophrenia tend to find substance use a relief method for psychiatric symptoms or side effects of antipsychotics [2]. The reward deficiency syndrome and neurodevelopmental theory of schizophrenia have recently been introduced to explain the prevalence of AUD among patients with schizophrenia [2].

The comorbidity of AUD is associated with poor clinical outcomes in schizophrenia, which are low treatment compliance, an increased rehospitalization rate, and a high relapse rate [4, 5]. Patients with schizophrenia with comorbid AUD experience adverse life events, such as unemployment and divorce [6]. In addition, the comorbid AUD negatively impacts patients with schizophrenia through poor adjustment toward lives and its association with depressive symptoms and disruptive behaviors [7]. A previous study reported that patients with schizophrenia with AUD have more than a two-fold risk of violence compared to those without AUD [8].

As aforementioned, previous studies on the effect of alcohol use on patients with schizophrenia showed that AUD aggravated psychiatric symptoms and treatment noncompliance. However, most studies had been conducted before the 2000s and had small sample size, including a total of less than 300 subjects. Considering that most randomized control trials recruit subjects from a few hospitals or medical institutions, participants in previous studies could not have reflected the characteristics of the total population of interest. Furthermore, many previous studies had a cross-sectional design, which was an obstacle for examining the long-term effect of alcohol use [9].

The aim of the present study was to investigate clinical indicators of treatment, including the rates of psychiatric hospitalizations and emergency room (ER) visits and medication possession ratio (MPR), in patients with schizophrenia with comorbid AUD. In order to overcome the limitations of previous studies, we used nationwide population data reflecting real-clinical practice in a large population. We analyzed these clinical outcomes in patients with schizophrenia with or without comorbid AUD and time-varying patterns of clinical outcomes before and after the diagnosis of AUD. We aimed to identify the effect of comorbidity of AUD on clinical outcomes of schizophrenia.

2. Methods

2.1. Data source

South Korea has a public medical insurance system based on fee-for-service, known as the National Health Insurance (NHI) system, covering approximately 98% of the country's population [10, 11]. It is mandatory for all South Koreans to register with the NHI. Thus, medical claims of the entire population are recorded in the Health Insurance Review Agency (HIRA) database [12]. The claim data in the HIRA database includes information on patients' visits or admissions to medical institutions, diagnoses, and demographics, such as age and sex [11, 13].

2.2. Study sample and design

We used the HIRA claim data from January 1, 2007 to December 31, 2016. the following inclusion criteria were applied to identify an incident cohort of patients with schizophrenia: 1) at least one claim of the diagnostic code F20 (schizophrenia) from January 1, 2008 to December 31, 2016 (The diagnostic code is based on the Korean Standard Classification of Diseases, a version of International Classification of Disease 10.); 2) no prescription of antipsychotic medication within 1 year preceding the diagnosis of schizophrenia; 3) starting of antipsychotic treatment within 3 days after the diagnosis of schizophrenia; and 4) onset age ranging from 12 to 80 years at the diagnosis of schizophrenia. The exclusion criteria were psychotic disorder due to another medical condition, dementia, substance-induced psychotic disorder, substance intoxication with perceptual disturbances, moderate or severe intellectual disability, and autism spectrum disorder that should not have been diagnosed before the diagnosis of schizophrenia.

Next, we selected the comorbid AUD group from patients with schizophrenia. This group was identified by the diagnostic code F10 (AUD) after the diagnosis of schizophrenia. To evaluate the impact of the diagnosis of AUD on clinical outcomes of schizophrenia, we excluded patients who had been diagnosed with schizophrenia and AUD simultaneously. Subsequently, we selected control patients with schizophrenia, matched for the onset age, sex, and observation period. We performed a matched case–control study, comparing the rates of psychiatric admissions and ER visits and MPR between the comorbid AUD and control groups. Within-group analysis was also conducted to investigate differences in clinical outcomes before and after the diagnosis of AUD within each group.

This study was approved by the Institutional Review Board (IRB) of the Asan Medical Center (IRB No. 2018 – 0131).

The requirement for informed consent was exempted because of the use of anonymous and de-identified data.

2.3. Definitions of outcomes

Main outcomes included the rates of psychiatric admissions and ER visits and MPR. Psychiatric admission and ER visits have been used as the outcomes reflecting the prognosis of several psychiatric disorders in previous studies [6, 14, 15]. Psychiatric admission was determined as hospitalization because of the main diagnosis of a psychiatric disorder. The duration of admission ranged from 14 to 180 days. We removed the events of hospitalization that had occurred within 30 days from the prior discharge. MPR, a common measure for medication adherence, was calculated as a ratio of days of medication supply divided by the follow-up period.

We also calculated the number of treatment discontinuations and duration of the first antipsychotic treatment episode. Treatment discontinuation was defined as no antipsychotic prescription within 28 days from the expected date of the next antipsychotic prescription. The first antipsychotic treatment episode was defined from the date of the schizophrenia diagnosis to the first treatment discontinuation.

2.4. Statistical analyses

We compared continuous and categorical variables using Student's t and chi-square tests, respectively. Multivariate linear regression analysis was performed for the interaction effect of dependent variables between comorbid AUD and control groups. For post-hoc tests, the unpaired *t*-test was used for between-group analyses and paired *t*-test for within-group analyses. The statistical significance level was set at 0.05. All data were processed using the R program ver. 3.5.1 (R Development Core Team, Vienna, Austria).

3. Results

3.1. Demographic and clinical characteristics of the study population

Of a total of 64,442 patients with incident schizophrenia, 1,598 (2.48%) were in the comorbid AUD group. There were significant differences in the onset age, sex, and observation period between schizophrenia with (n = 1,598) and without (n = 62,844) AUD groups. The comorbid AUD group showed a higher onset age (44.3 ± 12.2 vs. 40.8 ± 15.7 years, $p < 0.001$), greater male prevalence (75.1% vs. 44.8%, $p < 0.001$), and longer observation period (5.1 ± 2.5 vs. 4.0 ± 2.8 years, $p < 0.001$) compared to the control group. Of the 62,844 patients with schizophrenia without AUD, 1,598 were selected as controls after matching for the onset age, sex, and observation period (Table 1).

Table 1
Demographic and clinical characteristics of the study population

Variable	Schizophrenia with AUD (n = 1,598)	Matched controls (n = 1,598)	*p*-value
Onset age for schizophrenia, mean (SD), years	44.3 (12.2)	44.2 (12.4)	0.873
Onset age for comorbid AUD, mean (SD), years	46.1 (12.1)		
Sex, n (%)			1.000
Male	1,200 (75.1)	1,199 (75.0)	
Female	398 (24.9)	399 (25.0)	
Observation period, mean (SD), years	5.1 (2.5)	5.1 (2.5)	0.941
Total duration of antipsychotic treatment, mean (SD), years	2.6 (2.2)	3.5 (2.5)	< 0.001
Duration of the first antipsychotic treatment, mean (SD), days	202.6 (337.8)	344.0 (507.9)	< 0.001
Number of antipsychotic drugs in the total observation period, mean (SD)	4.0 (2.0)	3.4 (1.9)	< 0.001
Number of the treatment discontinuations[a] in the total observation period, mean (SD)	3.4 (3.0)	2.6 (2.9)	< 0.001

Abbreviations: AUD, alcohol use disorder; SD, standard deviation

[a] defined as no antipsychotic prescription within 28 days from the expected date of the next prescription

Compared to the control group, the comorbid AUD group was prescribed a higher number of antipsychotics during the total observation period (4.0 ± 2.0 vs. 3.4 ± 1.9, $p < 0.001$). The mean total duration of antipsychotic treatment was significantly longer in the control group than in the comorbid AUD group (3.5 ± 2.5 vs. 2.6 ± 2.2, $p < 0.001$). There were significant differences in the mean number of treatment discontinuations and duration of the first antipsychotic treatment between the groups. On average, the comorbid AUD and control groups had 3.4 ± 3.0 and 2.6 ± 2.9 treatment discontinuations, respectively. The mean duration of the first antipsychotic treatment was significantly longer in the control group than in the comorbid AUD group (344.0 ± 507.9 vs. 202.6 ± 337.8 days, $p < 0.001$).

3.2. Main outcomes

The decrease in the rates of psychiatric admissions and ER visits was greater in the comorbid AUD group compared to the control group, with significant group-by-time interaction effects (psychiatric admission: t = -4.604, $p < 0.001$; ER visit: t = -2.456, $p = 0.014$). While the control group showed decreased MPR after the diagnosis of AUD, the comorbid AUD group had increased MPR after the diagnosis of AUD, with a significant group-by-time interaction effect (t = 9.180, $p < 0.001$) (Fig. 1).

Table 2 exhibits results of both between- and within-group analysis. All outcome variables were worse in the comorbid AUD group compared to the control group both after and before the diagnosis of AUD. Higher rates of psychiatric admissions (t = 5.826, $p < 0.001$) and ER visits (t = 3.074, $p = 0.002$) and lower MPR (t = 16.346, $p < 0.001$) were found in the comorbid AUD group than in the matched control group before the diagnosis of AUD.

In the comorbid AUD group, the rates of psychiatric hospitalizations (t = 6.684, $p < 0.001$) and ER visits (t = 3.377, $p < 0.001$) significantly decreased after the diagnosis of AUD, and MPR significantly increased after the diagnosis of AUD (t = 9.333, $p < 0.001$). In the control group, after the diagnosis of AUD, the rate of psychiatric admissions significantly decreased (t = 14.168, $p < 0.001$), and the rate of ER visits (t = 7.062, $p < 0.001$) and MPR (t = 3.168, $p = 0.002$) significantly decreased.

Table 2
Within- and between-group comparisons in the rates of psychiatric admissions and ER visits and MPR

	Schizophrenia with AUD (n = 1,598)			**Matched controls (n = 1,598)**			**Between-group t-value[a]**		**Interaction effect (group * time) *p*-value[b]**
Variable	Before	After	Within-group t-value[a]	Before	After	Within-group t-value[a]	Before	After	
Psychiatric admission, /person-year, mean (SD)	6.17 (29.63)	1.20 (2.35)	6.684***	1.81 (4.14)	0.29 (1.12)	14.168***	5.826***	13.974***	< 0.001
ER visit, /person-year, mean (SD)	1.88 (18.32)	0.33 (1.06)	3.377***	0.46 (2.30)	0.05 (0.31)	7.062***	3.074**	10.135***	0.014
MPR, mean (SD)	0.51 (0.41)	0.63 (0.31)	9.333***	0.75 (0.42)	0.71 (0.28)	3.168**	16.346***	7.656***	< 0.001

Abbreviations: AUD, alcohol use disorder; SD, standard deviation; ER, emergency room; MPR, medication possession ratio

[a] unpaired *t*-test was used for between-group analyses and paired *t*-test for within-group analyses.

[b] multivariate linear regression analysis was used for the interaction effect

**$p = 0.002$, ***$p < 0.001$.

4. Discussion

Previous studies have shown the high prevalence and risk of substance use among individuals with psychotic disorders [2, 4, 16]. However, most previous studies on alcohol use in patients with schizophrenia had small sample size, a cross-sectional design, or a short observation period. To the best of our knowledge, this is the first nationwide population study on the effect of alcohol use on clinical outcomes of schizophrenia. The HIRA claim database was used to select the incident cohort of schizophrenia, from which the comorbid AUD group was selected as the case group. With matched controls, between- and within-group analyses were conducted to compare the rates of psychiatric admissions and ER visits and MPR. There were significantly higher rates of psychiatric admissions and ER visits and lower MPR in the comorbid AUD group compared to the control group before and after the diagnosis

AUD. The decrease in the rates of psychiatric admissions and ER visits after the diagnosis of AUD was significantly greater in the comorbid AUD group compared to the control group. After the diagnosis of AUD, MPR decreased in the control group but increased in the comorbid AUD group.

The prevalence of AUD among patients with schizophrenia was lower in this study compared to previous studies although the study population was sufficiently large. Several previous studies showed that individuals with psychotic disorders had a higher prevalence of alcohol abuse compared to the general population [2, 16]. A meta-analysis of 60 studies [6] worldwide showed a median prevalence of current AUD in schizophrenia of 9%. Another meta-analysis reported a lifetime prevalence of AUD in schizophrenia of 24.3% [1]. The discrepancy from previous studies may be attributed to the use of claim data from clinical practice in this study. Considering that clinicians focus on chief complaints, which are mainly auditory hallucinations or delusions, of patients with a psychotic disorder, comorbid psychiatric diagnoses, such as AUD and substance use disorder, could be disregarded in clinical practice because of the very low prevalence of illegal drug abuse and dependence in South Korea [17]. Moreover, since the incident cohort of our study was composed of first episode schizophrenia patients, a mean observation period of 5.1 years in this study might not be sufficiently long to determine the lifetime prevalence of AUD among patients with schizophrenia.

The onset age and sex ratio differed between the comorbid AUD (n = 1,598) and the patients with only schizophrenia (n = 62,844). The mean onset age of schizophrenia was significantly higher in the comorbid AUD group (44.3 ± 12.2 years) than in the patients with only schizophrenia (40.8 ± 12.7 years). The mean observation period was longer in the comorbid AUD group (5.1 ± 2.5 years) than in the patients with only schizophrenia (4.0 ± 2.8 years), consistent with previous studies. This might imply the distinct characteristic of the schizophrenia with comorbid AUD. Similar findings were also found in previous studies. An Indian comparative study showed that patients with schizophrenia with comorbid AUD were older at the onset of schizophrenia compared to the controls [18]. A Swedish study reported a late onset age of schizophrenia and longer illness duration in patients with a history of substance abuse although without statistical significance [19]. The late onset age of schizophrenia and shorter duration of illness were found in a survey conducted in 1994 in South Westminster, including 271 patients with schizophrenia with lifetime prevalence of alcohol abuse of 22.1% [20]. The larger proportion of men in the comorbid AUD group in this study was consistent with results of some previous studies on AUD in schizophrenia [4, 18, 19, 21].

Regarding antipsychotics use, to date, there has been no well-designed comparative study between patients with schizophrenia with and without comorbid AUD. In our study, there was a shorter mean total duration of antipsychotics treatment and higher mean number of prescribed antipsychotics in the comorbid AUD group compared to the control group. The number of treatment discontinuations was also higher in the current study. These results suggest that antipsychotic treatment of patients with schizophrenia with comorbid AUD would be complicated and challenging. Patients with schizophrenia with comorbid AUD could show lower drug compliance or need more antipsychotics to control psychiatric symptoms despite drug compliance.

A prospective community study reported the association of alcohol use in schizophrenia with a higher rate of rehospitalization. Drake et al. examined the pattern of alcohol use among 115 patients with schizophrenia. According to that study, alcohol use was associated with medication noncompliance, increased symptomatology, and a higher rate of rehospitalization. Even minimal alcohol use predicted rehospitalization [14], consistent with our study. In our study, all outcome variables were worse in the comorbid AUD group compared to the control group, regardless of the time point. The results indicated that in patients with schizophrenia with comorbid AUD, poorer treatment compliance and clinical outcomes before the diagnosis of AUD improved after the diagnosis of AUD. The improvement after the diagnosis of AUD might be attributable to clinicians reconsidering other factors influencing clinical outcomes, such as family education, a psychiatric history, and engagement in psychiatric care in the

community when making the comorbid diagnosis of AUD. Clinical outcomes in the comorbid AUD group were worse even before the diagnosis of AUD probably because schizophrenia with comorbid AUD is a distinct subtype of schizophrenia; however, further research is required to achieve confirmative evidence.

To our knowledge, this was the first nationwide population-based study on the effect of comorbidity of AUD on clinical outcomes of schizophrenia. Unlike previous studies, which had mostly been performed in the 1990s, our study had a large sample size and utilized various types of variables as the marker of clinical outcomes. This could be strengths of our study. In addition to between-group comparisons, we performed within-group comparisons to observe the time-varying patterns of dependent variables. This comparative design was not found in previous studies on AUD or schizophrenia.

This study had a few limitations. First, it was based on the claim data from clinical practice, not created for research purposes, introducing a possibility of disregarding comorbid psychiatric diagnoses. Thus, the prevalence of AUD among patients with schizophrenia was lower in this study than in previous studies. This may limit the generalizability of our results. Second, patients with comorbid AUD in this study might not represent the entire population of interest. The comorbid AUD group could comprise severe cases of AUD, considering the high prevalence of alcohol-related disorders in South Korea [22, 23], suggesting that mild alcohol abuse could be disregarded in clinical practice.

5. Conclusions

Clinical outcomes were worse in the comorbid AUD group than in the control group before and after the diagnosis of AUD. Considering that patients with schizophrenia with comorbid AUD had poorer clinical outcomes even before the diagnosis of AUD, schizophrenia with comorbid AUD could be a distinct subtype of schizophrenia. After the diagnosis of AUD, clinical outcomes significantly improved in the comorbid AUD group. Clinicians should recognize psychiatric comorbidities even when they first evaluate patients with schizophrenia. Further research is required to provide confirmatory findings of the association of AUD with schizophrenia.

Abbreviations

AUD, alcohol use disorder

ER, emergency room

MPR, medication possession ratio

NHI, National Health Insurance

HIRA, Health Insurance Review Agency

IRB, Institutional Review Board

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of the Asan Medical Center (IRB No. 2018-0131). The requirement for informed consent was exempted because of the use of anonymous and de-identified data.

Consent for publication

Not applicable

Availability of data and materials

Data availability is not applicable to this article as no new data were created or analyzed in this study.

Competing interests

The authors declares that they have no competing interests

Funding

Not applicable

Authors' contributions

SJA and SWJ conceived the idea and proposed the design of the study. SJA, SWJ and JSL acquired the data and conducted the statistical analysis. All the authors discussed the results. YJC, WHC, YTJ and HRK contributed for interpretation of the data. SJA wrote the original draft manuscript. JSL and SWJ critically revised the manuscript.

Acknowledgements

Not applicable

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