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Comorbid substance use disorders in schizophrenia: a latent class approach

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Abstract

Schizophrenia is a complex psychiatric disorder with a characteristic disease course and heterogeneous etiology. While substance use disorders and a family history of psychosis have individually been identified as risk factors for schizophrenia, it is less well understood if and how these factors are related. To address this deficiency, we examined the relationship between substance use disorders and family history of psychosis in a sample of 1,219 unrelated patients with schizophrenia. The lifetime rate of substance use disorders in this sample was 50%, and 30% had a family history of psychosis. Latent class mixture modeling identified three distinct patient subgroups: (1) individuals with low probability of substance use disorders; (2) patients with drug and alcohol abuse, but no symptoms of dependence; and (3) patients with substance dependence. Substance use was related to being male, to a more severe disease course, and more acute symptoms at assessment, but not to an earlier age of onset of schizophrenia or a specific pattern of positive and negative symptoms. Furthermore, substance use in schizophrenia was not related to a family history of psychosis. The results suggest that substance use in schizophrenia is an independent risk factor for disease severity and onset.

Keywords

schizophrenia; substance use disorders; family history of psychosis; dependence; disease course; major depressive disorder

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Conflict of Interest Statement

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

B.K. conceived the study design, obtained grant support, performed the analysis, interpreted the results, and wrote the paper.

1. Introduction

Schizophrenia is a severe, complex psychiatric disorder characterized by lack of feeling or emotion, lack of initiative, and alterations in thoughts, perceptions, and behavior. Delusions and hallucinations, as well as misinterpretation of reality, are present in many patients as well (American Psychiatric Association, 2013). The prevalence of schizophrenia is about 0.5% worldwide (Saha et al., 2005) and the age of onset ranges from adolescence to adulthood, but the cause of the disorder remains unknown (National Institute of Mental Health, n.d.). About a third of patients have a family history of psychosis, and twin studies have supported the hypothesis that genetic risk factors could lead to the manifestation of the disorder (Owen et al., 2010; Sullivan et al., 2003). However, the search for causal genetic mutations has been challenging (Claes et al., 2012). In addition, de novo genetic mutations (Xu et al., 2011), prenatal adverse events (Brown, 2011; Brown and Patterson, 2011; Rothman and Greenland, 1998), and severe use of alcohol and illegal substances have been discussed as other risk factors (Barondes, 1999; Connell, 1958; Griffiths et al., 1972; Horowitz, 1969; Malone et al., 2010; McLaren et al., 2010; Minozzi et al., 2010; Moore et al., 2007; Roncero et al., 2014; Vollenweider et al., 1998).

Substance use disorders are defined as conditions in which either abuse of or dependence on substances, such as alcohol, cocaine, opioids, phencyclidine, amphetamine, cannabis or nicotine, among others, has had negative effects on the patient's family and social life, work, or school, or has resulted in financial problems. According to DSM-IV criteria, substance use disorders have been differentiated into disorders of abuse or dependence (American Psychiatric Association, 2000). In substance abuse, the consumption of substances has led to impairment or distress, but criteria of dependence have not been met. Substance dependence is characterized by tolerance and symptoms of withdrawal. It is often implied that abuse is a less severe form of substance use disorder compared to dependence, and this is reflected in the new DSM-V classifications (American Psychiatric Publishing, n.d.). Genetic risk factors appear to contribute to the manifestation of substance use disorders. In several studies, a family history of substance use was an important predictor of disease onset and disease severity in substance abusers without comorbid psychiatric diagnoses (Bierut et al., 1998; Boyd et al., 1999; Coviello et al., 2004; Kendler et al., 2008; Merikangas et al., 1998).

The relationship between substance use disorders and schizophrenia has been extensively explored in multiple population-based studies (Kendler et al., 1996; Kessler et al., 1994; Regier et al., 1990). So far, convincing evidence has been found for a causal, dose-dependent relationship between substance use disorders and the onset of schizophrenia, if the onset of substance use disorders preceded the onset of schizophrenia (Andreasson et al., 1987; Miller et al., 2001; Tien and Anthony, 1990; van Os et al., 2002; Zammit et al., 2002). On the other hand, significant predictors of comorbid substance use disorders in patients with schizophrenia were male gender, low educational attainment, previous violent offending, and a family history of substance use disorders (Cantor-Graae et al., 2001; Dixon, 1991; Westermeyer, 2006). Patients with schizophrenia and comorbid substance use disorders were less likely to adhere to treatment and more likely to have adverse disease outcomes (McLean et al., 2012; Murthy and Chand, 2012). But even during the first episode of schizophrenia, substance users had more severe psychotic symptoms and an earlier age of

onset compared to non-users (Mauri et al., 2006; Picci et al., 2013; Schimmelmann et al., 2012). In patients with a dual diagnosis, high rates of substance use disorders were found in first- and second-degree relatives of the patients, suggesting that genetic risk factors for substance use disorders and an adverse family environment could have contributed to the onset and severity of substance use disorders in patients with a dual diagnosis (Comtois et al., 2005; Wilson et al., 2013). Even though the risk for comorbid substance use disorders in patients with schizophrenia is well recognized, not enough effort has been made to study the relationship between family history of psychosis and substance use disorders in patients with schizophrenia. Hence, we have focused on the relationship between familiarity of schizophrenia and substance use disorders in a large sample of patients ascertained for genetic studies.

2. Methods

2.1. Sample

The sample consisted of 1,219 unrelated individuals of European descent and was provided by the Foundation for the National Institutes of Health Genetics Association Information Network (phs000021.v3.p2; GAIN Collaborative Research Group et al., 2007). All individuals were 18 years or older. The methods for recruitment and ascertainment have been described in detail elsewhere (Suarez et al., 2006) and hence, only a brief summary will be given here. All individuals had been interviewed and assessed with the Diagnostic Interview for Genetics Studies (DIGS) by trained health care professionals (NIMH Center for Collaborative Genomics Research and Mental Disorders, n.d.). The DIGS is an extensively validated, structured clinical instrument developed by principal investigators of the National Institute of Mental Health (NIMH) for the assessment and differential diagnosis of major mood and psychotic disorders (Nurnberger et al., 1994). The instrument consists of 27 subscales for the assessment major depressive disorder (according to DSM-IV), mania/hypomania, dysthymia and hyperthymic personality, psychosis, alcohol abuse and dependence, drug abuse and dependence, comorbidity assessment, suicidal behavior, anxiety disorders, eating disorders, and antisocial personality disorder. In addition, the instrument also contains the Modified Structured Interview for Schizotypy (MSIS), a modified Mini-Mental status examination; the Global Assessment Scale (GAS); the Scale for the Assessment of Negative Symptoms (SANS)/Scale for the Assessment of Positive Symptoms (SAPS); SIS ratings; and the OPCRIT. In addition, information on demographics, medical history, family history, somatization, the longitudinal disease course of psychiatric disturbances, medical record information, and an assessment of the reliability of the obtained information rated by the interviewer were also collected. Information gathered throughout the interview was rated for reliability, and, finally, non-hierarchical best-estimate consensus diagnoses (Leckman et al., 1982) were reached by at least three independent raters according to DSM-IV criteria (DSM-IV; American Psychiatric Association, 2000).

2.2. Variables included in the model

We included the following DSM-IV-criteria-based categorical comorbid diagnoses as indicators in the Latent Class Analysis (LCA): (1) alcohol dependence (ALCD), (2) substance dependence other than cannabis (SUBD), (3) cannabis abuse (including

dependence) (CANNABIS), (4) alcohol abuse (ALCA), and (5) substance abuse other than cannabis (SUBA). In addition, we included the diagnosis of major depressive disorder (DEP) in our model because previous studies have indicated a strong correlation between symptoms of depression and comorbid substance use disorders in schizophrenia (Meesters et al., 2014). First, we conducted the LCA without covariates in the model in order to understand the substantive interpretation of the latent classes. Then, we included additional auxiliary variables as covariates, including gender (coded as 1 for male and 2 for female), family history of psychosis (coded as 0 if absent and 1 if present), and the chronologic order of onset of schizophrenia and substance use disorders (coded as 0 and 1), indicating whether or not substance use disorders had been diagnosed before the onset of schizophrenia. Age of onset of schizophrenia was also included as a continuous variable. The total number of acute symptoms prior to the interview was a categorical variable, ranging from 1 to 7. The variable “symptom pattern” rated the predominance of positive or negative symptoms over the entire course of the disease, but at least over the duration of one year. This variable had five categories: (1) continuously positive, (2) predominantly negative, (3) predominantly positive converting to predominantly negative, (4) negative converting to positive, and (5) continuous mixture of positive and negative symptoms. The variable “pattern of severity” evaluated the degree of impairment caused by the disorder over the disease course adjusted for the disease duration. The variable had five categories: (1) episodic shift, (2) mild deterioration, (3) moderate deterioration, (4) severe deterioration, and (5) relatively stable. The variable “classification of longitudinal disease course” measured the longitudinal disease course and required that at least one year had elapsed since the initial onset of active-phase symptoms. The classification categories were (1) episodic with inter-episode residual symptoms, (2) episodic with no inter-episode residual symptoms, (3) continuous, (4) single episode in partial remission, (5) single episode in full remission, and (6) other or unspecified pattern. For individuals with less than one year of retrospective information, these variables were coded as missing.

2.3. Latent class mixture modeling

The LCA was performed in the statistical software program Mplus, Version 5 (Muthén and Muthén, 1998-2014) as described previously (Kerner et al., 2011). The estimation maximization (EM) algorithm was used to estimate the latent class membership for each individual based on the probability of endorsing a profile of variables (Muthén and Shedden, 1999). To avoid local maxima in the loglikelihood, we used 200 random sets of starting values. We compared models with an increasing number of classes until the Bayesian Information Criterion (BIC) reached a minimum. The BIC was calculated for the different class solutions, where the model with the smallest BIC was selected as the best (Nylund et al., 2007). We also compared the entropy of the latent class solutions and other fit indices, including the Akaike Information Criterion (AIC; Akaike, 1987), the BIC and sample size adjusted BIC (Schwarz, 1978), the Lo-Mendel-Rubin (LMR) test (Lo et al., 2001), and the Bootstrapped Likelihood Ratio Test (BLRT; McLachlan, 1987). Complete data were available on all variables included in the LCA. Complete data on the covariates were also available for 1,079 patients, but data were missing for the following variables: age of onset of schizophrenia (13 individuals), disease pattern (118 individuals), disease severity (73 individuals), longitudinal disease course (79 individuals), and total number of symptoms

prior to the interview (58 individuals). Missing data were predominantly found in individuals in whom the disease course had not been long enough to categorize it with accuracy. Observations with missing data on covariates were deleted in analyses involving covariates.

In this latent class framework, C denotes a latent variable and U stands for the binary, categorical, or count observed indicator variables. Let C denote a latent categorical variable with K classes, $C_i = (c_{i1}, c_{i2}, \dots, c_{iK})$, where $c_{ik} = 1$ if individual i belongs to class k and zero if otherwise. For U , conditional independence is assumed given c_i ,

$$P(u_{i1}, u_{i2}, \dots, u_{i\tau} | c_i) = P(u_{i1} | c_i) P(u_{i2} | c_i) P(u_{i\tau} | c_i) \quad (1)$$

2.4. Wald test of mean equality for potential latent class predictors in mixture modeling

To evaluate additional potential class predictors, we included auxiliary variables in the model using the pseudo class method previously described in detail elsewhere (Clark and Muthén, 2009; Mplus Technical Appendices, 2010; Wang et al., 2005). We tested the equality of means across the latent classes using the Wald Test of Mean Equality based on draws from the posterior probabilities. The magnitude of the mean differences between the classes was interpreted as an indicator of the strength of the prediction that the auxiliary variable influenced the class membership (Asparouhouv and Muthén, 2007, 2014; Bandeen-Roche et al., 1997). After estimating the latent class model without including covariates, multiple imputation was used to derive the latent class membership variable from the posterior distribution obtained by the LCA model estimation. Then, the imputed class variables were analyzed together with the auxiliary variables using the multiple imputation technique developed by Rubin (1987). Conditional class specific means were evaluated for each auxiliary variable based on the estimated latent class model (option e in Mplus). Posterior probability-based multiple imputations with two degrees of freedom were used for the overall test and with one degree of freedom for the pair-wise tests.

3. Results

3.1. Sample characteristics

The ethnicity of the sample was Caucasian, and the majority of individuals (70%) were male (Table 1). The mean age of the sample was 42.68 years ($SD = 9.46$), and the average age of onset of schizophrenia was 21.21 years ($SD = 7.58$), indicating that most individuals in this data set had been ill for at least 20 years. Only one third of all cases with schizophrenia (31%) reported a family history of psychosis. Substance use disorders were prevalent in the sample (54%). The most commonly used substances were alcohol (43%), followed by cannabis (35%), and other illegal substances (27%). Substance use disorders preceded the onset of schizophrenia in about two-third of cases with substance use, and in about one-third of cases substance use disorders had been diagnosed after the onset of schizophrenia. Cannabis use was strongly correlated with other substance use disorders ($r(1217) = .64, p < .01$), particularly with alcohol dependence ($r(1217) = .53, p < .01$), substance dependence ($r(1217) = .41, p < .01$), and alcohol abuse ($r(1217) = .39, p < .01$) (Table 2). Dependence on illegal substances other than cannabis was also strongly correlated with alcohol

dependence ($r(1217) = .58, p < .01$). In addition, some individuals (21%) had been diagnosed with major depressive disorder (according to DSM-IV) (DEP), but DEP was negatively correlated with cannabis use ($r(1217) = -.09, p < .01$), substance dependence ($r(1217) = -.15, p < .01$), and substance abuse ($r(1217) = -.21, p < .01$).

3.2. Heterogeneity in schizophrenia with regard to substance use disorders

Based on the presence of comorbid substance use disorders and their correlations, the sample of patients with schizophrenia could be divided into three subclasses (Figure 1, Table 3 and Table 4). Latent Class 1 was characterized by low probability of substance use disorders. About half the sample (54%) belonged to this class, and about one-third (35%) was female. Individuals in this latent class had a higher probability of having been diagnosed with major depressive disorder (according to DSM-IV) in addition to schizophrenia than individuals in the other two latent classes. The average age at assessment was 45.21 years ($SE = .48$), and the average age of onset of schizophrenia was 21.43 years ($SE = .27$). Only some of the individuals in this class (9%) had been diagnosed with substance use disorders before the onset of schizophrenia. About one-third of the patients had a family history of psychosis (31%). Despite treatment, the average number of acute symptoms during a 2-day interval prior to the diagnostic interview was 4.47 ($SE = .06$). Latent Class 2 consisted of 234 individuals (19%) with a high probability of reporting abuse of alcohol and illegal substances. The majority of patients in this latent class were male (81%). The average age at interview was 38.77 years ($SE = .84$) and the average age of onset of schizophrenia was 21.04 years ($SE = .44$). The majority of patients in this latent class (72%) had been diagnosed with substance use disorders before the onset of schizophrenia, and about one-third (34%) had a family history of psychosis. The average number of acute symptoms in a 2-day interval prior to the interview was 4.27 ($SE = .12$). Latent Class 3 consisted of 325 individuals (27%). Individuals in this subclass had a high probability of reporting symptoms of dependence on alcohol and drugs; the majority of the patients (82%) were male. The average age was 41.99 years ($SE = .59$), and the average age of onset of schizophrenia was 20.78 ($SE = .43$). In the majority of these cases (65%), the onset of substance use disorders preceded the onset of schizophrenia, and less than one-third of these individuals (28%) reported a family history of psychosis. The average number of acute symptoms 2 days prior to the interview was 4.80 ($SE = .09$).

3.3. Predictors and outcomes of substance use disorders in schizophrenia

The Wald test of mean equality was used to further characterize the latent classes and to identify potential confounding latent class predictors. No significant mean differences were found between the classes with respect to age of onset of schizophrenia, family history of psychosis, and disease pattern (Table 5). We also did not detect significant differences in the chronological order of onset of substance use disorders and schizophrenia in the classes with comorbid substance use disorders. However, significant mean differences were found in gender distribution and longitudinal disease course in all comparisons involving Latent Class 1. Latent Class 1 had the highest percentage of females (35%) compared to Latent Class 2 (19%) and Latent Class 3 (18%), and also a lower percentage of individuals with severe, chronic deterioration during the disease course (51%) compared to Latent Class 3 (58%). One-third of individuals (30%) in Latent Class 1 experienced a disease course of

only moderate deterioration with some resolution of symptoms compared to only one-fourth of individuals (25%) in Latent Class 3. In comparison, Latent Class 2 had the highest percentage of individuals with only moderate deterioration over the disease course (38%) and the lowest percentage of individuals with severe chronic deterioration (42%). Latent Class 3 had the highest average number of acute symptoms during the 48 hours prior to the interview ($M = 4.80$, $SE = .09$).

4. Discussion

We have studied the relationship between substance use disorders and schizophrenia in a large sample of adult patients ascertained for genetic studies. About half of the sample had been diagnosed with comorbid substance use disorders during their lifetime, and about one-third of the sample had been dependent on alcohol and illegal substances. Our results indicate that substance dependence increased the probability of having more severe acute symptoms at the time of assessment compared to patients without comorbid substance use disorders, and substance use was also related to more severe deterioration in cognitive and social abilities over the disease course. Similar results have been previously reported, with a special focus on alcohol dependence in schizophrenia (Jones et al., 2011). Given the cross-sectional design and the retrospective recall of the data, it had not been possible in this study to determine if substance use disorders predicted the course and severity of schizophrenia, or vice versa. However, in our sample, the majority of the individuals with comorbid substance use disorders (65%) had been diagnosed before the onset of schizophrenia, suggesting that substance use disorders could have contributed to the onset of schizophrenia. In the remaining cases (35%), the onset of substance use disorders followed the onset of schizophrenia. These results suggest that the relationship between substance use disorders and schizophrenia could be bidirectional, a conclusion that has been supported by other studies (Foti et al., 2010; Leeson et al., 2012; Manrique-Garcia et al., 2014). In summary, our results indicate a negative, long-term, disease-modifying effect of substance use on the disease course of schizophrenia, despite potential short-term gain or symptom relief (Derosse et al., 2010).

It is generally understood that schizophrenia and substance use disorders have strong genetic risk factors. A family history of psychosis increases the risk of schizophrenia (Wicks et al., 2010), and a family history of substance use increases the risk of substance use disorders (Hill et al., 1994). Since substance use disorders also increase the risk of schizophrenia, it could be assumed that a family history of substance use disorders would increase the risk of schizophrenia mediated through substance use. In fact, several reports have supported this assumption (Faridi et al., 2009; Grant et al., 2011; Jones et al., 2011). However, our results indicate that a family history of schizophrenia was not related to a higher risk of substance use compared to sporadic cases in our mixed sample of familial and sporadic cases of schizophrenia. This finding might indicate that the genetic risk factors for schizophrenia and substance use disorders could be unrelated and this conclusion is also supported by other studies in the literature (López-Moreno et al., 2010).

Previous studies have reported a strong relationship between substance use and an earlier age of onset of schizophrenia (Donoghue, 2014), and also more severe symptoms of

depression (Cuffel et al., 1993; Degenhardt, 2003; Kerfoot, 2011). In our study, we could not confirm these results. In our sample, the average age of onset in the non-using patient population was 21 years, which is almost a decade earlier than the average age of onset in non-users in other studies (for example, see Donoghue et al., 2014). The discrepancy between these results could potentially be explained by demographic differences between the studies. An earlier age of onset has been associated with year of birth, season of birth, family history, residence, and gender (Albus and Maier, 1995; Alda et al., 1996; Ritsner et al., 2005; Stompe et al., 2000). Similarly, we did not confirm a relationship between major depressive disorder and substance use disorders in patients with schizophrenia, and these results are also consistent with other reports (Degenhardt, 2007; Tsai, 2013). Previous studies have identified functional impairment as the strongest predictor of depressive symptoms in older patients with schizophrenia, followed by chronic physical disorders, and social isolation (Meesters et al., 2014). Loss, shame, and longer duration of untreated psychosis with persistence of low-level residual symptoms have been associated with symptoms of depression in younger patients with schizophrenia (Upthegrove et al., 2014).

Our analysis has several limitations: (1) Reliance on self-reported data could lead to underreporting of substance use disorders. We admit that prospective studies with direct urine testing for substance use would have been ideal. However, since we focused on a clinical diagnosis of substance use disorders according to DSM-IV criteria with evidence supported by multiple sources including interview-based scales, self-rated scales, and the use of collateral sources (e.g., information from other family members and medical records), as well as ratings of the reliability of the information by at least three independent raters according to Best Estimation Procedures, we are confident that high standards of reliability of the clinical diagnosis have been met. In addition, the use of probability-based multivariate statistical methods addresses some degree of uncertainty in the classification of individual patients. (2) In our study, retrospective recall could have introduced uncertainty about disease onset, despite the utilization of several sources of information, including medical records. Prospective longitudinal studies could provide more reliable results about cause and effect. (3) Information on genetic risk was limited to data on family history of psychosis as a proxy. Direct examination of sequence data would allow a more precise evaluation of potential genetic risk factors. (4) Information about disease characteristics, disease trajectories, and symptom severity was captured as summary variables. This approach significantly reduces inter-individual variability and might have oversimplified the actual complexity of the disease course. (5) Information on family history of substance use disorders was missing. (6) Detailed information on treatment variables, such as medication and other therapeutic interventions was missing and could have contributed to the differences in disease outcome. The limitations of our study are not specific to our analysis, but are common to secondary analysis of existing data. Sequencing studies in large samples will be required to directly evaluate whether substance use disorders and schizophrenia share genetic risk factors.

In summary, our results indicate significant heterogeneity in schizophrenia with regard to genetic and environmental risk factors, as well as disease severity, disease trajectory, and disease outcome. Further work is needed to identify factors that determine inter-individual variability in schizophrenia. Our results indicate that a family history of psychosis is not

related to an increased risk of substance use disorders compared to sporadic cases. Increased knowledge about risk factors for substance use in schizophrenia could provide more precise predictions of disease course, improve treatment response and outcomes, and lead to more effective interventions.

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Highlights

- About 50% of patients with schizophrenia do not abuse drugs or alcohol
- Patients with comorbid substance use can be divided into subgroups based on severity reflected in abuse or dependence
- Alcohol and substance use disorders are highly correlated in schizophrenia.
- Comorbid substance use disorders were related to gender, symptoms severity and longitudinal disease course.
- A family history of psychosis was unrelated to the risk of developing comorbid substance use disorders in a mixed sample of sporadic and familial cases.

Figure 1.

Latent class solution for co-morbid conditions in schizophrenia.

Co-morbid conditions indicate heterogeneity in schizophrenia (SZ). Latent class analysis (LCA), also referred to as latent class mixture modeling, is a multivariate statistical approach to heterogeneity in data. The figure shows the co-morbidity profile of the three latent classes of SZ patients. Latent Class 1 (red line and ○ symbol) (54% of the sample) had a low probability of being diagnosed with a co-morbid psychiatric condition. Class 2 (green line and ▲ symbol) (27% of the sample) consisted of SZ patients with low probability of endorsing alcohol or substance dependence, but alcohol abuse, substance abuse and cannabis use were prevalent. Class 3 (blue line and □ symbol) (19% of the sample) was SZ patients with a high probability of endorsing alcohol dependence and substance dependence. The x-axis indicates the co-morbid conditions included in the LCA. The y-axis represents the probability of endorsing co-morbid conditions scaled from 0% to 100%. ALCD, alcohol dependence; SUBD, dependence on illegal substances other than cannabis; CANNAB, cannabis abuse; ALCA, alcohol abuse; SUBA, substance abuse other than cannabis; DEP, major depressive disorder (according to DSM-IV).

Table 1

Demographic characteristics of the schizophrenia (SZ) sample.

Number of individuals, N (%)	1,219 (100)
Gender, male, N (%)	857 (70)
Age at interview, mean (<i>SD</i>)	42.68 (9.46)
Age of onset of schizophrenia, mean (<i>SD</i>)	21.21 (7.58)
Ethnicity, Caucasian, N (%)	1,219 (100)
Positive family history of psychosis, N (%)	378 (31)
Individuals with	
drug and alcohol related disorders, N (%)	664 (54)
alcohol abuse, N (%)	200 (17)
alcohol dependence, N (%)	310 (26)
cannabis abuse, N (%)	422 (35)
illegal substance abuse, N (%)	161 (13)
illegal substance dependence, N (%)	169 (14)
major depressive disorder ^I , N (%)	256 (21)
drug and alcohol abuse before onset of SZ, N (%)	432 (36)
drug and alcohol abuse after onset of SZ, N (%)	232 (18)

^I according to DSM-IV

Table 2

Co-morbidity of substance use disorders

	CANNAB	ALCD	ALCA	SUBD	SUBA
CANNAB					
ALCD	.53*				
ALCA	.39*	-.61*			
SUBD	.41*	.58*	.58*		
SUBA	.64*	.18*	.44*	.05	
DEP	-.09*	-.05	-.01	-.15*	-.21*

The table gives the correlation coefficient $r(1,217)$ for substance use disorders and alcohol use disorders. Significant results at $p < .01$ are marked with *. CANNAB, cannabis use, ALCD, alcohol dependence, ALCA, alcohol abuse, SUBD, substance dependence, SUBA, substance abuse, DEP, mayor depressive disorder (according to DSM-IV).

Table 3

Fit indices for latent class solutions in schizophrenia with comorbid drug and alcohol-related conditions.

# of classes	AIC	BIC	SABIC	Entropy	LMR adjusted LRT	BLRT
1	7277.403	7308.038	7288.979	1	p< .001	p< .001
2	6847.308	6913.684	6872.390	.741	p< .001	p< .001
3	6598.868	6700.984	6637.455	.759	p< .001	p= .006
4	6597.937	6735.793	6650.030	.768	p= .02	p= .02

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; SABIC, sample size adjusted BIC; LMR, Lo-Mendel-Rubin, LRT, likelihood ratio test, BLRT, Bootstrapped Likelihood Ratio Test.

Table 4

Probability of endorsing comorbid conditions by latent class

	Latent Class 1	Latent Class 2	Latent Class 3
	<i>N</i> = 660 (54%)	<i>N</i> = 234 (19%)	<i>N</i> = 325 (27%)
Alcohol dependence	.05 (SE = .02)	.02 (SE = .03)	.83 (SE = .06)
Substance dependence	.04 (SE = .01)	.08 (SE = .03)	.37 (SE = .03)
Cannabis abuse	.03 (SE = .02)	.82 (SE = .06)	.69 (SE = .05)
Alcohol abuse	.10 (SE = .02)	.70 (SE = .07)	.02 (SE = .01)
Substance abuse	< .01 (SE = .01)	.44 (SE = .05)	.01 (SE = .01)
Major depressive disorder ^{<i>1</i>}	.23 (SE = .02)	.19 (SE = .03)	.21 (SE = .03)

The probability of endorsing indicator variables differed from class to class. Individuals in Latent Class 1 had the highest probability of endorsing symptoms of depression. Individuals in Latent Class 2 had the highest probability of endorsing illegal substance and alcohol abuse, whereas individuals in Latent Class 3 endorsed disorders of drug and alcohol dependence. The probability of endorsing cannabis abuse was high in Latent Class 2 and in Latent Class 3.

^{*1*} according to DSM-IV

Table 5

Distribution of gender, age of onset, and family history of psychosis.

	Gender		Age of Onset of Schizophrenia		Family History of Psychosis ²		Substance Use Disorder before Schizophrenia	
	Chi-Square	P value	Chi-square	P value	Chi-Square	P value	Chi-Square	P value
Overall test	25.64	<.01	1.04	.6	3.05	.22	N/A	N/A
LC1 vs. LC2	20.69	<.01	.53	.47	1.17	.28	N/A	N/A
LC1 vs. LC3	26.07	<.01	1.52	.22	.81	.37	N/A	N/A
LC2 vs. LC3	.01	.91	.17	.68	2.73	.1	1.90	.17

	Disease Pattern		Disease Severity		Disease Course		Number of Acute Symptoms	
	Chi-Square	P value	Chi-Square	P value	Chi-Square	P value	Chi-Square	P value
Overall test	.55	.76	7.61	.02	5.04	.08	13.65	<.01
LC1 vs. LC2	.13	.72	5.38	.02	3.89	.05	2.08	.15
LC1 vs. LC3	.25	.62	<.01	.99	4.18	.04	8.16	<.01
LC2 vs. LC3	.48	.49	4.02	.05	.03	.86	11.70	<.01

Table 5 gives the results of the Wald test. Posterior probability-based multiple imputations with two degrees of freedom were used for the overall test and one degree of freedom for the pairwise tests. The results indicate statistically significant differences in sex and number of acute symptoms across the latent classes. LC, Latent Class. (N = 1,219)