

Antipsychotic use and associating factors among persons with substance-induced psychosis and first-episode psychotic disorder- A nationwide register-linkage study

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ABSTRACT

Background: Antipsychotic use after first-episode psychotic disorder (FEPD) has been widely studied, but data on substance-induced psychosis (SIP) are lacking.

Objectives: To examine the prevalence and associated factors of antipsychotic use in individuals with incident SIP compared to a matched FEPD cohort.

Methods: From Swedish healthcare registers, 7320 incident SIP cases (2006–2016) were identified and matched 1:1 by age, sex, and year with FEPD cases. The point prevalence of antipsychotic use was assessed biannually from three years before to three years after the incident diagnosis. Associations between any antipsychotic use during one year post-diagnosis and sociodemographic, clinical, and work-related factors were estimated using modified Poisson regression to obtain unadjusted and age- and sex-adjusted risk ratios (RRs) with 95% CIs. This register-based analysis followed RECORD reporting standards.

Results: The point prevalence of antipsychotic use peaked six months after the first psychotic episode (23% in SIP vs 54% in FEPD) and remained approximately stable thereafter (20% vs 50% at three years). During the first year, the cumulative prevalence of any antipsychotic use was 43% in SIP and 73% in FEPD. Among SIP patients, younger age, female sex, non-European origin, and prior psychiatric comorbidity particularly anxiety, depression, ADHD, and personality disorders were the strongest correlates of antipsychotic use. Functional impairment indicators such as long-term sickness absence and disability pension were also associated with increased use. In FEPD, age, depression, autism-spectrum diagnosis, and short-term sickness absence showed similar but weaker patterns. Olanzapine was the most commonly used antipsychotic in both cohorts.

Conclusions: Despite diagnostic definitions describing SIP as transient, a substantial proportion of patients continued antipsychotic treatment beyond the acute phase. These findings emphasise that younger age, psychiatric comorbidity, and psychosocial vulnerability strongly influence prescribing decisions in SIP and highlight the need for evidence-based, subtype-specific treatment guidelines.

1. Introduction

Antipsychotic medications are pivotal in managing psychotic disorders, including schizophrenia (Keating et al., 2017; Leucht et al., 2022;

Rubio et al., 2021; Solmi et al., 2022). Recommendations concerning treatment of first-episode psychotic disorder (FEPD) emphasise early pharmacological intervention with antipsychotic medications, linking these approaches to better long-term outcomes (Keating et al., 2017;

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Leucht et al., 2022; Siskind et al., 2022; Lian et al., 2022; Solmi et al., 2022; Bécharard et al., 2024). In addition to acute phase treatment, antipsychotic use is also recommended for the maintenance phase in the pharmacological treatment of FEPD (Addington et al., 2013; Shimomura et al., 2020). This knowledge informs clinical practices, leading to targeted treatment strategies that enhance patient recovery and better functioning.

Substance-induced psychosis (SIP) represents a unique psychosis directly triggered by substance use, characterised by hallucinations, delusions and disorganised thinking. The diagnostic criteria for SIP differ significantly between the International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). While ICD-10 allows for psychotic symptoms to persist for up to six months, DSM-5 typically limits the duration to a closer temporal link, requiring symptoms to resolve within one month of substance use cessation (World Health Organisation; Lian et al., 2022). This distinction highlights a fundamental variability in the duration criteria of psychotic symptoms, which may influence the treatment strategies, particularly the use of antipsychotics (AP).

SIP is generally considered an acute and self-limiting condition that often resolves following sustained abstinence; however, symptom duration and outcome vary substantially, and a subset of individuals experience recurrent or persistent psychosis or transition to a schizophrenia-spectrum disorder despite substance cessation. This may lead to an assumption that antipsychotic use may also be restricted to the acute phase only. However, in both SIP and FEPD, symptoms varying in duration can span from short, brief episodes to long, extended episodes which last for months, which complicates the antipsychotic treatment span (Catalan et al., 2024). During the acute phase of SIP, antipsychotics are usually prescribed to manage psychotic symptoms (Chuenchom et al., 2024; Fluyau et al., 2019). Given the absence of specific treatment guidelines for SIP, clinicians often rely on FEPD management principles when initiating antipsychotics to stabilise acute symptoms, prevent harm, and monitor for transition to primary psychotic disorders. This overlap underscores the need for evidence-based recommendations tailored to SIP. Unlike the well-documented prescribing patterns with AP use for FEPD (Fusar-Poli et al., 2017; Keating et al., 2017; Rubio et al., 2021), there is a lack of empirical data on antipsychotic use among persons with incident SIP. Various psychoactive substances have been associated with the onset of psychotic episodes, though our dataset captures these only at the diagnostic category level (ICD-10 F1X.5). Substances associated with inducing psychosis, including cannabinoids, alcohol, amphetamine, cocaine, nicotine, kratom and cathinone. These substances present an average to high possibility of leading to psychotic episodes, underscoring the need for tailored interventions that encourage individuals to refrain from consumption (Fiorentini et al., 2021).

This study also emphasises the necessity of developing preventive methods rather than focusing solely on treatment for individuals with SIP. While several studies have explored the effectiveness of antipsychotics in individuals with psychotic disorders, long-term treatment outcomes remain largely underexplored (Brunette et al., 2011; Denissoff et al., 2024; Green et al., 2003; Schnell et al., 2014; Sevy et al., 2011), with only a single study addressing this aspect in depth (Denissoff et al., 2024). The existing studies revealed notable research gaps, including a limited focus on specific substances, insufficient longitudinal studies, and further investigation in these areas to enhance understanding of SIP and antipsychotic treatments (Ricci et al., 2024). Previous studies highlight significant variations in antipsychotic prescribing patterns and differences in the prevalence of use by clinical and sociodemographic factors (Harro et al., 2020; Taipale et al., 2021; Goppers et al., 2023; Lally et al., 2017; Murray et al., 2016).

Given the knowledge gap in SIP treatment, there is a pressing need to examine real-world antipsychotic use among individuals with incident SIP. This study aims to compare the prevalence of antipsychotic use between persons with SIP and FEPD, identify clinical and

sociodemographic factors associated with antipsychotic prescribing in SIP, and investigate the rate of antipsychotic use across types of SIP during the first year post-diagnosis.

2. Methods

2.1. Study population

Incident SIP cases ($n = 7320$) during 2006–2016 were identified from the Swedish National Patient Register (NPR) and matched 1:1 with persons with FEPD by age, sex, and calendar year of diagnosis.

SIP was defined as per the ICD-10 diagnostic codes F1X.5, excluding F17.5 (namely, F10.5, F11.5, F12.5, F13.5, F14.5, F15.5, F16.5, F18.5 and F19.5) (Jeyapalan et al., 2024). FEPD was defined as ICD-10 F20–F29.

This study follows the RECORD reporting recommendations for observational research using routinely collected health data.

Swedish national registers allow linkage of individual-level data through unique personal identity numbers assigned to all residents. These registers include the National Patient Register (in- and outpatient diagnoses), the Prescribed Drug Register (dispensed medications), and LISA (sociodemographic and labour market data). Linkages were performed by Statistics Sweden using pseudonymized identifiers.

2.1.1. Information on antipsychotic medication use

The Prescribed Drug Register data included all reimbursed antipsychotic drug purchases in community pharmacies in Sweden, according to the Anatomic Therapeutic Chemical (ATC) classification, i.e., N05A, excluding N05AN01 (lithium). This classification system groups drugs according to their active ingredients, based on the targeted organ or system, and their therapeutic, pharmacological, and chemical properties (Hollingworth and Kairuz, 2021).

The PRE2DUP (From Prescriptions to Drug Use Periods) method was utilised to estimate drug use periods based on dispensing data, considering individual usage patterns (Tanskanen et al., 2015). This method uses personal purchase histories and expert-defined parameters for each individual and each medication, making it more accurate and flexible than earlier models that assumed specific doses. The PRE2DUP method considers possible inpatient care periods when drug use is not recorded on the registers and drug stockpiling.

The point prevalence of outpatient antipsychotic drug use was estimated based on drug use periods calculated with the PRE2DUP method. Time points were 14-day periods, measured every six months, from 3 years before the first diagnosis until three years after the first diagnosis. Persons who were hospitalized for more than nine days during any 14-day period were excluded from the analysis at that specific time point. Persons who died, emigrated, or for whom data linkage ended before the specified time point were censored. In addition, the prevalence of antipsychotic use during the first year after diagnosis was defined.

2.2. Background information

Sociodemographic variables included age, sex, and country of origin (Sweden, other European countries, and the rest of the world). In addition, information on the family situation during the previous year, prior to the diagnosis of SIP/FEPD, was collected from the Longitudinal Register for Health Insurance and Labour Market Studies (LISA).

Previous clinical in- and outpatient diagnoses since 1996 and before the first SIP or FEPD diagnosis were defined using ICD-10 diagnosis codes from the NPR. Psychiatric conditions included any mental and behavioural disorder (F00–F99), depression (F32–F33), anxiety disorders (F40–F43), eating disorders (F50), personality disorders (F60–F69), mental retardation (F70–79), autism-spectrum disorders (ASD, F84), and Attention-deficit/hyperactivity disorder (ADHD, F90).

The Charlson comorbidity Index (CCI) quantifies the burden of somatic diseases that impact mortality risk. It independently predicts

mortality and long-term survival (Charlson et al., 1987). The analyses used the CCI as a three-class variable with 0, 1, or ≥ 2 conditions.

Work- and income-related factors were assessed during the previous calendar year before the SIP/FEPD episode. Disability pension and sickness absence were derived from Micro-data for analyses of social insurance (MiDAS) and employment-related variables from the LISA register. Unemployment during the previous year was used as a three-class variable: 1) no unemployment, 2) <180 days, and 3) ≥ 180 days. Information concerning the total duration of sickness absence during the previous year was analysed as a three-class variable: 1) no sickness absence; 2) less than 90 days; and 3) ≥ 90 days. Information concerning disability pension at the time of SIP/FEPD diagnosis was analysed as a two-class variable (yes/no).

2.3. Statistical methods

Univariate analyses were performed to estimate associations between individual characteristics and any antipsychotic use during the first year after diagnosis among persons with SIP and FEPD, respectively.

Both unadjusted and age- and sex-adjusted risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using modified Poisson regression with robust error variance.

This approach was chosen to directly estimate relative risks rather than odds ratios, which can overestimate effects when outcomes are common. Adjusted models included only age and sex as covariates.

2.4. Ethical considerations

The study was approved by the Regional Ethics Review Board of Stockholm, Sweden (decision 2007/762-31).

3. Results

The study population consisted of $N = 7320$ persons with incident SIP, with a mean age of 35.02 (SD 13.3) years, and 79.4% of them were men.

The point prevalence of antipsychotic use before the inc3 years before the first diagnosis: 3.3% in SIP, 8.1% in FEPD (Fig. 1). The prevalence peaked at six months after the first psychotic episode among

both the SIP and FEPD groups. At that time point, 23% of persons with SIP were using antipsychotics, while the respective figure among persons with FEPD was 54% (Fig. 1). Point prevalence of use at six months after diagnosis was the highest among persons with cannabis-SIP (32%), followed by multi-substance SIP (27%), amphetamine-SIP (20%), and alcohol-SIP (13%) (Supplementary Fig. 1). After three years, 20% of persons with SIP and 50% of persons with FEPD used antipsychotics.

Fig. 2 shows the prevalence of antipsychotic use and the distribution of usage of different antipsychotic agents across subtypes of SIPs and FEPD groups during the first year after diagnosis. Overall, 43.3% of persons with SIP and 72.5% of persons with FEPD used antipsychotics. Olanzapine was the most common specific antipsychotic in both groups. However, of those who used antipsychotics during the first year, persons with SIP were more likely to use olanzapine than persons with FEPD (35.4% vs. 27.0%, respectively), whereas risperidone (10.4% in FEPD vs. 6.3% in SIP) and use of multiple antipsychotics during the first year (41.8% vs. 34.9%) were more common in FEPD. Cannabis-SIP showed the highest antipsychotic treatment rate across subtypes of SIP (64.6%), followed by multi-use SIP (50.1%), amphetamine-SIP (38.4%) and alcohol-SIP (25.2%). Olanzapine was more common in cannabis-SIP (43.7%) than in other SIP types (24.3–34.7%). Quetiapine was slightly more commonly used in amphetamine-SIP (10.3%). Multiple antipsychotic use was relatively common in SIP subtypes, ranging from 24.7% among alcohol SIP to 38.3% among multi-use SIP.

Fig. 3 shows the prevalence of antipsychotic use among persons with SIP during the first year after the incident SIP episode, stratified by receiving a primary psychotic disorder diagnosis within one year of follow-up (no/yes). Within one year, of persons with cannabis-SIP, 32.2% were diagnosed with primary psychotic disorder, i.e. any ICD-10 diagnosis code F20–F29. Of them, 75.4% used antipsychotic medication during the first year compared to 59.5% among those persons with SIP who did not receive the diagnosis of primary psychotic disorder. Prevalence of antipsychotic use in persons with cannabis-SIP with a later diagnosis of primary psychotic disorder was very similar to those with FEPD (72.5%, see Fig. 2). Concerning other SIP types, 13.9% of amphetamine-SIP and 32.3% of multi-use/other SIP were diagnosed with primary psychotic disorder during the first year of follow-up. Within one year, of persons with cannabis-SIP, 32.2% were diagnosed with primary psychotic disorder. Of them, 75.4% used antipsychotic

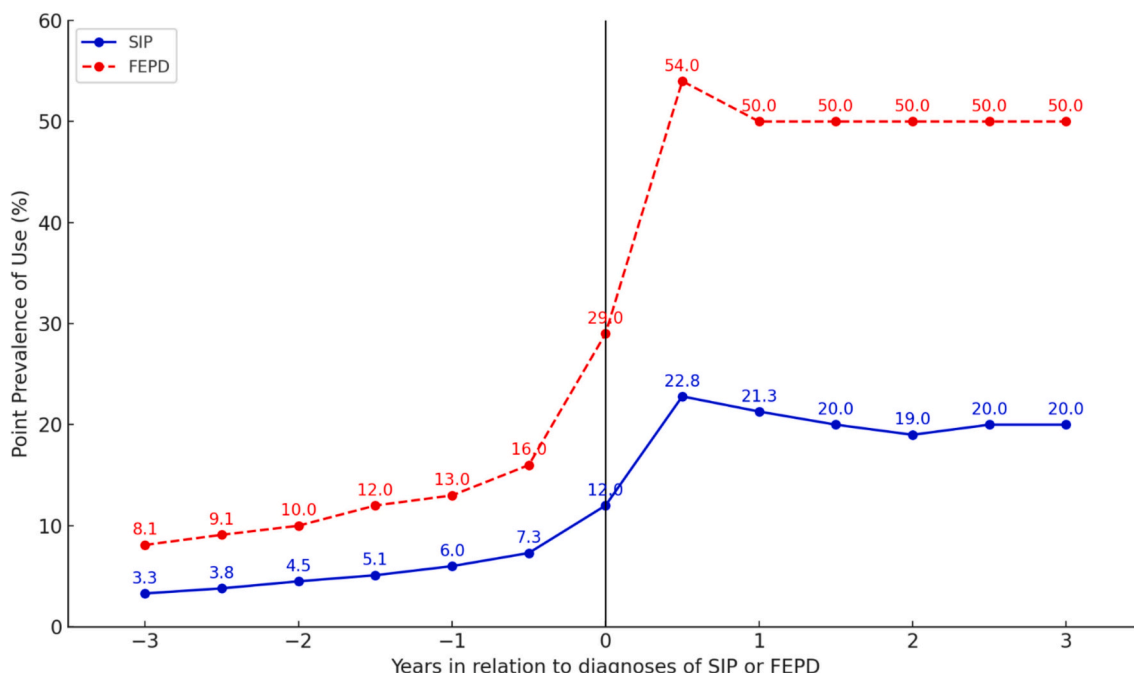


Fig. 1. The prevalence of antipsychotic use every six months from 3 years before until 3 years after the incident psychotic episode for SIP and FEPD.

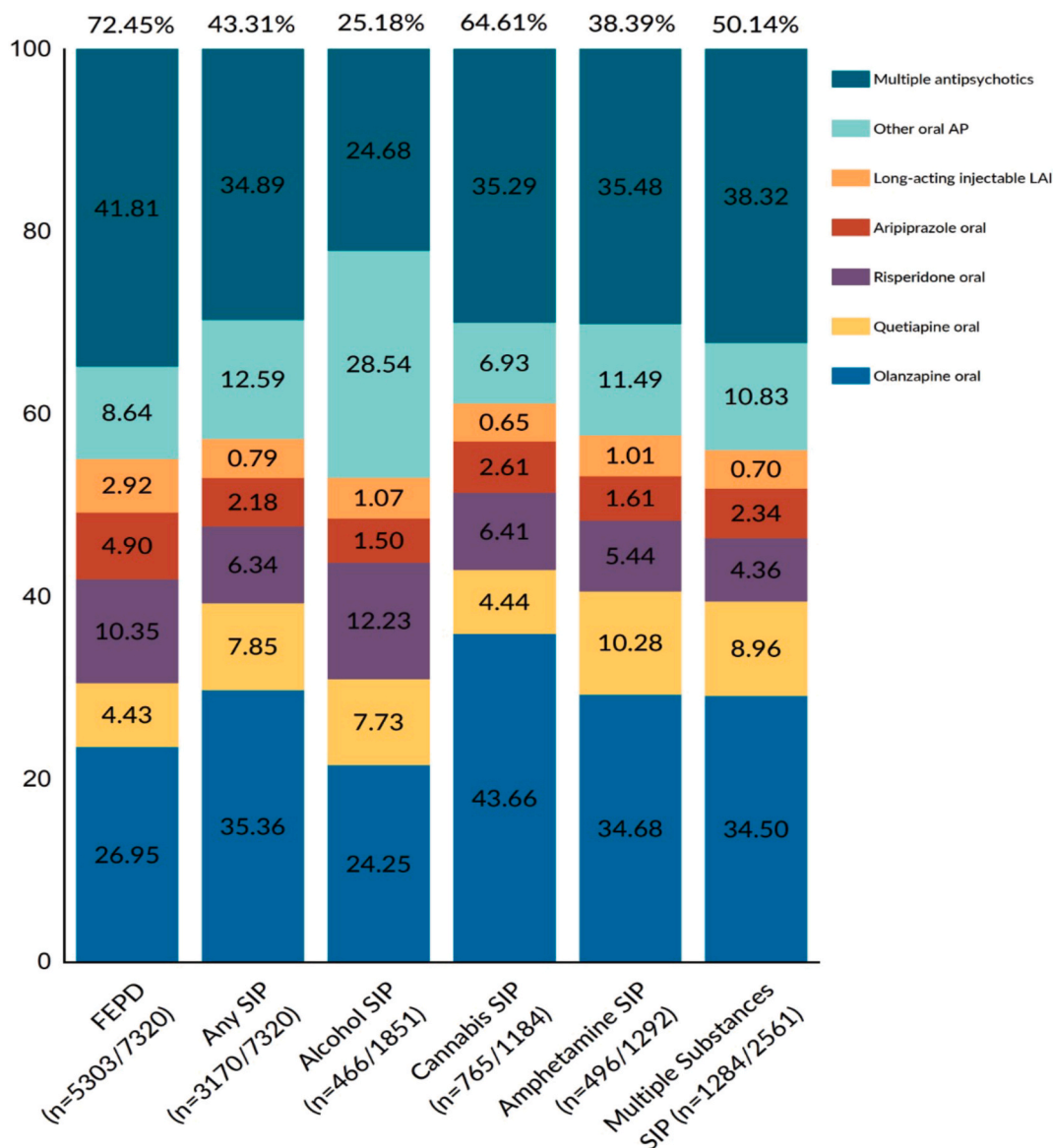


Fig. 2. Prevalence and distribution of antipsychotic use among different SIPs and any FEPD patients during the first year. Multiple antipsychotics means the use of more than one during a year.

medication during the first year compared to 59.5% among those who did not receive the diagnosis of primary psychotic disorder. Rates of antipsychotic use among those with amphetamine-SIP (69.4%) and multi-use/other SIP (75.4%) with a subsequent primary psychotic disorder diagnosis were relatively similar to FEPD (Supplement Fig. 2).

Table 1 present the sociodemographic, clinical, and work-related characteristics associated with antipsychotic use during the first year after the first psychotic episode among persons with substance-induced psychosis (SIP) and first-episode psychotic disorder (FEPD).

Across both cohorts, younger age was the strongest determinant of antipsychotic use. Among SIP patients, 55.9% of those aged 16–29 years and 32.4% of those aged 30–49 years received antipsychotics compared with only 11.7% in the 50–65-year group (age- and sex-adjusted RR = 2.00 [1.82–2.20] and 1.52 [1.38–1.68], respectively). The same trend appeared in FEPD, with younger adults showing higher treatment rates (adjusted RR = 1.09 [1.05–1.14] for 16–29 years).

Female sex was modestly associated with a greater likelihood of antipsychotic use in both groups (adjusted RR ≈ 1.08).

Regarding country of origin, SIP patients born outside Europe were more likely to use antipsychotics (14.2% vs 11.2%; RR = 1.10

[1.03–1.19]), whereas those from other European countries showed slightly lower use (RR = 0.88 [0.77–1.00]). In contrast, among FEPD, non-European origin was not associated with higher use, suggesting differing prescribing or help-seeking patterns between diagnostic groups.

Psychiatric comorbidity before the index episode was a key driver of antipsychotic treatment, particularly among SIP patients. The presence of any prior psychiatric disorder increased the likelihood of antipsychotic use (80.1%; RR = 1.26 [1.18–1.35]). Strong associations were observed for anxiety disorder (43.9%; RR = 1.36 [1.29–1.43]), depression (30.0%; RR = 1.32 [1.25–1.39]), ADHD (18.3%; RR = 1.21 [1.14–1.29]), and personality disorder (14.6%; RR = 1.30 [1.22–1.40]), with similar but weaker patterns in FEPD where depression (30.3%; RR = 1.05 [1.03–1.09]) and autism-spectrum diagnosis (6.4%; RR = 1.12 [1.07–1.17]) were significant.

Conversely, previous substance-related diagnoses predicted lower antipsychotic use in FEPD (RR = 0.94 [0.90–0.97]), whereas in SIP this factor was slightly positive (RR = 1.16 [1.09–1.22]). A history of suicide attempts increased the probability of treatment in SIP (RR = 1.07 [1.01–1.14]).

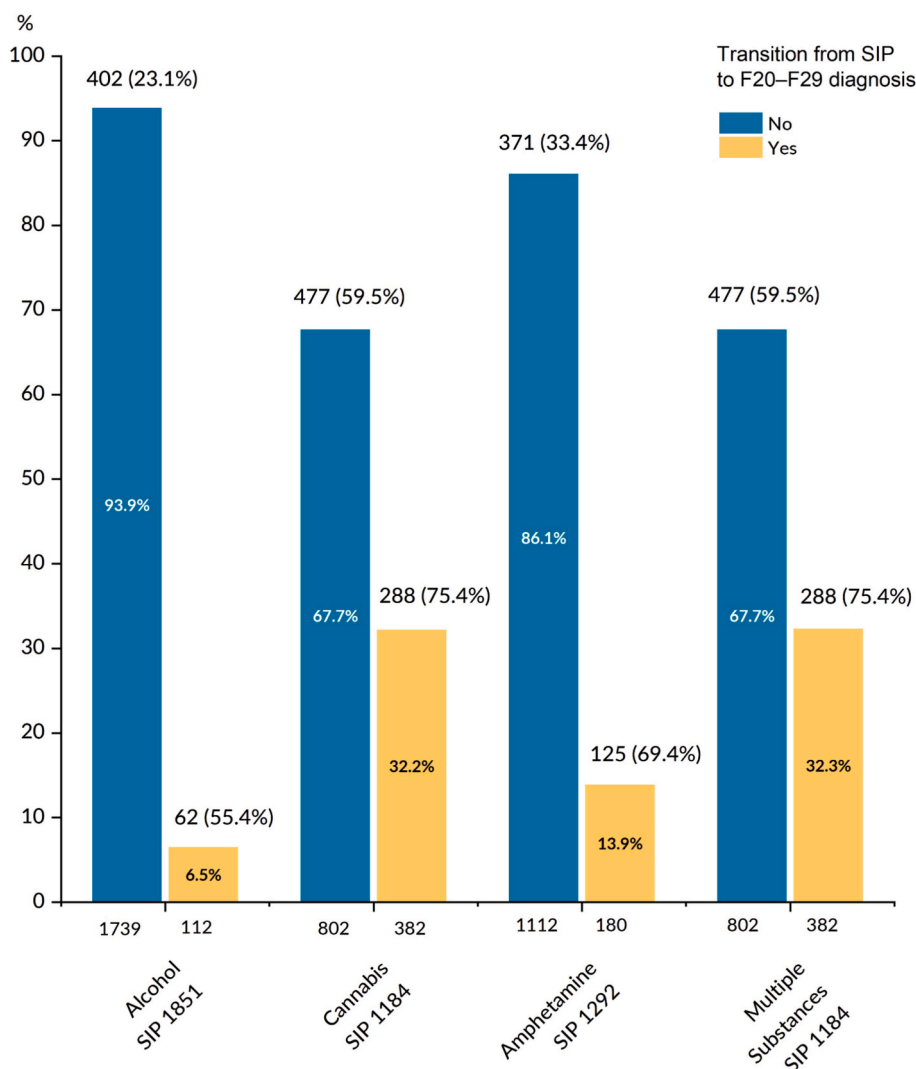


Fig. 3. Transition from SIP to primary psychotic disorder diagnosis (F20–F29 diagnosis) (yellow) versus SIP cases without transition (blue) within the first year. Prevalence of antipsychotic use during the first year (% indicated above each column) across different SIP types. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Somatic comorbidity, measured by the Charlson index, showed an inverse relationship with antipsychotic use in both groups. Individuals with one or more chronic conditions were less likely to receive antipsychotics (SIP ≥ 1 : RR = 0.88 [0.78–0.99]; FEPPD ≥ 2 : RR = 0.77 [0.66–0.91]).

Work-related indicators also differentiated treatment patterns. Long-term sickness absence (≥ 90 days) was consistently associated with antipsychotic use in both SIP (10.0%; RR = 1.28 [1.18–1.38]) and FEPPD (10.4%; RR = 1.06 [1.02–1.11]). Among SIP patients, disability pension and short-term unemployment (< 180 days) also predicted higher use (RR = 1.26 [1.17–1.35] and 1.05 [0.99–1.11], respectively). In contrast, long-term unemployment (≥ 180 days) was linked with reduced use among FEPPD (RR = 0.91 [0.85–0.98]). Individuals with recent employment were slightly less likely to use antipsychotics (SIP 26.9% vs 31.2%; RR = 0.89 [0.84–0.94]).

4. Discussion

Our study, utilising national-level register data from Sweden, is the first to provide detailed insights into the prevalence of antipsychotic use and associated factors among individuals diagnosed with incident substance-induced psychosis (SIP). Our findings indicate that, in real-world settings, a substantial proportion of individuals with SIP receive

antipsychotic prescriptions following their first psychotic episode. Our findings indicate that after their first psychotic episode, a significant portion of SIP patients receive antipsychotic treatment during their outpatient follow-up. Use of antipsychotic medication was particularly pronounced among those with cannabis-induced psychosis.

The association of antipsychotic use with younger age, female sex, and prior psychiatric diagnoses—including anxiety, depression, ADHD, and personality disorders suggests that these factors may serve as early indicators of vulnerability for developing persistent psychotic disorders. Moreover, functional and social impairment indicators, such as long-term sickness absence and disability pension, were strongly linked with antipsychotic use, reflecting clinicians' responses to more complex or unstable psychosocial situations. Identifying such risk patterns could support earlier intervention and monitoring strategies.

The results also revealed that individuals of non-European origin were more likely to receive antipsychotics in SIP but less likely in FEPPD, highlighting possible differences in clinical presentation, cultural perceptions of care, or access pathways. The observed associations between prior antipsychotic use, sickness absence, and disability welfare status before SIP or FEPPD onset may signal underlying prodromal functional impairment or the detrimental effects of substance misuse on psychosocial stability. This pattern underscores the need for comprehensive screening of substance use at all psychiatric contacts, including first

Table 1

Characteristics of antipsychotic (AP) users vs. non-users during the first year after incident psychotic episode among patients with substance-induced psychosis (SIP, n = 7320) and 1:1 matched cohort of other first-episode psychotic disorders (FEPD).

	SIP				Age- and sex adjusted risk ratio (95%CI)	FEPD				
	AP non-users N = 4150		AP users N = 3170			AP non-users N = 2017		AP users N = 5303		Age- and sex adjusted risk ratio (95%CI)
	n	%	n	%		n	%	n	%	
Age										
16–29	1583	38.1	1773	55.9	2.00 (1.82–2.20)	850	42.1	2504	47.2	1.09 (1.05–1.14)
30–49	1537	37.0	1027	32.4	1.52 (1.38–1.68)	727	36.0	1855	34.9	1.06 (1.01–1.10)
50–65	1030	24.8	370	11.7	1	440	21.8	944	17.8	1
Sex										
Male	3329	80.2	2485	78.9	1	1669	82.7	4145	78.2	1
Female	821	19.8	685	21.6	1.08 (1.01–1.14)	348	17.3	1158	21.8	1.08 (1.04–1.12)
Country of origin										
Sweden	3350	80.7	2563	80.9	1	1387	68.8	3802	71.7	1
Europe	335	8.1	156	4.9	0.88 (0.77–1.00)	98	4.6	244	4.6	0.99 (0.92–1.06)
Rest of the World	465	11.2	451	14.2	1.10 (1.03–1.19)	532	26.4	1257	23.7	0.96 (0.93–1.00)
Psychiatric morbidity										
Any psychiatric disorder	3128	75.4	2539	80.1	1.26 (1.18–1.35)	1187	58.8	3244	61.2	1.02 (0.99–1.06)
Previous substance-related diagnosis	2800	67.5	2196	69.3	1.16 (1.09–1.22)	510	25.3	1120	21.1	0.94 (0.90–0.97)
Anxiety disorder	1255	30.2	1391	43.9	1.36 (1.29–1.43)	723	35.9	1959	36.9	1.00 (0.97–1.03)
Depression	852	20.5	952	30.0	1.32 (1.25–1.39)	517	25.6	1609	30.3	1.05 (1.03–1.09)
ADHD	478	11.5	579	18.3	1.21 (1.14–1.29)	176	8.7	480	9.1	1.00 (0.95–1.05)
Personality disorder	388	9.4	464	14.6	1.30 (1.22–1.40)	257	12.7	561	10.6	0.94 (0.89–0.98)
Autism spectrum diagnosis	68	1.6	117	3.7	1.31 (1.17–1.47)	77	3.8	339	6.4	1.12 (1.07–1.17)
Suicide attempts	905	21.8	778	24.5	1.07 (1.01–1.14)	246	12.2	581	11.0	0.95 (0.91–1.00)
Charlson's comorbidity index						1808	89.6	4915	92.7	
0	3662	88.2	2944	92.9	1	154	7.64	323	6.1	1
1	389	9.4	187	6.0	0.88 (0.78–0.99)	55	2.7	65	1.2	0.94 (0.88–1.00)
≥2	99	2.4	39	1.2	0.94 (0.72–1.23)	77	3.8	339	6.4	0.77 (0.66–0.91)
Work-related factors										
Any employment during the previous year	1294	31.2	854	26.9	0.89 (0.84–0.94)	605	30.0	1674	31.6	1.02 (0.99–1.06)
Unemployment										
0 days	2927	70.5	2088	65.9	1	1488	73.8	4042	76.2	1
<180 days	932	22.5	868	27.4	1.05 (0.99–1.11)	386	19.1	976	18.4	0.97 (0.93–1.00)
≥180 days	291	7.0	214	6.8	1.01 (0.91–1.12)	143	7.1	285	5.4	0.91 (0.85–0.98)
Sickness absence										
0 days	3493	84.2	2575	81.2	1	1711	84.8	4330	81.7	1
<90 days	345	8.3	277	8.7	1.12 (1.02–1.22)	125	6.2	423	8.0	1.08 (1.03–1.13)
≥90 days	312	7.5	318	10.0	1.28 (1.18–1.38)	181	9.0	550	10.4	1.06 (1.02–1.11)
Disability pension	791	19.1	575	18.1	1.26 (1.17–1.35) ^x	528	26.2	1398	26.4	1.02 (0.99–1.06)

episode and non-psychotic presentations. Routine integration of toxicological screening and improved detection methods for emerging psychoactive substances could facilitate earlier identification of at-risk individuals and timely intervention.

Our findings indicate that, in real-world settings, a significant proportion of individuals with SIP were assessed as requiring antipsychotic treatment after the initial psychotic episode. Prevalence of antipsychotic use peaked at six months after the first psychotic episode among both the SIP and FEPD groups. Among those who transitioned from a SIP diagnosis to a primary psychotic disorder diagnosis (ICD-10 F20–F29), antipsychotic use occurred at rates comparable to those with first-episode psychotic disorder (FEPD). Despite diagnostic definitions underlining that psychotic symptoms in SIP are transient, antipsychotic use was also highly prevalent among individuals with SIP who did not transition to a psychotic disorder diagnosis. Notably, antipsychotic use cannot be fully explained by diagnostic transitions from SIP to other psychotic disorders, highlighting a potential gap between clinical practice and established diagnostic frameworks. While SIP is formally defined as a transient and substance-linked psychosis, our findings and prior longitudinal studies (Starzer et al., 2018; Rognli et al., 2023) support the view that for many individuals, SIP may represent a transitional phase toward a chronic psychotic disorder rather than a strictly reversible state. This continuum perspective underscores the clinical importance of ongoing monitoring and early intervention after a first SIP

episode, especially in cannabis- and multi-substance cases. The sustained 26% rate of antipsychotic use three years after cannabis-SIP suggests that some patients may have undiagnosed primary psychotic disorders, such as schizophrenia. In Scandinavian practice, delayed or conservative diagnostic labelling may contribute to this under-recognition (Isohanni et al., 1997), raising also concerns about the validity of register-based SIP classifications. These findings highlight the need for clinical validation to distinguish between transient SIP and emerging psychotic disorders.

Another key finding from the analysis was that psychiatric comorbidities were more consistently and strongly associated with antipsychotic use in SIP than in FEPD. This suggests that clinicians may perceive SIP patients with prior psychiatric disorders as having higher relapse or transition risk, prompting extended pharmacological treatment. In contrast, among FEPD patients, the presence of depression or autism spectrum disorder predicted higher use. In contrast, substance-related or personality disorders were associated with lower use, possibly reflecting differing treatment priorities or symptom profiles.

One interesting finding was the stability in point prevalence of antipsychotic use beyond the first-year post-diagnosis (Fig. 1). However, our analysis did not examine individual-level persistence, for instance, whether the same individuals continued use across time points. Future studies could explore such treatment trajectories to better understand long-term medication adherence and clinical decision-making.

Continuation of antipsychotic use beyond the acute phase is recommended as the first-line treatment for first-episode psychosis, with numerous studies demonstrating its benefits (Fusar-Poli et al., 2017; Van Der Gaag et al., 2013). These benefits include improved outcomes across various measures, such as preventing relapse of psychosis and premature death (Taipale et al., 2022; Tiuhonen et al., 2018). In contrast, there is no evidence-based guidelines for long-term antipsychotic use following an incident SIP episode, even though clinical practices in real-world settings seem to favour the continuation of antipsychotic medication among a significant proportion of individuals experiencing SIP.

The prevalence of antipsychotic use varied across SIP types. Previous studies have not defined clear-cut criteria of substance-induced psychosis; guidelines suggest that the choice of medication should be an individual process, potentially favouring atypical antipsychotics due to their lower risk of extrapyramidal symptoms compared to typical antipsychotics (Karimi and Pooyanmehr, 2024). Those with cannabis- and multi-use-SIP demonstrated the highest prevalence of antipsychotic use, and this was evident regardless of whether they transitioned to a primary psychotic disorder diagnosis. These two groups tend to exhibit the highest rates of antipsychotic use, possibly due to the severity, persistence, and recurrence of psychotic symptoms in these populations evaluated by clinicians prescribing antipsychotic medication. Thus, this may reflect a greater clinically assessed need for treatment or efforts to prevent psychosis relapse among those with cannabis- and multi-use-related psychotic episodes. As assumed, clinicians might prescribe more antipsychotic treatments as a preventive measure, although there are yet no evidence-based guidelines to support this practice (Alsuhaibani et al., 2021).

Previous research has reported high transition rates to schizophrenia among individuals with cannabis-induced psychosis (Murrie et al., 2020, Kendler et al., 2019, Rognli et al., 2023). Also, in our recent studies, we have found high psychosis relapse rates (Ellilä et al., 2025; Mustonen et al., 2025). Concerning SIP relapses, the highest relapse rates were observed for those with cannabis-induced psychosis (Ellilä et al., 2025). Although clinicians may initially diagnose these cases as brief psychotic episodes triggered by cannabis use, their clinical features may more closely resemble primary psychotic disorders such as schizophrenia (Yeisen et al., 2017). Multi-SIP individuals use various substances that may impact brain function differently (Unterrainer et al., 2019), leading to more frequent psychotic episodes (Ellilä et al., 2025) and might have a continued need for ongoing medication, which leads to high personal antipsychotic use.

In contrast, individuals with amphetamine- or alcohol-related SIP exhibited lower rates of antipsychotic use, which could indicate a reduced perceived clinical need for treatment or challenges with adherence to medication regimens. The observed associations between functional impairment markers (sickness absence and disability pension) and antipsychotic use suggest that social and occupational instability may influence treatment continuation decisions, potentially reflecting attempts to stabilise functioning rather than purely manage psychotic symptoms. Our findings underscore the importance of tailoring antipsychotic treatment to specific SIP subtypes and highlight the need for subtype-specific evidence on the safety and effectiveness of continued antipsychotic use, as well as pharmacological guidelines to optimise treatment outcomes across the spectrum of SIP presentations.

Of the background factors, among persons with SIP, younger individuals were more likely to use antipsychotics, and higher rates were also shown in persons born outside of Europe compared to Swedish-born persons. On the other hand, in FEPD, persons born outside Europe showed a lower prevalence of antipsychotic use. Our results show these differences may, however, also be related to differences in the substances used, with alcohol use and alcohol-SIP being more prevalent in those born in Europe. The updated analysis reinforces these demographic contrasts and highlights the importance of culturally sensitive care pathways for immigrant populations.

Unemployment and long-term sickness absence were additional

factors associated with antipsychotic use in SIP patients. This finding aligns with broader psychiatric literature that suggests socioeconomic stressors significantly impact treatment adherence and outcomes (Sendt et al., 2015; Rubio et al., 2021).

Notably, the prevalence of multiple antipsychotic use was high across SIP and FEPD cohorts. This may reflect treatment of partial response, comorbid substance use, or transitions between medications. Given known risks such as metabolic burden and interaction effects, this finding underscores the need for further study on the rationale and safety of polypharmacy in SIP management.

To understand clinical practices in terms of antipsychotic medication use during outpatient treatment for first psychotic episodes, we compared antipsychotic use in SIP to that in FEPD. Oral olanzapine was the most commonly used antipsychotic in both populations, consistent with previous Swedish pharmacoepidemiologic studies (Denissoff et al., 2024; Mustonen et al., 2025). Although olanzapine is widely prescribed in Sweden, national and international guidelines do not list it as a preferred first-line treatment due to its metabolic adverse effects. Its high prevalence in our cohort may reflect clinical familiarity, perceived efficacy in cannabis-related psychoses, or differences in tolerability profiles compared to other antipsychotics. Notably, olanzapine use was highest among individuals with cannabis-induced psychosis, covering nearly half of those receiving any antipsychotic treatment. While some evidence supports olanzapine use in cannabis-induced psychosis (De Hert et al., 2011, Mustonen et al., 2025). Its preference warrants further investigation, particularly given concerns about metabolic side effects in long-term use (Zapata et al., 2022).

Future research could further benefit from stratifying first-episode psychotic disorder (FEPD) cases by the presence or absence of comorbid substance use disorder to determine whether antipsychotic treatment patterns, relapse rates, and functional outcomes differ between ‘pure’ and comorbid psychosis cases. Such analyses could help clarify whether substance misuse drives treatment continuation or reflects broader illness severity.

Our findings highlight that substance misuse comorbidity profoundly influences morbidity, functional impairment, and clinical trajectories in psychiatry, reinforcing the necessity for systematic substance-use screening in early-psychosis services.

5. Strengths and limitations

Our study draws strength from the use of comprehensive national registry data, which provides data on antipsychotic medication use among persons with SIP and FEPD. The substantial sample size was sufficiently large to enable a detailed comparison of antipsychotic medication use across different SIP subtypes, providing insights that can inform clinical practice and health policy. Additionally, the validated PRE2DUP method was utilised to construct drug use periods, which provided antipsychotic medication use for various substance use individual variability. In addition, the study design, a matched control design, allowed us to compare antipsychotic use over an extended period, which enabled us to strengthen our observation of the association with clinical factors and sociodemographic confounders.

An additional strength of this analysis is the inclusion of functional and social variables (sickness absence, unemployment, and disability pension), which provided new insights into the interplay between psychosocial functioning and treatment use after psychosis onset. This represents one of the few studies to integrate employment-related data with psychiatric treatment patterns in both SIP and FEPD cohorts.

However, several limitations should be considered when interpreting the findings. The research did not capture the severity of psychotic symptoms, onset, or recurrence over the follow-up period, which may influence the treatment trajectories. The registry does not provide details on whether the person continued or ceased substance use, which, with SIP, may also develop chronic psychotic symptoms after this observation window. We do not have information on the continuation of

substance use.

The registers did not enable detailed separation of less prevalent substance-induced psychoses such as those associated with hallucinogens or novel psychedelics. Consequently, specific conclusions regarding these substances cannot be drawn, representing a limitation given the growing clinical and research interest in their psychotogenic potential.

Another limitation is that the registers lack information on symptom profiles, including negative or cognitive symptoms, which are increasingly recognized as important predictors of long-term outcomes. Prior work suggests that substances such as cannabis and nicotine may exacerbate or mask negative symptomatology in schizophrenia spectrum disorders (Sabe et al., 2020). Future clinical studies integrating symptom-level assessments could clarify how such features relate to treatment continuation and transition risk.

Another limitation concerns the interpretation of prior antipsychotic use, sickness absence, and disability-benefit status observed before the SIP or FEPD episode. These variables may represent both the functional impact of substance misuse and prodromal impairment preceding psychosis. This ambiguity warrants further longitudinal and clinical studies combining register data with detailed assessments of functioning and substance use.

Despite these limitations, our study provides valuable insight and evidence into antipsychotic medication use among different SIP subgroups. It will be key to future research, combining register data with clinical assessments and follow-up of substance use subgroups to refine treatment guidelines.

6. Conclusions

Although substance-induced psychosis (SIP) is regarded as a short-lived psychotic episode according to diagnostic systems, a significant proportion of patients in real-world settings continue using antipsychotic medication beyond the acute phase. Our updated analyses show that younger age, female sex, non-European origin, and the presence of prior psychiatric comorbidities especially anxiety, depression, ADHD, and personality disorders were the strongest correlates of antipsychotic use during the first year after SIP onset. In addition, functional impairment markers such as long-term sickness absence and disability pension were strongly associated with antipsychotic treatment, underscoring the complex interplay between psychosocial disadvantage and clinical severity in treatment decisions.

In comparison, among individuals with FEPD, the associations with age, depression, and autism spectrum diagnosis were weaker but followed similar patterns. These contrasts indicate that treatment decisions in SIP may reflect both the acute symptom burden and the clinician's perception of relapse or transition risk.

Our findings indicate that antipsychotic use is particularly prevalent among individuals with cannabis-induced psychosis, highlighting an area that warrants further investigation. The persistence of antipsychotic use despite the transient diagnostic definition of SIP suggests that a substantial subgroup may represent early or misclassified primary psychoses, or clinically complex cases with significant psychiatric and functional comorbidity.

Future studies should triangulate registry-based data with clinical assessments to clarify whether prolonged antipsychotic use in SIP reflects diagnostic uncertainty, relapse prevention, or adherence to evolving clinical practice. Mixed-method designs combining quantitative prescription data and qualitative clinician perspectives could provide deeper insights into treatment rationales.

In the absence of established treatment guidelines for SIP, our findings emphasise the need for evidence-based, subtype-specific, and functionally informed guidelines for SIP management, drawing on frameworks established for first-episode psychotic disorders (FEPD). Future research should focus on evaluating long-term outcomes of antipsychotic use across SIP subtypes to optimise care and refine diagnostic accuracy.

CRedit authorship contribution statement

Jeyaniroshan Jeyapalan: Writing – review & editing, Writing – original draft, Visualization, Validation, Conceptualization. **Heidi Taipale:** Validation, Supervision, Methodology, Formal analysis, Data curation. **Antti Tanskanen:** Data curation. **Jari Tiihonen:** Data curation. **Ellenor Mittendorfer-Rutz:** Data curation. **Solja Niemelä:** Visualization, Validation, Supervision, Project administration, Investigation, Data curation.

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Declaration of competing interest

Drs Taipale, Tanskanen, Tiihonen, and Mittendorfer-Rutz reported participating in research projects funded by grants from Janssen-Cilag to their employing institution outside the submitted work. In addition, Dr. Taipale reported receiving personal fees from Gedeon Richter, Janssen, Lundbeck, and Otsuka. Dr. Tiihonen reports personal fees outside the submitted work from Healthcare Global Village, HLS Therapeutics, Janssen, Lundbeck, Orion Pharma, Otsuka, Teva, and WebMD Global.

Dr. Niemelä reports receiving personal fees from DNE Pharma, Lundbeck, Otsuka, Recordati, and Takeda outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2026.01.003>.

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