

# Associations between antipsychotic use, substance use and relapse risk in patients with schizophrenia: real-world evidence from two national cohorts

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## Background

Research on the effectiveness of pharmacotherapies for schizophrenia and comorbid substance use disorder (SUD) is very sparse, and non-existent on the prevention of the development of SUDs in patients with schizophrenia.

## Aims

To compare the real-world effectiveness of antipsychotics in schizophrenia in decreasing risk of developing an initial SUD, and psychiatric hospital admission and SUD-related hospital admission among patients with an SUD.

## Method

Two independent national cohorts including all persons diagnosed with schizophrenia ( $N = 45\,476$ ) were followed up for 22 (Finland: 1996–2017) and 11 (Sweden: 2006–2016) years. Risk of developing an SUD was calculated with between-individual models, and risks of psychiatric and SUD-related hospital admission were calculated with within-individual models, using Cox regression and adjusted hazard ratios (aHRs) for using versus not using certain antipsychotics.

## Results

For patients with schizophrenia without an SUD, clozapine use (Finland: aHR 0.20, 95% CI 0.16–0.24,  $P < 0.001$ ; Sweden: aHR 0.35, 95% CI 0.24–0.50,  $P < 0.001$ ) was associated with lowest risk

of developing an initial SUD in both countries. Antipsychotic polytherapy was associated with second lowest risk (aHR 0.54, 95% CI 0.44–0.66) in Sweden, and third lowest risk (aHR 0.47, 95% CI 0.42–0.53) in Finland. Risk of relapse (psychiatric hospital admission and SUD-related hospital admission) were lowest for clozapine, antipsychotic polytherapy and long-acting injectables in both countries. Results were consistent across both countries.

## Conclusions

Clozapine and antipsychotic polytherapy are most strongly associated with reduced risk of developing SUDs among patients with schizophrenia, and with lower relapse rates among patients with both diagnoses.

## Keywords

Antipsychotics; schizophrenia; substance use; clozapine; polypharmacy.

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Schizophrenia is a common mental disorder<sup>1</sup> that accounts for a tremendous healthcare burden,<sup>2</sup> and is frequently comorbid with substance use disorders (SUDs).<sup>3</sup> Substance use not only increases the risk of developing psychotic symptoms, but also negatively affects the course of illness.<sup>4,5</sup> Possible consequences of comorbid substance use include worsening of psychotic symptoms, treatment non-adherence, pharmacodynamic interactions with prescribed agents, increased risk of medical comorbidities, increased violence (both as offenders and victims) and suicides.<sup>5–7</sup> Patients with schizophrenia and comorbid SUD also show increased service utilisation (e.g. emergency room visits, hospital admissions) and premature mortality.<sup>5–7</sup> Although schizophrenia and SUDs are associated with premature death, their comorbidity shows additive effects on mortality. Generally, patients with co-occurring schizophrenia and SUD are considered relatively challenging to treat because of severe positive symptoms, more frequent relapses and frequently observed medication non-adherence.<sup>8</sup>

To our knowledge, the European First Episode Schizophrenia Trial (EUFEST) and Clinical Intervention Trial of Antipsychotics Effectiveness (CATIE) are the largest clinical trials that have investigated SUD subgroup differences in treatment response for patients with schizophrenia. In EUFEST, SUDs were not associated with

outcome,<sup>9</sup> whereas in CATIE, patients with moderate substance use showed relatively poor response to antipsychotics.<sup>10</sup> Similarly inconsistent results have been found in several small-scale studies, including small randomised clinical trials, case reports and small observational studies.<sup>11–14</sup> Although researchers and clinicians have suggested that atypical antipsychotics and, in some cases, clozapine should be preferred for patients with comorbid schizophrenia and SUD,<sup>15</sup> to date there is little evidence to inform prescribing guidelines.<sup>16,17</sup> In a recent systematic review, authors cautioned against the use of conventional long-acting injectables (LAIs) in this patient group because of the risk of increased drug craving, although the authors note that evidence on the use of LAIs in this patient group is still very scarce.<sup>18</sup> Since then, at least one study with a follow-up of 1 year has investigated the effectiveness of atypical LAIs in this patient group and found favourable effects on quality of life, general functioning (as evaluated with Clinical Global Impression rating scales) and substance craving.<sup>19</sup> Patients with schizophrenia and comorbid SUD have also been shown to have more extrapyramidal symptoms than patients without an SUD,<sup>20</sup> which would then favour clozapine treatment, as clozapine may decrease the risk and severity of extrapyramidal symptoms. Finally, a recent meta-analysis noted important limitations to the current evidence for the use of antipsychotics in schizophrenia and comorbid SUD, highlighting the need for large-scale, good-quality studies into this topic.<sup>15</sup>

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In summary, research on the effectiveness of pharmacotherapies for schizophrenia and comorbid SUD is very sparse, and more importantly, non-existent on the prevention of the development of SUDs in patients with schizophrenia. Therefore, we studied which antipsychotics are associated with the lowest risk of the initial onset of SUD in schizophrenia, and the most effective treatments for preventing relapses in schizophrenia and comorbid SUD. To that end, we collected cohorts totalling more than 45 000 patients with schizophrenia, from two independent national registries.

## Method

### Study cohorts

We had access to two nationwide cohorts of persons with schizophrenia from Finnish and Swedish national registries, and refer to them as the Finnish and the Swedish cohorts throughout this paper. The Finnish cohort included all persons treated for schizophrenia (ICD-10 codes F20 and F25<sup>21</sup> and ICD-8 and -9 code 295) in in-patient care during 1972–2014 in Finland, who entered the cohort at age <46 years. The cohort was identified from the Hospital Discharge Register (HDR) maintained by the National Institute of Health and Welfare. Data were collected from the HDR (all hospital care periods with diagnoses, 1972–2017), Prescription Register (reimbursed prescription drug purchases, 1995–2017) and Causes of Death Register from Statistics Finland (1972–2017). The follow-up period started on 1 January 1996 for persons diagnosed before that, and at the first discharge from in-patient care for persons diagnosed during 1996–2014. The follow-up period ended at death or 31 December 2017, whichever occurred first. This Finnish cohort included 30 860 persons with schizophrenia.

The Swedish cohort included all persons with schizophrenia diagnoses (ICD-10 codes F20 and F25) and registered schizophrenia treatment contact between 1 July 2006 until 31 December 2013 in Sweden, who entered the cohort at age <46 years. Schizophrenia diagnoses were derived from the National Patient Register (maintained by the National Board of Health and Welfare, in-patient and specialised out-patient care) and the MiDAS Register (disability pensions and sickness absence, maintained by the Swedish Social Insurance Agency). Data were collected from the National Patient Register (all hospital care periods and specialised out-patient visits with diagnoses, July 2005 to December 2016), the Prescribed Drug Register (maintained by the National Board of Health and Welfare, prescription drug purchases July 2005 to December 2016), the Causes of Death Register (maintained by the National Board of Health and Welfare, causes of death 2006–2016) and the LISA register (maintained by Statistics Sweden, demographic characteristics). The follow-up period started on 1 July 2006 for persons diagnosed before that, and at the first recorded diagnoses for persons diagnosed during July 2006 to December 2013. The follow-up period ended at death or 31 December 2016, whichever occurred first. The Swedish cohort included 14 616 persons. The cohort and methods have been described previously.<sup>22</sup>

The main differences between the cohorts are the shorter follow-up time for the Swedish cohort (11 v. 22 years, i.e. years 2006–2016 for the Swedish cohort and years 1996–2017 for the Finnish cohort) and the Finnish cohort only including individuals with a history of hospital admission owing to schizophrenia (the Swedish cohort also included patients identified using diagnoses obtained from disability pensions, sickness absences and specialised out-patient care contacts). The age limit for inclusion was set at <46 years to reduce both risk of survival bias and the number of iatrogenic SUDs arising from benzodiazepine and opioid prescriptions

(e.g. for patients undergoing major surgery or starting to suffer from geriatric sleep disorders).

The Regional Ethics Board of Stockholm approved this research project (decision number 2007/762–31). Permissions were also granted by pertinent institutional authorities at the Finnish National Institute for Health and Welfare (permission number THL/847/5.05.00/2015), the Social Insurance Institution of Finland (permission number 65/522/2015) and Statistics Finland (permission number TK53-1042-15). The study was registry-based and no contact was made with the participants of the study; therefore, according to legislation in both countries and as per our previous publications, obtaining informed consent from participants was not required.

### Substance misuse

SUDs were defined as ICD-10 diagnoses F10–F19 excluding F17 (nicotine abuse), utilising both in-patient and specialised out-patient care registers. F17 (nicotine abuse) was excluded because it is very severely underreported in the registries, and including it would have led to serious skewing of the data. SUD was defined categorically: a person was considered as not having an SUD until the first recorded diagnoses, and having an SUD after the first recording. Some persons already had an SUD at cohort entry, whereas some persons were transferred from a 'non-SUD' to SUD group during follow-up. In the Finnish cohort, the non-SUD group included 22 750 persons and the SUD group included 8642 persons (2853 new onsets of an SUD) during follow-up. In the Swedish cohort, there were 10 102 persons in the non-SUD group and 4836 persons in the SUD group (1043 new onsets of SUD) during follow-up. The group compositions are shown in Supplementary Figure 1 available at <https://doi.org/10.1192/bjp.2022.117>.

### Exposure

Antipsychotics were defined as Anatomical Therapeutic Chemical classification codes N05A (lithium N05AN01 excluded), and further categorised into oral versus LAIs according to their drug formulation (oral antipsychotics referred to in the text if not explicitly stated as 'LAI'). Polytherapy refers to the concomitant use of two or more antipsychotics. Antipsychotics were categorised as aripiprazole, clozapine, olanzapine, quetiapine, risperidone, other oral, any LAI or antipsychotic polytherapy. Drug purchases recorded in the register data were modelled into drug use periods with the PRE2DUP method.<sup>23</sup> The method estimates drug use on a day-by-day basis and is based on the calculation of sliding averages of the daily dose in defined daily dosages according to individual drug use patterns, and it takes time periods of hospital care into account (when drugs are provided by the caring unit and not recorded in the registers). All exposures were defined time dependently, i.e. they are updated every time anything changes. Time-dependent or time-varying exposure means that changes in medication use versus non-use and changes in the medication regimen were followed up and updated in the models. For each time interval, medication treatments were categorised as currently ongoing or not.

### Outcomes

Outcomes were onset of SUD (diagnosed either in in-patient or specialised out-patient care settings) for patients with schizophrenia but no history of SUD (ICD-10 codes F10–F19, excluding F17); and psychiatric hospital admission (ICD-10 codes F20–F29) and SUD-related hospital admission (ICD-10 codes F10–F19, excluding F17) for patients with schizophrenia and comorbid SUD. Hospital admissions were used as a proxy for relapse.

## Overview of statistical analyses

All statistical analyses were conducted independently in the Finnish and Swedish cohorts, using SAS for Windows version 9.4. Further details on the analysis models are given and pictured in the Supplementary Methods (Supplementary Figs 1 and 2). Results are presented as adjusted hazard ratios (aHRs) with 95% confidence intervals. The *P*-values for the analyses were corrected for multiple comparisons on a per-graph basis, using the Benjamini–Hochberg false discovery rate correction with a 0.05 threshold for statistical significance. Correlations between the countries for outcome measures for the different antipsychotic exposures used were calculated with Pearson's correlation (statistical significance threshold:  $P < 0.05$ ; R Statistical Software version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria, <https://www.r-project.org/>).

## Statistical analyses to compute risk of initial development of an SUD in patients with schizophrenia (between-individuals model)

Traditional multivariate-adjusted Cox regression models were used for analyses of the outcome development of initial SUD. This means that individuals undergoing certain exposures (receiving clozapine) were compared with individuals not undergoing this exposure (not receiving clozapine). This analysis may be affected by bias arising from permanent or long-term individual characteristics if the exposure groups differ with regards to these characteristics (e.g. if patients prescribed clozapine are more often male than those who are not prescribed clozapine, this may cause gender-based bias). To reduce risk of such bias, the analyses were therefore adjusted for gender, age at cohort entry, number of previous hospital admissions owing to psychosis, time since first schizophrenia diagnosis, continuously updated variables for current versus no use of medications (lipid-modifying agents, opioid analgesics, non-opioid analgesics, anticholinergic anti-Parkinson drugs, prior use of LAI) and continuously updated variables for the following diagnoses: cardiovascular disease, diabetes, asthma/chronic obstructive pulmonary disease, previous cancer or previous suicide attempt.

## Statistical analyses to compute risk of hospital admission in patients with schizophrenia and comorbid SUD (within-individual model)

Among persons with schizophrenia and comorbid SUD, the outcomes psychiatric hospital admission and SUD-related hospital admission were analysed as recurrent events (i.e. events that may happen multiple times for the same person) and analyses were conducted with within-individual design, using stratified Cox regression.<sup>22</sup> This means that individuals are compared against themselves when undergoing different exposures, and can contribute to data sets of different exposures if they switched their medication regimens during follow-up (e.g. using oral olanzapine for the first 10 months, then 5 months using no medication, then 3 months using clozapine followed by 2 years of polytherapy with clozapine and aripiprazole). The risks derived from these comparisons within individuals are then pooled for each exposure. Since an individual is compared against themselves, this analysis method eliminates bias from permanent or long-term characteristics. However, only persons having an outcome event can contribute to within-individual analyses, which leads to a lower number of individuals in the analyses than in between-individual comparisons. The analyses were adjusted for time-varying covariates, which were sequential order of treatments use of antidepressants, use of benzodiazepines or Z-drugs, use of mood stabilisers and lithium, and time since cohort entry. For analyses on psychiatric hospital admission, the most common (five or ten, depending on analysis) specific

antipsychotics were included, in addition to polytherapy, and the rest were grouped as 'other (first/second generation) orals'. Sensitivity analyses were conducted and are outlined in more detail in the Supplementary Methods.

## Results

### Descriptive statistics

In the Finnish cohort, a total of 30 860 persons with schizophrenia were included, of whom 8110 (26%) had a diagnosis of SUD (SUD group: mean age 32.9, s.d. 7.8 years, 71.9% men; non-SUD group: mean age 33.8, s.d. 7.8 years, 52.5% men). The Swedish cohort ( $n = 14\ 616$ ) followed a similar pattern, although the prevalence of SUD was slightly higher (31%,  $n = 4514$ ) and they were slightly older (SUD group: mean age 34.3, s.d. 7.6, 70.4% men; non-SUD group: mean age 35.2, s.d. 7.4, 58.2% men) than in the Finnish cohort. A flowchart of the study cohorts and groups is shown in Supplementary Figure 1. Persons without an SUD had a slightly higher proportion of their out-patient time spent on antipsychotics (80.3% in the Finnish cohort, 78.7% in the Swedish cohort) than persons with an SUD (75.7% in the Finnish cohort, 73.3% in the Swedish cohort).

### Risk of developing an initial SUD

During follow-up (Finnish cohort: median 18.2 years, interquartile range (IQR) 10.0–22.0; Swedish cohort: 9.9 years, IQR 6.7–10.5), 2853 out of 25 603 (11.1%) patients in the Finnish non-SUD cohort and 1043 out of 11 145 (9.4%) patients in the Swedish non-SUD cohort were diagnosed with their first SUD (Table 1), and time to developing an SUD is described in Supplementary Figure 3. Persons who developed an SUD were more likely to be men, younger and have previous suicide attempts than those who did not develop an SUD (Table 1). In the Swedish cohort (where information was available), the proportion on disability pension was similar (57.1% SUD, 58.2% non-SUD). Among persons without SUD, use of clozapine was associated with the lowest risk of developing an initial SUD in both countries (Finland: aHR 0.20, 95% CI 0.16–0.24; Sweden: aHR 0.35, 95% CI 0.24–0.50). In both countries, use of aripiprazole (Finland: aHR 0.36, 95% CI 0.24–0.55; Sweden: aHR 0.70, 95% CI 0.51–0.95), antipsychotic polytherapy (Finland: aHR 0.47, 95% CI 0.42–0.53; Sweden: aHR 0.54, 95% CI 0.44–0.66), olanzapine (Finland: aHR 0.49, 95% CI 0.42–0.57; Sweden: aHR 0.67 (0.53–0.84) and any LAI (Finland: aHR 0.62, 95% CI 0.51–0.75; Sweden: aHR 0.70, 95% CI 0.52–0.93) were also associated with lower risk of developing an initial SUD, whereas risperidone, quetiapine and other oral antipsychotics showed associations with reduced risk in the Finnish, but not the Swedish cohort (Fig. 1). Of all of the specific monotherapies, use of quetiapine was associated with the highest SUD risk. The results were highly consistent between the two countries (Pearson's  $r = 0.87$ ,  $P = 0.005$ ; Fig. 2(a)). Clozapine use was also associated with the lowest risk of development of an initial SUD when compared head-to-head with the most common antipsychotic, olanzapine, in the Finnish cohort (aHR 0.30, 95% CI 0.20–0.44) and the Swedish cohort (aHR 0.34, 95% CI 0.12–0.92; Supplementary Fig. 4). In this comparison analysis, clozapine and polytherapy were the only treatments consistently outperforming olanzapine across both countries (Supplementary Fig. 4).

All sensitivity analyses confirmed the main results (Supplementary Figs 5–7). The numbers of events and person-years in each treatment category are shown in Supplementary Table 1.

**Table 1** Baseline characteristics of persons without comorbid substance use disorder at the start of follow-up who did or did not develop substance use disorder during follow-up, for both cohorts of patients with schizophrenia

	Finnish cohort			Swedish cohort		
	No SUD, <i>n</i> = 22750	SUD, <i>n</i> = 2853	<i>P</i> -value	No SUD, <i>n</i> = 10102	SUD, <i>n</i> = 1043	<i>P</i> -value
Male gender, % ( <i>n</i> )	52.5 (11 936)	63.0 (1796)	<0.0001	58.2 (5880)	64.0 (667)	0.0030
Mean age (s.d.), years	34.3 (7.8)	32.5 (7.9)		35.2 (7.4)	32.7 (8.2)	
Number of previous psychiatric hospital admissions, % ( <i>n</i> )			0.0003			0.0052
1	28.0 (6380)	30.9 (882)		41.8 (4218)	46.8 (488)	
2–3	32.5 (7394)	33.2 (948)		22.2 (2243)	21.3 (222)	
>3	39.5 (8976)	35.9 (1023)		36.0 (3641)	31.9 (333)	
Time since first schizophrenia diagnoses, years ( <i>n</i> )			<0.0001			<0.0001
≤1	42.8 (9748)	52.3 (1492)		34.3 (3464)	43.8 (457)	
>1–5	12.2 (2774)	13.2 (376)		16.8 (1700)	19.7 (205)	
>5	45.0 (10 228)	34.5 (985)		48.9 (4938)	36.5 (381)	
Previous suicide attempt, % ( <i>n</i> )	8.4 (1915)	11.3 (323)	<0.0001	6.1 (620)	9.7 (101)	<0.0001
On disability pension at baseline, % ( <i>n</i> )	Not applicable	Not applicable		58.2 (5881)	57.1 (595)	0.4662

SUD, substance use disorder.

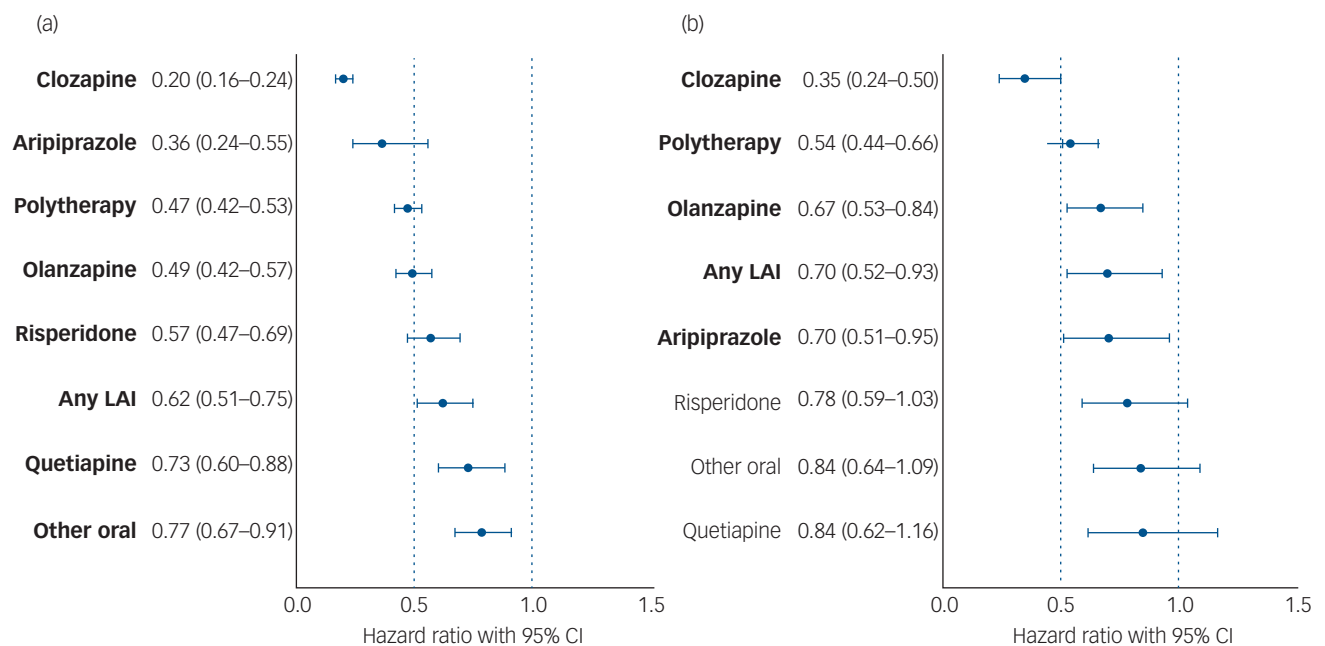
### Risk of psychiatric hospital admission

Median follow-up time for hospital admissions in persons with an SUD was 11.6 years (IQR 6.1–17.7) in the Finnish cohort and 8.6 years (IQR 5.5–10.5) in the Swedish cohort; 5948 persons (73.3%) in the Finnish cohort and 2991 persons (66.3%) in the Swedish cohort experienced psychiatric hospital admission at least once. Compared with non-use of antipsychotics (the within-individual model), use of any antipsychotic was associated with a 40% reduction in risk of psychiatric hospital admission in patients with schizophrenia and comorbid SUD (Finland: aHR 0.61, 95% CI 0.58–0.64; Sweden: aHR 0.60, 95% CI 0.56–0.64). For patients with schizophrenia and comorbid SUD, risk of psychiatric hospital admission was lowest during use of clozapine (Finland: aHR 0.51, 95% CI 0.48–0.54; Sweden: aHR 0.51, 95% CI 0.44–0.58), antipsychotic polytherapy (Finland: aHR 0.57, 95% CI 0.54–0.59; Sweden: aHR 0.47, 95% CI 0.44–0.51), any LAI (Finland: aHR

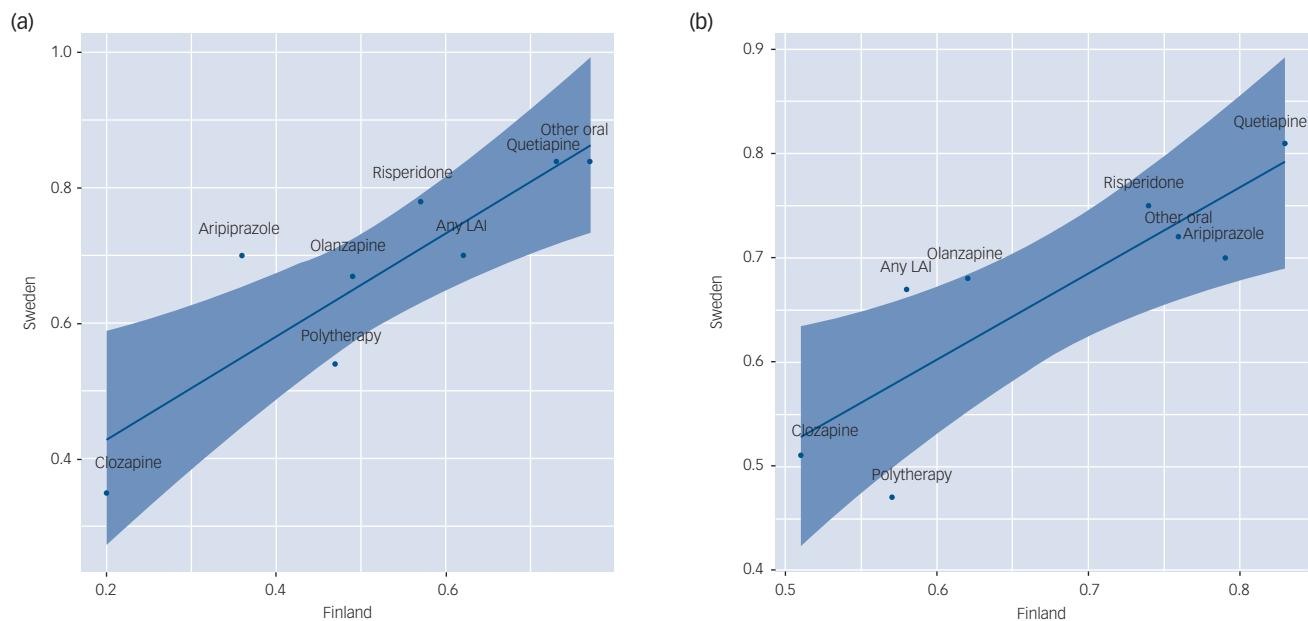
0.58, 95% CI 0.54–0.62; Sweden: aHR 0.67, 95% CI 0.62–0.74) and olanzapine (Finland: aHR 0.62, 95% CI 0.58–0.66; Sweden: aHR 0.68, 95% CI 0.61–0.75), compared with non-use (Fig. 3(a), 3(b), Supplementary Table 1). Use of any specific antipsychotic treatment was associated with reduced risk of psychiatric hospital admission in both countries, but use of quetiapine was associated with the least reduction in risk (Finland: aHR 0.83, 95% CI 0.76–0.90; Sweden: aHR 0.81, 95% CI 0.70–0.94). These beneficial associations of reduced risk for psychiatric hospital admission observed for specific antipsychotic treatments in patients with SUD were similar between the two countries ( $r = 0.84$ ,  $P = 0.009$ ; Fig. 2(b)).

### Risk of SUD-related hospital admission

Among persons with an SUD, 3971 people (49.0%) in the Finnish cohort and 2199 people (48.7%) in the Swedish cohort were



**Fig. 1** Risk of first substance use disorder (among those without substance use disorder) associated with use of specific antipsychotics, in a between-individuals model. (a) Finnish cohort. (b) Swedish cohort. Exposures significant after Benjamini–Hochberg false discovery rate correction for multiple comparisons with a 0.05 threshold are bolded. Hazard ratios are adjusted for covariates. LAI, long-acting injectable.



**Fig. 2** (a) Correlation of effectiveness of antipsychotic treatments (i.e. of adjusted hazard ratios) in preventing development of an initial substance use disorder in patients with schizophrenia between the Finnish and Swedish cohorts (Pearson's  $r = 0.87$ ,  $P = 0.005$ ,  $N = 8$  antipsychotics). The linear regression curve is depicted with a red line and the 95% confidence interval area for the curve is shown in dark grey.  $x$ -axis shows adjusted hazard ratios in Finland and  $y$ -axis shows adjusted hazard ratios in Sweden. (b) Correlation of effectiveness of antipsychotic treatments (i.e. of adjusted hazard ratios) in reducing risk for psychiatric hospital admission in patients with schizophrenia and comorbid substance use disorder between the Finnish and Swedish cohorts (Pearson's  $r = 0.84$ ,  $P = 0.009$ ,  $N = 8$  antipsychotics). The linear regression curve is depicted with a red line and the 95% confidence interval area for the curve is shown in dark grey.  $x$ -axis shows adjusted hazard ratios in Finland and  $y$ -axis shows adjusted hazard ratios in Sweden.

admitted to hospital because of an SUD during follow-up. In individuals with schizophrenia and comorbid SUD, use of any antipsychotic was associated with a 19% reduction of risk of SUD-related hospital admission in Finland (aHR 0.81, 95% CI 0.76–0.85) and a 21% reduction in Sweden (aHR 0.79, 95% CI 0.73–0.85), compared with no use of antipsychotics. Of specific treatments, use of clozapine (Finland: aHR 0.59, 95% CI 0.53–0.66; Sweden: aHR 0.71, 95% CI 0.54–0.94), antipsychotic polytherapy (Finland: aHR 0.75, 95% CI 0.70–0.79; Sweden: aHR 0.60, 95% CI 0.55–0.66) or LAIs (Finland: aHR 0.79, 95% CI 0.71–0.87; Sweden: aHR 0.84, 95% CI 0.75–0.94) were associated with reduced risk in both countries, whereas olanzapine was only associated with reduced risk in the Finnish cohort (Finland: aHR 0.86, 95% CI 0.78–0.94; Sweden: aHR 0.92, 95% CI 0.82–1.04) (Fig. 3(c), 3(d), Supplementary Table 1). These beneficial associations of reduced risk of SUD-related hospital admission observed for specific antipsychotic treatments in patients with schizophrenia and comorbid SUD were similar between the two countries ( $r = 0.71$ ,  $P = 0.049$ ; Supplementary Fig. 8).

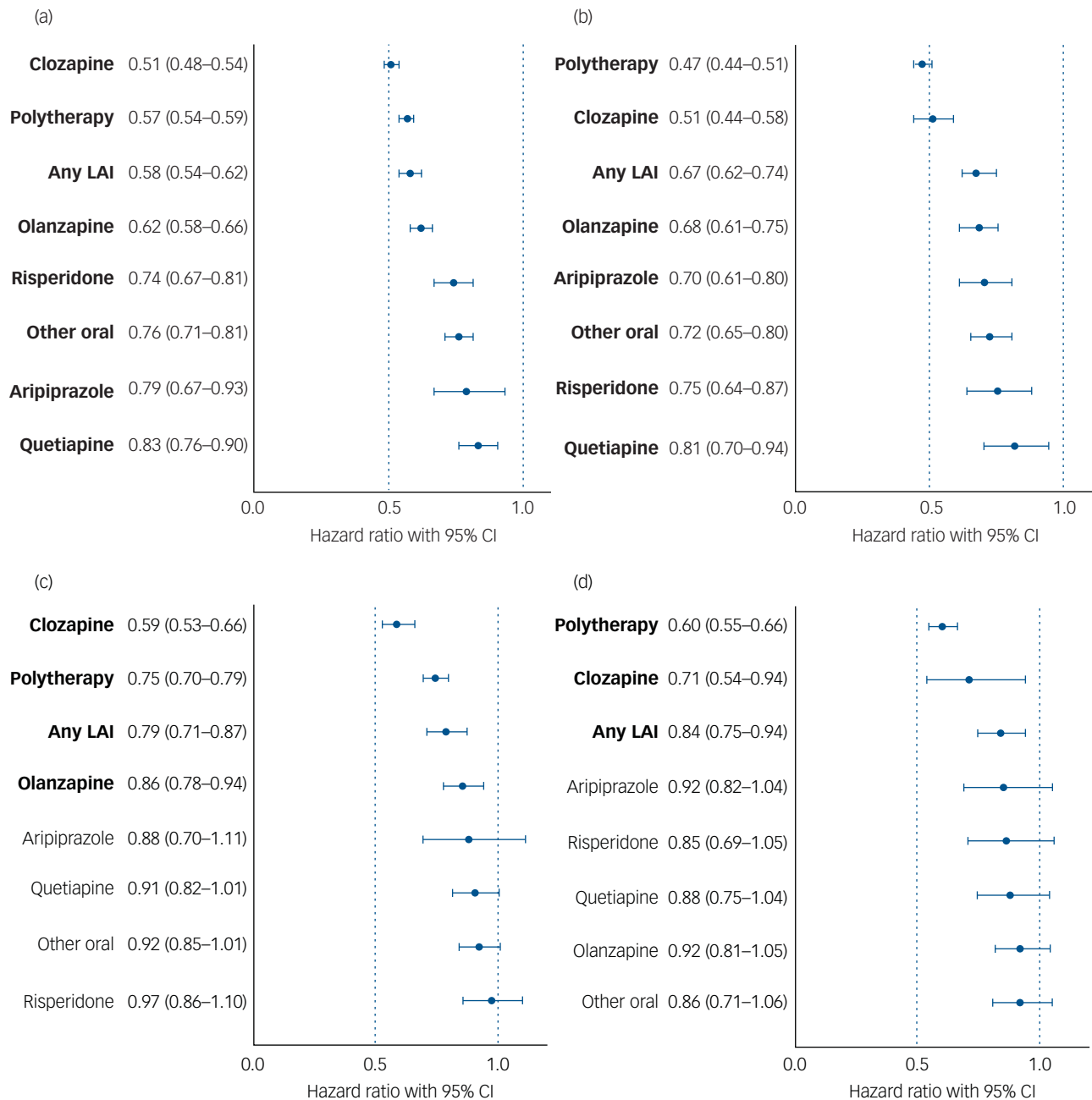
## Discussion

This real-world study provides, for the first time, consistent evidence from two independent cohorts that clozapine use is associated with lower risk of developing an SUD in patients with schizophrenia, compared with no use or use of other antipsychotics. We also show that in patients with schizophrenia and comorbid SUD, clozapine, antipsychotic polytherapy and LAIs are consistently associated with the lowest risks of psychiatric hospital admission and SUD-related hospital admission. Thus, the results are positive for the treatment of schizophrenia, as antipsychotic treatments have now been consistently shown to also be effective for those with comorbid SUD.

Our findings are in line with a recent meta-analysis showing superior efficacy of clozapine in schizophrenia and comorbid SUD,<sup>15</sup> and other studies pointing toward clozapine's superiority over other antipsychotics in the treatment of individuals with schizophrenia and comorbid SUD.<sup>13</sup> For example, clozapine has been shown to reduce the subjective effects of cocaine, although it may increase serum cocaine levels, indicating it may be useful in the treatment of cocaine addiction.<sup>24</sup> Others have found that patients with schizophrenia are more likely to remit from alcohol use when using versus not using clozapine, and when using clozapine versus risperidone.<sup>25</sup>

One possible mechanism explaining our findings relates to the effect some antipsychotics may exert on craving. Although not extensively studied, evidence suggests that clozapine reduces craving, whereas other antipsychotic agents have less of an effect on craving.<sup>15</sup> Given evidence that high D2-receptor occupancy increases substance use risk,<sup>26</sup> clozapine's relatively low D2-receptor affinity may reduce cue reactivity and craving.<sup>27</sup> Reduced craving may result in less frequent and lower amounts of substance use in patients with schizophrenia who are prone to developing SUDs and in patients with schizophrenia and comorbid SUD, diminishing their odds of mental and physical symptom worsening and thus of readmission to hospital. Alternatively, our findings could be an indication that the self-medication hypothesis of substance use in schizophrenia holds true, at least to some extent: it is possible that patients on antipsychotics may experience less symptom severity, and so be at lower risk of using drugs to relieve symptoms and thus developing an SUD.

Use of clozapine, antipsychotic polytherapy and LAIs were associated with the lowest risks of both SUD-related and psychiatric hospital admissions among persons with schizophrenia and comorbid SUD. The results on polypharmacy are in line with previous results from nationwide cohorts showing a favourable



**Fig. 3** (a) and (b) Risk of psychiatric hospital admission associated with use of specific antipsychotics among those with comorbid substance use disorder, in a within-individual model. (a) Finnish cohort. (b) Swedish cohort. Exposures significant after Benjamini–Hochberg false discovery rate correction for multiple comparisons with a 0.05 threshold are bolded. LAI, long-acting injectable. (c) and (d) Risk of substance use disorder-related hospital admission associated with antipsychotic use in those with comorbid substance use disorder, in a within-individual model. (c) Finnish cohort. (d) Swedish cohort. Exposures significant after Benjamini–Hochberg false discovery rate correction for multiple comparisons with a 0.05 threshold are bolded. Hazard ratio are adjusted for covariates. LAI, long-acting injectable.

outcome compared with oral monotherapies among persons with schizophrenia in general.<sup>22,28</sup> Possibly, the additive effects of antipsychotics in those who are prescribed antipsychotic polytherapy increase the beneficial effects of the antipsychotics. Patients with schizophrenia and comorbid SUD have been reported to have lower adherence to antipsychotics than other patients with schizophrenia.<sup>8</sup> Among patients with schizophrenia in general, LAIs have been associated with better adherence and lower risk of hospital admission than their oral counterparts, especially in observational studies.<sup>27</sup> However, only a few previous studies examining LAI use among persons with schizophrenia


and comorbid SUD exist and this literature is inconsistent (see Supplementary Material).

### Strengths and limitations

As an observational study, our results are associations and do not prove causality. However, to corroborate our findings, we used two individually analysed nationwide cohorts from two countries with similar, although not identical, healthcare systems, and stratified our analyses across different calendar time periods. The consistent results across main and sensitivity analyses, as well as across countries and calendar times, lend support to the robustness of

our findings and their generalisability to other countries with similar healthcare systems. As the cohorts used were nationwide, the results provided are thus likely to reflect real-world settings. The most significant weaknesses of observational studies are related to confounding by indication. To combat this, the analyses were performed as within-individual analyses (apart from the analyses of developing an SUD, where this was impossible), where an individual is used as their own control, to eliminate bias arising from permanent individual characteristics. Sensitivity analyses were also performed for the between-individual comparisons, and the analyses were corrected for a variety of covariates as well as multiple comparisons. However, the registries used do not contain all of the information used in clinical decision-making, and some residual confounding is bound to remain. For example, we were not able to account for the effects of psychosocial treatment or psychotherapy. Finally, SUDs may sometimes go undiagnosed.

Overall, our study provides consistent evidence across countries that antipsychotic use in patients with schizophrenia is associated with reduced risk of developing an SUD, compared with non-use of antipsychotics. We found that clozapine and antipsychotic polytherapy were most strongly associated with both reduced risk of developing SUDs among patients with schizophrenia and with lower relapse rates in patients with both diagnoses.

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## Supplementary material

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## Data availability

The data-sets analysed in this study are not publicly available due to participant privacy and security concerns. Researchers can apply for access to these data from the register holders: for Finnish data, the Social Insurance Institution of Finland (Prescription Register), the Finnish National Institute for Health and Welfare (Hospital Discharge Register) and Statistics Finland (Causes of Death Register); for Swedish data, the National Board of Health and Welfare (National Patient Register, Prescribed Drug Register), Statistics Sweden death and sociodemographic data in the LISA Register, and the Swedish Social Insurance Agency (MIDAS Register).

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## Author contributions

All authors conceived the study. H.T. and A.T. performed the statistical analyses. M.L. and J.J.L. wrote the first draft. All authors revised and approved the final draft.

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## Declaration of interest

J.T., E.M.-R., H.T. and A.T. have participated in research projects funded by grants from Janssen-Cilag and Eli Lilly to their employing institution. H.T. reports personal fees from Janssen-Cilag and Otsuka. J.T. reports personal fees from the Finnish Medicines Agency (Fimea), European Medicines Agency (EMA), Eli Lilly, Janssen-Cilag, Lundbeck and Otsuka; is a member of the advisory board for Lundbeck; and has received grants from the Stanley Foundation and Sigríd Jusélius Foundation. M.L. is a board member of Genomi Solutions and Nursie Health; has received honoraria from Sunovion, Orion Pharma, Otsuka, Janssen-Cilag and Lundbeck; received research funding from The Finnish Medical Foundation and Emil Aaltonen Foundation; and participated in research funded by Janssen-Cilag. A.B. and J.L. declare no competing interests.

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## Reflection

### John Conolly – a legacy and a future obligation

Kevin Towers, Amrit Sachar, Claire Hilton , Yuepeng Wang and Derek Tracy 

On 27 May 2022, English Heritage unveiled a ‘Blue Plaque’ celebrating the life and work of Dr John Conolly (1794–1866). These plaques have celebrated those who have done the extraordinary in London since the scheme’s foundation in 1866.

Here, the building was the old Hanwell Asylum, currently St Bernard’s Hospital in West London NHS Trust, and the extraordinary was the work Conolly did after appointment as its resident physician in 1839. In the face of staff opposition, and against the ethos of contemporary methods, within 3 months he had mechanical restraints<sup>1</sup> – chains, strait-jackets and the like – removed and banished from use in hundreds of patients. It heralded a sea-change in practice that rippled out from Hanwell across the public asylums.

Conolly was born in Lincolnshire, of Irish ancestry. Fast forward a period in the army, marriage and studies in medicine at Edinburgh where he achieved his MD with a dissertation on mental health, and stints at the humane Retreat hospitals in Lincoln and York. In an interesting historical twist, he ended up the father-in-law of one Henry Maudsley.

He was a regular author for the journal that would later be the *BMJ*, appointed a professor at University College London and, with others, formed an association that would eventually become the British Medical Association. Humanitarianism permeated his life, and he spoke out against the death penalty and campaigned for girls’ education. His handwritten notes across his own printed work demonstrate growth in understanding, reflectiveness and a willingness to admit mistakes – one notable insertion stating ‘A great mistake. J.C. 1844’.<sup>2</sup>

The Plaque helps counter-balance stereotypical myths that only bad occurred in our past, but also challenges us on what our descendants will question about our contemporary mental health practices. Will it be the lack of progress on the persistently higher rates of detention of Black Caribbean patients despite years of highlighted data, or how Black and minority ethnic NHS staff continue to have worse outcomes on every workforce measure? What will they say of diagnoses of personality disorder and substance use disorders routinely leading to the denial of care, or our early talk of co-production not actually giving patients a seat, but just creating another table?

Decades of unambiguous information on inequity, yet glacial progress despite people so impatient for change. Conolly went against the Victorian grain, achieving in months what people could not have envisioned in years. If the pandemic has taught us anything, it is that if there is a need and a will for rapid change, it can happen. Disruption and system disruptors are needed now.

Conolly’s legacy may best be summed up in his own words, ‘the great and only real substitute for restraint is invariable kindness’; his obligation to us is to disrupt the systems around us while inequity continues to pervade mental healthcare.

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1 His work ‘The treatment of the insane without mechanical restraints’, written in 1856, can be accessed here: <https://archive.org/details/treatmentofinsan00cono>.  
2 See King’s College London – Online exhibitions: Mind matters: neuroscience and psychiatry (<https://kingscollections.org/exhibitions/specialcollections/mind-matters/from-alienism-to-psychiatry/john-conolly>, retrieved 5 June 2022).