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Optimizing antipsychotic dosing for relapse prevention in cannabis-induced psychosis: A nationwide cohort study

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ABSTRACT

Background: Cannabis-induced psychosis (CIP) carries a high risk of relapse. Research has shown that antipsychotic medications are effective in relapse prevention after first diagnosed CIP. Given that antipsychotics carry the potential for dose-related adverse effects, understanding the optimal dose is critical. Therefore, we conducted a dose–response analysis to evaluate the real-world effectiveness of oral antipsychotics in preventing relapse after CIP.

Methods: We used data from linkage of administrative and health care registers from Sweden to identify all individuals with first diagnosis of CIP (ICD-10 F12.5). We modelled oral antipsychotic exposure (aripiprazole, clozapine, risperidone, olanzapine, quetiapine, antipsychotic polytherapy, other oral antipsychotics) as time-dependent using validated PRE2DUP-method. Dose–response association of antipsychotic exposure and outcome were examined across three predefined daily dose (DDD) categories (<0.6, 0.6–<1.4, ≥1.4) using within-individual models in a stratified Cox-regression analysis. The primary outcome was hospitalization for any psychotic episode, defined as schizophrenia-spectrum disorder (F20–F29) or substance-induced psychosis (F1x.5) as the main diagnosis.

Results: We identified 1,772 individuals aged 16-64 years with first-time CIP between 2006 and 2021. Antipsychotic polytherapy was associated with reduced risk of psychosis hospitalization across all dose ranges (HRs=0.54–0.65). Clozapine (0.6–<1.4 DDDs/day), olanzapine (≥0.6 DDDs/day), aripiprazole (0.6–<1.4 DDDs/day), risperidone (<0.6 DDDs/day), and other oral antipsychotics (0.6–<1.4 DDDs/day) were effective, while quetiapine showed no significant benefit.

Conclusions: Findings indicate dose-dependent real-world effectiveness of antipsychotics in CIP, with most agents performing best at 0.6–<1.4 DDDs/day. These results support optimizing dosing of oral antipsychotic medications for relapse prevention after CIP to balance efficacy and adverse effects.

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1. Introduction

Cannabis use associates with mental-ill health, with evidence suggesting deleterious effects particularly in psychotic disorders (D'Souza et al., 2022). The effects include non-adherence with higher risk of relapse (Schoeler et al., 2017) and treatment-resistance(Arsalan et al., 2019) that are especially seen in psychotic disorders with cannabis use. Our previous research has shown that antipsychotic medications have real-world effectiveness in preventing subsequent hospitalizations after cannabis-induced psychosis (CIP) (Mustonen et al., 2025). In CIP, a condition where psychotic symptoms are expected to resolve over time according to diagnostic manuals but may persist longer (Murrie et al., 2020; World Health Organization, 2004), we recently reported that antipsychotic treatment, particularly long-acting injectable (LAI) formulations, clozapine, and oral aripiprazole, is effective in relapse prevention (Mustonen et al., 2025). However, evidence stemming from schizophrenia -related research suggest that not all doses of antipsychotics are effective in preventing relapses, and that risk of relapse may not decrease by increasing dose (Taipale et al., 2022). Given that some antipsychotics also carry the potential for dose-related adverse effects (Sabé et al., 2023), understanding the optimal dose is critical. Therefore, we conducted a dose–response analysis to evaluate the real-world effectiveness of oral antipsychotics in preventing relapse after CIP. These findings aim to inform clinicians on optimal dosing strategies to improve outcomes while minimizing adverse effects.

2. Methods

2.1. Setting

We used linkage of several Swedish nationwide registers covering all individuals with Swedish residency. Swedish residents are assigned unique personal identification number, that makes it possible to link various registers after de-identification. The registers include the National Patient Register (NPR), Micro Data for Analyses of Social Insurance (MiDAS), Prescribed Drug Register (PDR), and Longitudinal Integration Database for Health Insurance (LISA). NPR includes information of inpatient and specialised outpatient care periods, while the MiDAS includes data on sickness absence and disability pension. From NPR and MiDAS registers, we identified individuals aged 16–64 years with a first diagnosis of cannabis-induced psychosis (CIP; ICD-10 F12.5) between January 2006 and December 2021. To ensure incident cases, individuals with prior substance-induced psychosis (F1x.5), schizophrenia-spectrum disorders (F20–F29), or bipolar disorder (F30–F31) before CIP were excluded. Sociodemographic data (age, sex, education, country of birth, occupation) were obtained from LISA. We used data from the REWHARD consortium that was supported by the Swedish Research Council (grant number 2021- 00154). The research project was approved by the Regional Ethics Board of Stockholm, Karolinska Institutet, Stockholm, Sweden (decision 2007/762-31 and Dnr 2021-06441-02). According to current Swedish law, the use of registry data for research purposes does not require informed consent from individuals held in these registries.

2.2. Exposures

Medication data (July 2005–December 2023) from PDR were classified by ATC code N05A (excluding lithium). Based on our previous findings (Mustonen et al., 2025), this study considered the most frequently used oral antipsychotics (risperidone, aripiprazole, olanzapine quetiapine) that were analyzed individually; other less frequently used oral monotherapies were pooled to provide sufficient sample for modelling. In addition, clozapine was analysed individually as it is a clinically special case and safety of clozapine dosing is of particular relevance in patients with co-occurring schizophrenia and SUD. Concurrent use of ≥2 antipsychotics was defined as antipsychotic polytherapy. The medication classes were studied separately, with use of specific pharmacotherapy compared with non-use of that medication class (e.g. reference category for risperidone is non-use of antipsychotics). Long-acting injectables (LAIs) were excluded from the oral dose-category framework because their fixed dosing intervals and formulation-specific pharmacokinetics render daily oral dose categories non-comparable. Medication data were modelled into medication use periods (i.e. when medication use started and ended) with the PRE2DUP (from prescription drug purchases to drug use periods) method (Tanskanen et al., 2015). Exposure to specific pharmacotherapies was modelled in a time-dependent manner and updated in the models when any change to pharmacotherapy in use happened (i.e. switch, add-on, discontinuation).Data with <5 events were suppressed.

2.3. Outcomes

The primary outcome was hospitalization for any psychotic episode, defined as schizophrenia-spectrum disorder (F20–F29) or substance-induced psychosis (F1x.5) as the main diagnosis.

2.4. Statistics

We examined dose–dependent associations between antipsychotic dose ranges (defined daily doses (DDD): <0.6, 0.6–<1.4, ≥1.4) and calculated adjusted hazard ratios (aHRs) and 95% confidence intervals (CI) for the risk hospital admission caused by psychotic relapse using within-individual models and stratified Cox regression model in which each individual formed his or her own stratum. This reduces selection bias as it considers time-invariant factors such as baseline comorbidities and genetics. The follow-up time was reset after each outcome event, meaning that main outcomes were treated as recurrent events. Patients were followed up from CIP – diagnosis until emigration (LISA), death (CDR) or end of the data linkage (December 2023), whichever occurred first.

The DDDs corresponded to <6 mg, 6–<14 mg, and ≥14 mg/day of olanzapine; <9 mg, 9–<21 mg, and ≥21 mg/day of aripiprazole; <3 mg, 3–<7 mg, and ≥7 mg/day of risperidone; <240 mg, 240–<560 mg, and ≥560 mg/day of quetiapine; and <180 mg, 180–<420 mg, and ≥420 mg/day of clozapine.

Covariates included treatment sequence, time since cohort entry, and time-varying use of other psychotropics (medications for SUD [N07BB, N07BC], ADHD [N06BA], mood stabilizers [N03AF01, N03AG01, N03AX09, N05AN01], antidepressants [N06A], benzodiazepines [N05BA, N05CD, N05CF]). As a sensitivity analysis, we ran between-individual Cox regression models that were further adjusted for age, sex, disability pension, prior cannabis-related hospitalizations, and comorbidities (brain injury, epilepsy, personality disorders, overdoses, suicide attempts). For results, see Supplementary Fig 1. Covariate definitions are reported in Supplementary Table 1.

Statistical significance was considered at <0.05. Analyses were conducted in SAS version 9.4 for Windows (SAS Institute Inc.,Cary, NC, USA; https://www.sas.com/fi_fi/software/iml-sas9.html). Figures were created using R version 4.1.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/127).

3. Results

As previously reported (Mustonen et al., 2025), the sample included 1,772 individuals with CIP, of whom 1,490 (84.1%) were men. The mean (s.d.) age at first diagnosis was 26.6 (8.3) years. Of the cohort, 914 (51.3%) individuals were hospitalized for psychosis after cohort entry.

In the dose–response analysis, antipsychotic polytherapy across all dose ranges (<0.6 to ≥1.4 DDD/day) was associated with a significantly reduced risk of psychosis hospitalization (HRs 0.54–0.65). Clozapine at 0.6–<1.4 DDD/day (HR = 0.34; 95%CI 0.13-0.94), other oral antipsychotics at 0.6–<1.4 DDD/day (HR = 0.35; 95% CI 0.25-0.50),

aripiprazole at 0.6–<1.4 DDD/day (HR = 0.41; 95%CI 0.21-0.78), risperidone at <0.6 DDD/day (HR = 0.56; 95% CI 0.36-0.89) and olanzapine at 0.6–<1.4 (HR = 0.72; 95%CI 0.56-0.94), and ≥1.4 DDD/day (HR = 0.73; 95%CI 0.57-0.92) were also associated with significantly reduced risk. Quetiapine showed no significant effect in any dose range. Confidence intervals and all estimates are presented in Fig. 1. As expected, the between-individual models yielded weaker estimates. However, the relative ranking of dosage ranges largely paralleled that observed in the within-individual models (see Supplementary Fig. 1)

4. Discussion

In this real-world effectiveness study using nationwide data, oral antipsychotics were associated with a dose-dependent reduction in the risk of psychosis hospitalization. Clozapine showed the greatest effectiveness at 180–<420 mg/day, though limited sample size may have reduced statistical power for other dose ranges. Antipsychotic polytherapy was effective across all doses, while most antipsychotics demonstrated optimal effectiveness at 0.6–<1.4 DDD/day. Risperidone was effective only at <3 mg/day, which was also its most commonly used dose range. Our finding contrasts with our previous study (Mustonen et al., 2025), where risperidone did not show real-world effectiveness, emphasizing the importance of considering dose dependence when evaluating treatment outcomes. Also, DDD for risperidone may not accurately reflect clinical prescribing practices, as previously reported (Taipale et al., 2022). Olanzapine, the most frequently prescribed antipsychotic, was effective in relapse prevention at doses ≥6 mg/day. The therapeutic effect was comparable between the 6–<14

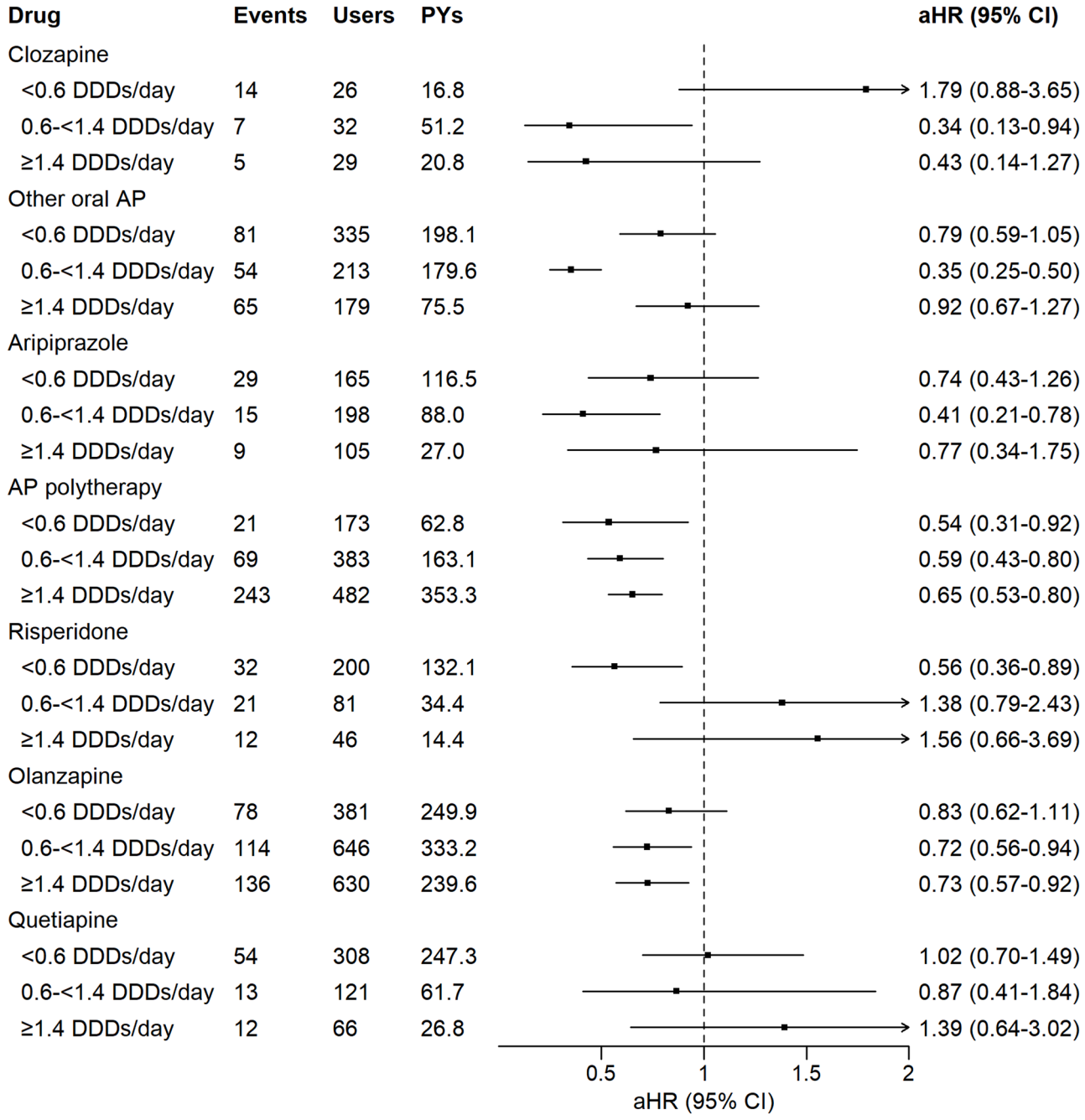

Fig. 1. Association of antipsychotic (AP) use with hospital admission caused by psychotic relapse by defined daily dose (DDD). aHR, adjusted hazard ratio; PYs, person years.

mg/day and ≥14 mg/day ranges. From a clinical perspective, the 6–<14 mg/day range appears optimal, with better balance between sustained antipsychotic effectiveness and a reduced risk of metabolic adverse effect. Aripiprazole at 9–<21 mg/day was the most effective specific antipsychotic after clozapine. However, its frequent use at <9 mg/day without effectiveness in this cohort suggests minimal doses should be avoided for relapse prevention after CIP. Importantly, quetiapine did not demonstrate reduced relapse risk in any dose range, pointing out its limited role in relapse prevention among individuals with CIP.

4.1. Strengths and limitations

This is the first study to examine dose-dependent associations between antipsychotic use and psychosis hospitalization after CIP, extending previous research and providing guidance for optimizing treatment. Nationwide register data enhance generalizability, and within-person modelling reduces confounding by familial and genetic factors. However, an important limitation of this study is the relatively small number of users and events in certain dose ranges and for some antipsychotics, which may have reduced the precision of these estimates indicated by wide confidence intervals among the less frequently used dose ranges. Furthermore, we identified individuals based on their first-time CIP-diagnosis and followed them over time. We did not have objective information (e.g. urine screens) on the continuation of cannabis use and thus were unable to stratify our analysis by differential cannabis trajectories. This is a major limitation, as continued cannabis use associates with worse prognosis in psychosis than discontinued use (Schoeler et al., 2016). However, as previously reported in this same sample (Mustonen et al., 2025), almost 70% of the sample were recorded with a subsequent CUD (F12.x) diagnosis by the end of the follow-up, suggesting persistence of these diagnoses after CIP.

5. Conclusions

Antipsychotics show dose-dependent real-world effectiveness in preventing psychosis relapse after CIP. Prescribers should generally aim for doses within the standard DDD range to optimize antipsychotic treatment for relapse prevention.

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Transparency declaration

AM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted and any discrepancies from the study as planned have been explained.

Research ethics

The project was approved by the Regional Ethical Review Board, Karolinska Institutet, Stockholm, Sweden (Dnr: 2007/762-31 and Dnr 2024-08708-02). According to current Swedish legislation, the use of registry data for research purposes does not require informed consent from the individuals included in these registries.

Availability of data

The data used in this study cannot be made publicly available due to privacy regulations. According to the General Data Protection Regulation, the Swedish law SFS 2018:218, the Swedish Data Protection Act, the Swedish Ethical Review Act, and the Public Access to Information and Secrecy Act, these types of sensitive data can only be made available for specific purposes, including research, that meets the criteria for access to this sort of sensitive and confidential data as determined by a legal review. Readers may contact Professor Ellenor Mittendorfer-Rutz (ellenor.mittendorfer-rutz@ki.se) regarding the data.

CRediT authorship contribution statement

Antti Mustonen: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Solja Niemelä:** Writing – review & editing, Supervision. **Alexander Denissoff:** Writing – review & editing, Supervision. **Marta Di Forti:** Writing – review & editing, Supervision. **Antti Tanskanen:** Writing – review & editing, Supervision, Software, Methodology, Formal analysis, Data curation. **Ellenor Mittendorfer-Rutz:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Jari Tiihonen:** Writing – original draft, Supervision, Investigation. **Heidi Taipale:** Writing – review & editing, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2026.116966.

References

Arsalan, A., Iqbal, Z., Tariq, M., Ayonrinde, O., Vincent, J.B., Ayub, M., 2019. Association of smoked cannabis with treatment resistance in schizophrenia. Psychiatry Res. 278, 242–247. https://doi.org/10.1016/j.psychres.2019.06.023.

D'Souza, D.C., DiForti, M., Ganesh, S., George, T.P., Hall, W., Hjorthøj, C., Howes, O., Keshavan, M., Murray, R.M., Nguyen, T.B., Pearlson, G.D., Ranganathan, M., Selloni, A., Solowij, N., Spinazzola, E., 2022. Consensus paper of the WFSBP task force on cannabis, cannabinoids and psychosis. world J. Biol. Psychiatry: Off. J. World Fed. Soc. Biol. Psychiatry 23, 719–742. https://doi.org/10.1080/15622975.2022.2038797.

Murrie, B., Lappin, J., Large, M., Sara, G., 2020. Transition of substance-induced, brief, and atypical psychoses to schizophrenia: a systematic review and meta-analysis. Schizophr. Bull. 46, 505–516. https://doi.org/10.1093/schbul/sbz102.

Mustonen, A., Taipale, H., Denissoff, A., Ellilä, V., Forti, M.D., Tanskanen, A., Mittendorfer-Rutz, E., Tiihonen, J., Niemelä, S., 2025. Real-world effectiveness of

antipsychotic medication in relapse prevention after cannabis-induced psychosis. Br. J. Psychiatry 1–7. https://doi.org/10.1192/bjp.2025.72.
Sabé, M., Pallis, K., Solmi, M., Crippa, A., Sentissi, O., Kaiser, S., 2023. Comparative effects of 11 antipsychotics on weight gain and metabolic function in patients with acute schizophrenia: a dose-response meta-analysis. J. Clin. Psychiatry 84. https://doi.org/10.4088/JCP.22r14490.
Schoeler, T., Monk, A., Sami, M.B., Klamerus, E., Foglia, E., Brown, R., Camuri, G., Altamura, A.C., Murray, R., Bhattacharyya, S., 2016. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. lancet. Psychiatry 3, 215–225. https://doi.org/10.1016/S2215-0366(15)00363-6.
Schoeler, T., Petros, N., Di Forti, M., Klamerus, E., Foglia, E., Murray, R., Bhattacharyya, S., 2017. Poor medication adherence and risk of relapse associated with continued cannabis use in patients with first-episode psychosis: a prospective analysis. Lancet Psychiatry 4, 627–633. https://doi.org/10.1016/S2215-0366(17)30233-X.
Taipale, H., Tanskanen, A., Correll, C.U., Tiihonen, J., 2022. Real-world effectiveness of antipsychotic doses for relapse prevention in patients with first-episode schizophrenia in Finland: a nationwide, register-based cohort study. Lancet Psychiatry 9, 271–279. https://doi.org/10.1016/S2215-0366(22)00015-3.
Tanskanen, A., Taipale, H., Koponen, M., Tolppanen, A.M., Hartikainen, S., Ahonen, R., Tiihonen, J., 2015. From prescription drug purchases to drug use periods - A second generation method (PRE2DUP). BMC Med. Inform. Decis. Mak. 15. https://doi.org/10.1186/s12911-015-0140-z.
World Health Organization, 2004. International Classification of Diseases, Tenth Revision (ICD-10). World Health Organization.