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Utilization and Cardiometabolic Risk

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Preface

The work presented in this thesis was conducted while employed at Clinical Pharmacology, Pharmacy, and Environmental Medicine at the University of Southern Denmark (SDU) and the Department of Psychiatry in Aabenraa.

I could not possibly foresee the amount of knowledge and the skills that I would gain during these years by working with such talented people – both in the Pharmacoepidemiology group at SDU and elsewhere. I am extremely grateful to Professor Jesper Hallas for accepting me as his mentee, supporting me, and giving me a solid base to explore the world of pharmacoepidemiology. I would also like to express my sincere gratitude to Professor Christoph U. Correll for his dedication to mentor me and for expanding my view of research and psychopharmacology to the international scene, and to Professor Kjeld Andersen for his continuous support and encouraging style of mentoring.

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Mikkel Højlund
Odense, June 2022

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Contents

List of abbreviations

5-HT:	5-hydroxytrypamine (serotonin)
AP:	Antipsychotic
ATC:	Anatomical Therapeutic Chemical (-classification system)
CI:	Confidence interval
D:	Dopaminergic (receptor)
DDD:	WHO Defined daily doses
EMA:	European Medicines Agency
FDA:	US Food and Drug Administration
H:	Histaminergic (receptor)
HbA1c:	Glycosylated haemoglobin A1c
HDL:	High-density lipoprotein cholesterol
hdPS:	High-dimensional propensity score
HR:	Hazard ratio
IRR:	Incidence rate ratio
LDL:	Low-density lipoprotein cholesterol
M:	Muscarinic (acetylcholine receptor)
MACE:	Major adverse cardiovascular event
MD:	Mean difference
N/n:	Number
OR:	Odds ratio
PPV:	Positive predictive value
RCT:	Randomized controlled trial
RR:	Risk ratio
SmPC:	Summary of product characteristics
SSRI:	Selective serotonin reuptake-inhibitor
US:	United States
WHO:	World Health Organization

List of papers

This thesis is based on the following papers:

Paper I:
Højlund M, Andersen JH, Andersen K, Correll CU, Hallas J
Use of antipsychotics in Denmark 1997-2018: a nation-wide drug utilization study with focus on off-label use and associated diagnoses
Epidemiol Psychiatr Sci 2021;30:e28

Paper II:
Højlund M, Lund LC, Andersen K, Correll CU, Hallas J
Association of Low-dose Quetiapine and Diabetes
JAMA Netw Open 2021;4:e213209

Paper III:
Højlund M, Andersen K, Ernst MT, Correll CU, Hallas J
Use of low-dose quetiapine increases the risk of major adverse cardiovascular events: results from a nationwide active comparator-controlled cohort study
Accepted for publication in World Psychiatry

Paper IV:
Højlund M, Støvring H, Andersen K, Correll CU, Hallas J
Impact of low-dose quetiapine use on glycosylated haemoglobin, triglyceride and cholesterol levels
Submitted

Related papers

Højlund M, Pottegård A, Johnsen E, Kroken RA, Reutfors J, Munk-Jørgensen P, Correll CU
Trends in utilization and dosing of antipsychotic drugs in Scandinavia: Comparison of 2006 and 2016
Brit J Clin Pharmacol. 2019;85(7):1598–606

Højlund M, Wagner CB, Wesselhoeft R, Andersen K, Fink-Jensen A, Hallas J
Use of chlorprothixene and the risk of diabetes and major adverse cardiovascular events: a nation-wide cohort study
Basic Clin Pharmacol Toxicol 2022;130(4):501-12

Højlund M, Rasmussen L, Olesen M, Munk-Olsen T, Pottegård A
Who prescribes quetiapine in Denmark?
Brit J Clin Pharmacol 2022 (Epub ahead of print).

Summary

Antipsychotics are generally approved for treatment of severe mental disorders, such as schizophrenia, mania, or bipolar disorder. However, they are frequently used in other psychiatric disorders for their anxiolytic, sedative, or hypnotic properties. Of all antipsychotics, quetiapine has become the most widely used in many countries, and with high rates of off-label use. When this PhD project was initiated, there was only sparse evidence on adverse events with off-label, low-dose use of quetiapine, and the long-term safety was yet to be explored. This project set out to i) map the extent of off-label use of antipsychotics in Denmark, and ii) to investigate the safety of low-dose quetiapine with regards to long-term adverse events, such as diabetes and cardiovascular disease. The following paragraphs summarize the four studies that constitute the PhD.

Study I assessed the occurrence of psychiatric, neurological, or cancer diagnoses ('relevant diagnoses') among all individuals who filled prescriptions for antipsychotics in Denmark between 1997 and 2018. The main findings were as follows: i) the group without diagnoses of severe mental disorders comprised 2 of 3 users in 2018; ii) while the proportion of users without records of relevant diagnoses had decreased from 1997 to 2018, the use in other diagnostic groups had increased (e.g. major depression, neurotic or stress-related conditions, and sleep disorders); iii) antipsychotics such as chlorprothixene, flupentixol, levomepromazine, and quetiapine were commonly prescribed to individu-

als without relevant diagnoses, and iv) quetiapine was the most frequently used antipsychotic in 2018, both overall (51% of users) and among those without relevant diagnoses (58% of users in this group).

Study II assessed the risk of diabetes with off-label use of quetiapine in low-doses ($\leq$50mg/day) among adults, using a new-user, active comparator-controlled cohort design. The incidence rate of diabetes was not higher among low-dose quetiapine-initiators than among a mentally ill reference-population of selective serotonin reuptake-inhibitor (SSRI) initiators. Furthermore, increasing cumulative doses of quetiapine, as low dose treatment, were not associated with an increased risk of diabetes. However, increasing cumulative dose was associated with increased risk of diabetes, when including off-label treatment with higher tablet strengths.

Study III assessed the risk of major adverse cardiovascular events (MACE: myocardial infarction, stroke, or death from cardiovascular causes) with off-label, low-dose use of quetiapine among adults in a new-user, active comparator-controlled cohort design. The risk of MACE was increased with initiation of low-dose quetiapine, compared to initiation of Z-drug-hypnotics or SSRIs. The increased risk of MACE was driven by an increased risk of death from cardiovascular causes among low-dose quetiapine-users, whereas no increase was found in the risk of myocardial infarction or stroke. However, the risk of stroke increased with continuous use.

Study IV investigated the effect of low-dose quetiapine-treatment on glycosylated hemoglobin A1c (HbA1c)-, triglyceride-, and cholesterol-levels in a new-user cohort design. Initiation of low-dose quetiapine was only associated with clear increases in fasting triglycerides and decreases in HDL cholesterol-levels, whereas HbA1c- and total/LDL cholesterol-levels did not change after initiation of low-dose quetiapine. However, among those with normal levels before initiation, use of low-dose quetiapine was associated with changes in both HbA1c- and cholesterol-

levels. Additionally, the study found that individuals with abnormal levels of HbA1c or cholesterols prior to initiation of low-dose quetiapine were more likely to be monitored after initiation of quetiapine, and that the proportion of low-dose quetiapine-users with available blood test results was low (<10%).

The present project contributes to the ongoing debate regarding the appropriateness and safety of off-label use of antipsychotic medications. First, it provides an updated and comprehensive assessment of antipsychotic use in Denmark, which can serve as a basis for future discussion, exploration, or intervention regarding off-label use of antipsychotics. Second, it provides novel data on the cardiometabolic safety of quetiapine in its increasingly common role – used in low doses as anxiolytic or hypnotic.

Resumé

Antipsykotika er som hovedregel kun godkendt til behandling af svære psykiske lidelser som skizofreni, mani og bipolar sygdom. Antipsykotika bruges dog ofte i behandlingen af andre psykiatriske tilstande på grund af deres angstdæmpende, sløvende og søvninducerende virkning. Quetiapin er det hyppigst brugte antipsykotika i mange lande verden over og andelen af individer som bruger quetiapin udenfor de godkendte indikationer ("off-label") er høj. Forud for dette ph.d.-projekt var der kun begrænset evidens omkring bivirkninger ved off-label, lavdosis brug af quetiapin og der fandtes ingen langtidsstudier omkring bivirkninger til denne form for behandling. Formålet med dette projekt var derfor i) at kortlægge det nuværende off-label forbrug af antipsykotika i Danmark, og ii) at undersøge den metaboliske og kardiovaskulære sikkerhed ved off-label brug af quetiapin i lave doser. De fire studier som afhandlingen er baseret på opsummeres i de følgende fire afsnit.

Delstudie I undersøgte forekomsten af psykiatriske, neurologiske eller onkologiske diagnoser ("relevante diagnoser") blandt individer som indløste recept på et antipsykotikum i Danmark i perioden fra 1997 til 2018. Hovedfundene i dette studie var i) at 2 ud af 3 individer som indløste recept på et antipsykotikum i 2018 ikke havde diagnoser for svær psykisk sygdom, ii) at mens andelen af individer som indløste recept på et antipsykotikum og ikke havde nogen relevant diagnose var faldet fra 1997 til 2018, så var andelen af individer som indløste recept på et an-

tipsykotisk lægemiddel steget i andre grupper (fx depression, nervøse og stress-betingede lidelser og søvnforstyrrelser), iii) at antipsykotika som chlorprothixen, flupentixol, levomepromazin og quetiapin var de antipsykotika som hyppigst blev udskrevet til individer uden relevante diagnoser, og iv) at quetiapin var det hyppigst brugte antipsykotikum i Danmark i 2018, både overordnet (51% af alle brugere) og blandt individer uden relevante diagnoser (58% af denne gruppe).

Delstudie II undersøgte risikoen for diabetes i forbindelse med off-label brug af quetiapin i lave doser ($\leq$50mg) blandt voksne i et aktiv komparator-kontrolleret kohorte design. Incidensen af diabetes blandt lav-dosis quetiapin-brugere var ikke højere end blandt en referencepopulation bestående af SSRI-brugere. Derudover var stigende kumulerede doser af quetiapin, som lav-dosis behandling, ikke forbundet med øget risiko for diabetes. Dog fandtes en øget risiko for diabetes ved brug af højere tabletstyrker af quetiapin (>50mg).

Delstudie III undersøgte risikoen for alvorlige kardiovaskulære begivenheder (myokardieinfarkt, apopleksi eller død af kardiovaskulære årsager) ved off-label brug af quetiapin i lave doser blandt voksne i et aktiv komparator-kontrolleret kohorte design. Risikoen for alvorlige kardiovaskulære begivenheder var øget ved off-label brug af quetiapin, sammenlignet med brug af hypnotika eller SSRI. Den øgede risiko blandt off-label brugere af quetiapin i lave doser var drevet af en øget risiko for død af kardiovaskulære årsager , mens risikoen for myokardieinfarkt eller apopleksi ikke var øget. Dog fandtes en øget risiko for apopleksi ved vedvarende brug af quetiapin i lave doser.

Delstudie IV undersøgte hvorvidt off-label, lav-dosis brug af quetiapin kan påvirke risikofaktorer for kardiometabolisk sygdom som langtidsblodsukker (HbA1c), triglycerid- og kolesterolniveauer. Brug af quetiapin i lave doser var forbundet med en stigning i (fastende) triglycerid-niveauer og et fald i HDL-kolesterol niveauer. Dog var lav-dosis brug af quetiapin forbundet med stigende HbA1c-niveauer og kolesterol-niveauer

blandt individer med normale værdier før opstart af quetiapin. To væsentlige bifund fra studiet var i) at individer med øgede niveauer af disse risikofaktorer var mere tilbøjelige til at få foretaget opfølgende målinger efter opstart af lav-dosis quetiapin, og ii) at under 10% af de off-label, lav-dosis quetiapin-brugere som kunne indgå i undersøgelsen havde registreret målinger af en eller flere af disse målinger i den nationale laboratoriedatabase.

Nærværende ph.d.-projekt bidrager til den igangværende debat om hensigtsmæssigheden og sikkerheden ved off-label brug af antipsykotisk medicin. Først ved at give et overordnet billede af det nuværende forbrug af antipsykotisk medicin i Danmark, som kan danne basis for videre forskning, diskussion og indsatser inden for dette felt. Dernæst ved frembringe nye data omkring risikoen for kardiometaboliske bivirkninger ved brug af quetiapin i den hyppigste anvendelse – i lave doser som angstdæmpende behandling eller som sovemedicin.

Introduction

Antipsychotics are potent medications. They can alleviate deliberating symptoms such as delusions and hallucinations. However, they are also associated with a wide range of adverse events, from mild to life-threatening.

The subject for this thesis arose from my clinical work. Many patients without psychotic disorders were prescribed *anti*-psychotic medications. Although the use of antipsychotics could be warranted for several other reasons than psychotic symptoms, e.g. relapse prevention in bipolar disorder or treatment of major depression, the extent of their use was considerable. Of all antipsychotics, quetiapine was the most frequently used, and many patients were prescribed quetiapine in low or modest doses for anxiolytic or hypnotic purposes. This led me to investigate the current and ongoing use of off-label antipsychotics in general and quetiapine in particular.

The literature on quetiapine is mostly concerned with the efficacy and safety of the relatively high doses used in the treatment of schizophrenia or bipolar disorder. The seemingly most predominant use, off-label and in low doses, was not thoroughly investigated, thus not providing any clear answer to whether this practice was safe or potentially problematic. An increased risk of cardiometabolic adverse events with the use of antipsychotics might be acceptable in the treatment of severe mental disorders where the alternative could be untreated psychosis, risk of sui-

cide or violence, or poor functional outcomes etc. However, if off-label, low-dose use of antipsychotics was associated with substantial risk, a public health problem would have been created by the increasing use. As modern medicine should be based on rational choices, preferably supported by evidence of benefit and harm, the idea was formed of investigating the safety of quetiapine in this role using Danish health care registers.

This thesis documents the current utilization of antipsychotics in Denmark with a focus on the use outside approved indications. Furthermore, it provides evidence on the risk of cardio-metabolic adverse events associated with use of quetiapine, off-label and in low doses. Collectively, this knowledge will serve as a basis for future initiatives to secure a more rational, evidence-informed, off-label use of antipsychotics.

The thesis is structured around six chapters: the first chapter provides an introduction to off-label use of antipsychotics, an introduction to quetiapine, and a summary of the current knowledge on adverse events with the use of quetiapine; the second chapter presents both the overall and specific aims for the thesis; the third chapter introduces the registers used when designing the four studies along with methodological choices in this process; the fourth chapter presents main results from the four studies; the fifth chapter discusses main findings, methodological issues, implications for off-label use of quetiapine; and the sixth chapter concludes on the four studies and discusses future directions for research in this area.

Background

This chapter begins with an introduction to the concept of off-label use and the potential reasons for off-label use of antipsychotics. Hereafter, it describes the pharmacodynamic potential of adverse effects with the use of quetiapine, the most commonly used antipsychotic. Lastly, it summarizes the preexisting evidence regarding cardio-metabolic adverse effects with the use of quetiapine.

Off-label use of antipsychotics

The European Medicines Agency (EMA) defines off-label use as 'use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration'.[1] Off-label use of medications can have several drivers.[2] Approval for additional indications for an already marketed drug is costly and time-consuming, and therefore less likely to be pursued by pharmaceutical companies. However, medications might be efficacious in other conditions than the approved indications based on its pharmacological mode of action; on this basis, off-label use can slowly become adopted within a medical specialty. Additionally, off-label use can arise from use in populations beyond those included in pivotal trials, e.g. children or adolescents, who might not have been included in these trials and thus not included in the resulting authorization.[3]

Generally, antipsychotics are approved for the treatment of schizophrenia and psychoses. Several antipsychotics are also approved for treatment of mania and bipolar disorder, and some antipsychotics have additional indications, e.g., neuropsychiatric disorders such as delirium, dementia, intellectual disability, Huntington's chorea, or psychosis in Parkinson's disease. Approved indications for antipsychotics marketed in Denmark are shown in Table 1 (p. 25). For many of these additional indications, the authorization is limited to specific situations and not for the disease in general, e.g. haloperidol is approved for short-term treatment of persistent aggression in dementia when non-pharmacological treatments have failed.[4]

Off-label use does not necessarily mean 'off-evidence' use. Second-generation antipsychotics have been found efficacious in other indications than the approved e.g. generalized anxiety disorder,[5] borderline personality disorder,[6] obsessive compulsive disorder,[7] and post-traumatic stress disorder.[8] However, the clinical utility of antipsychotics might not be limited to these indications/situations and another common reason for off-label use of antipsychotics is for sedative-hypnotic purposes. In these situations, antipsychotics with sedative properties might substitute the use of benzodiazepines, which are subject to problems with dependency, abuse, and adverse effects.[9]

Off-label use of antipsychotics has been found to be common across various countries and populations. A systematic review of drug utilization studies on antipsychotics found that off-label use comprised 40-75% of all antipsychotic use, and that second-generation antipsychotics, especially quetiapine, were most commonly associated with off-label use.[10] In Denmark, 54% of incident users of antipsychotics 2007-2012 did not have records of psychiatric diagnoses, suggesting potential off-label use and prescription by non-psychiatrists.[11] Furthermore, the core indications for antipsychotic-use, such as schizophrenia, other non-affective psychoses, and bipolar disorder, were only recorded for approximately 16% of incident users with records of psychiatric diagnoses within five years of their first prescription.[11]

Table 1: Approved indications for antipsychotics marketed in Denmark

Antipsychotic	Indication(s)
Amisulpride	Schizophrenia and other psychotic disorders
Aripiprazole	Schizophrenia
	Mania/bipolar disorder (acute treatment/relapse prevention)
Asenapine	Mania (acute treatment)
Brexpiprazole	Schizophrenia
Cariprazine	Schizophrenia
Chlorprothixene	Psychotic disorders, excl. depression
Clozapine	Schizophrenia (treatment-resistant)
	Psychosis in Parkinson's disease
Flupentixol	Psychotic disorders
	Major depression (without psychotic symptoms)
Haloperidol	Schizophrenia and schizoaffective disorder
	Delirium
	Mania/bipolar disorder (acute treatment)
	Acute psychomotor agitation (psychosis/mania)
	Alzheimer's and vascular dementia (persistent aggression)
	Autism and intellectual disability (persistent aggression)
	Tic disorders, incl. Tourette's syndrome
	Huntington's chorea
	Post-operative nausea and vomitting
Levomepromazine*	Psychotic disorders, excl. depression
Lurasidone	Schizophrenia
Melperone	Psychotic disorders, excl. depression
Olanzapine	Schizophrenia
	Mania/bipolar disorder (acute treatment/relapse prevention)
Paliperidone	Schizophrenia and other psychotic disorders
Perphenazine	Schizophrenia and other psychotic disorders
Periciazine*	Schizophrenia and other psychotic disorders
Prochlorperazine*	Schizophrenia and other psychotic disorders
	Hiccups, nausea, vomitting, and migraine
Pimozide	Schizophrenia and other psychotic disorders
	Huntington's chorea and other hyperkinesias
Pipamperone	Schizophrenia and other psychotic disorders
Quetiapine	Schizophrenia
	Mania/bipolar disorder (acute treatment/relapse prevention)
	Major depression (adjunctive to antidepressants)
Risperidone	Schizophrenia and other psychotic disorders
	Mania (acute treatment)
	Intellectual disability (persistent aggression)
	Alzheimer's dementia (persistent aggression)
Sertindole	Schizophrenia and other psychotic disorders
Sulpiride*	Schizophrenia and other psychotic disorders
Ziprasidone	Schizophrenia
	Mania/bipolar disorder (acute treatment/relapse prevention)
Zuclopenthixol	Psychotic disorders, excl. depression

Notes: Indications collected from www.pro.medicin.dk and summary of product characteristics (SmPC) for the individual antipsychotics. The left column lists neuropsychiatric conditions included as indications, but the exact wording in the SmPC might include further details on specific age groups or previous treatment attempts (e.g., insufficient response to non-pharmacological intervention). *Withdrawn from the Danish market prior to 2022.

How off-label use of antipsychotics has evolved in Denmark since 2012 has not been investigated. Neither has the specific antipsychotics used off-label, although low average daily quantities per user (<0.5 WHO defined daily dose (DDD) per day*) has been observed in 2016 for chlorprothixene, flupentixol, haloperidol, levomepromazine, quetiapine, and risperidone,[13] which might be indicative of off-label use. Of all antipsychotics currently approved in Denmark, quetiapine has been the most frequently used antipsychotic since 2009, with continuously increasing prevalence and decreasing mean doses since its introduction in 2001 (Figure 1).[14] Similar increases in both prevalence and off-label use have also been seen in countries such as Canada, Norway, and the United States.[15–19]

* The DDD "is the assumed average maintenance dose per day for a drug used for its main indication in adults".[12] For antipsychotics, the DDD represents doses for maintenance treatment in schizophrenia, e.g. the DDD for quetiapine is 400mg/day.

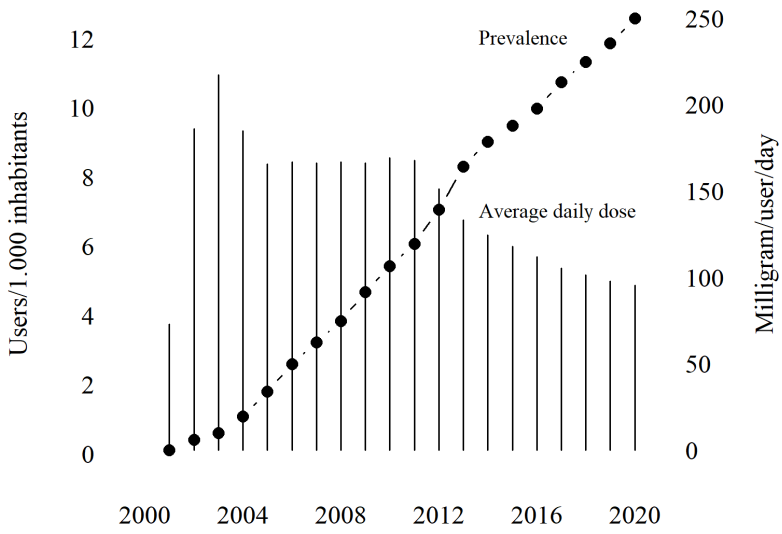


Figure 1: One-year prevalence (line: users/1,000 inhabitants) and average daily dose (bars: milligram/user/day) for quetiapine, Denmark 2000-2020 (source: https://medstat.dk/en).

Quetiapine

Quetiapine is a second-generation antipsychotic approved by US Food and Drug Administration (FDA), EMA, and the Danish Medicines Agency for treatment of schizophrenia and bipolar disorder.[20–22] Additionally, the extended-release formulation of quetiapine is approved for schizophrenia, bipolar disorder, and as adjunctive to antidepressant treatment in major depression.[21–23] Quetiapine gained FDA approval for schizophrenia in 1997 and was approved in Denmark in 2001.[22,24]

Pharmacodynamic properties of quetiapine

Like other second-generation antipsychotics, quetiapine is both a dopamine-2 (D_2) and a serotonin (5-HT) 2A-receptor antagonist.[24] In addition, quetiapine also has considerable affinity for α-adrenergic, histaminergic, muscarinic (M), and other serotonergic receptors (Table 2). Actions at these receptors are responsible for the intended antipsychotic, antimanic, and anxiolytic effects of quetiapine, but also involved in side effects such as sedation, dizziness, metabolic abnormalities etc..[25] At low doses (e.g. 50mg), the primary effect of quetiapine is antihistaminergic,[26] which might explain the frequent use as a sedative or hypnotic. Antagonism of the histamine-1 (H1)-receptor has been associated with both sedation and weight gain.[27,28]

Receptor	K_i (nM)
D_2	770
5-HT_{1A}	300
5-HT_{2A}	31
5-HT_{2C}	3500
α_1	8.1
α_2	80
H_1	19
M_1	120
M_2	630
M_3	1320
M_4	660

Table 2: Receptor profile for quetiapine. The equilibrium constant (K_i) describes the concentration of quetiapine (in nanomolar) needed for 50% of receptors to be occupied. Low K_i imply high affinity. Based on data from Correll Eur Psychiatry 2010.[29]

Quetiapine and diabetes

Use of antipsychotics has been associated with development of type 2 diabetes mellitus, and several pathophysiological mechanisms are likely involved:[30–32] Antagonistic effects on D_2, 5-HT_{2C}, H_1-receptors can both increase appetite and reduce energy

expenditure, resulting in weight gain and subsequent insulin resistance.[30] Furthermore, antipsychotics can impair insulin signaling, independent of weight gain, also resulting in insulin resistance.[30,31] Lastly, antipsychotics can affect pancreatic β-cells directly through D_2, 5-HT_{1A}, and M_3-receptor antagonism, reducing insulin sensitivity and secretion.[30,32]

Evidence from randomized controlled trials While use of clozapine and olanzapine have been found to increase blood glucose-levels, the impact of quetiapine is less clear.[33] A network meta-analysis of randomized controlled trials (RCTs) with quetiapine in schizophrenia found that quetiapine was associated with significant increases in body weight compared to placebo (mean difference [MD] 1.56kg; 95% confidence interval [CI] 1.09 to 2.04kg), but not with significant increases in blood glucose (MD 0.09mmol/L; 95%CI: -0.11 to 0.29).[33] Even though doses in the included trials were relatively high (average: 570 mg/day, range: 400-700), the average duration was short (8 weeks, range: 2-16), and longer follow-up might be needed to capture the full impact on blood glucose-levels.[33] and longer follow-up might be needed to capture the full impact on blood glucose-levels. Meta-analysis of RCTs, comparing quetiapine to placebo in various off-label indications*, found non-significant increases in weight gain (MD: 0.82kg; 95%CI: -0.02 to 1.65) and blood glucose (data not reported) with average doses of 180 mg/day (range: 25-800).[34] Again, the average follow-up was limited (12 weeks, range: 8-52).[34]

* Generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress-disorder, borderline personality disorder, and substance use disorders.

Evidence from observational studies Use of quetiapine has been associated with increased risk of diabetes, compared to use of antidepressants, in a large cohort study based on US claims data (n=12,094; HR: 1.36; 95%CI: 1.23 to 1.50).[35] However, this study included quetiapine-users regardless of daily dose or indications.[35] The risk of diabetes with use of quetiapine has also been investigated in a Danish nation-wide cohort study, including all quetiapine-users regardless of diagnoses.[36] Here,

the authors did not find an increased risk of diabetes with use of quetiapine, compared to population controls (RR: 0.71, 95%CI: 0.43-1.18).[36] Lastly, a US cohort study found that the risk of diabetes increased with daily dose of quetiapine, suggesting a significant increase in the risk of diabetes with daily doses >150mg, compared to daily doses ≤50mg (HR: 2.5; 95%CI: 1.3 to 4.7).[37] This study found a rate of diabetes with use of quetiapine ≤50mg/day of 7 new cases per 1,000 person-years of exposure, but did not compare this risk with non-exposed individuals.[37]

Retrospective chart reviews have also found increases in body weight[38,39] and fasting blood glucose[39] with the use of quetiapine in low doses (≤200mg/day): In 43 patients with various psychiatric disorders, receiving quetiapine in daily doses between 25 and 200mg for insomnia (average: 120mg/day), an average weight gain of 4.9kg was seen during an average follow-up of 11 months.[38]). In 403 patients under the Veterans Administration, receiving quetiapine in daily doses between 12.5 and 200mg (average 117mg/day) for various indications, significant increases in both body weight and fasting blood glucose were seen during an average follow-up of 3.7 years.[39] Concurrent use of other antipsychotics or psychotropic medications were allowed – and studies did not exclude individuals with severe mental illness, which has been associated with increased risk of metabolic abnormalities in itself.[40]

Quetiapine and cardiovascular disease

Use of antipsychotic drugs, in general, has been associated with increased risk of both cardiovascular morbidity and mortality.[41,42] The increased risk of cardiovascular morbidity is likely driven by dyslipidemia and hyperglycemia leading to atherosclerosis, hereby resulting in increased risk of hypertensive heart disease, coronary heart disease, and cerebrovascular events.[41,43] The increased risk of cardiovascular mortality is likely to stem from the abovementioned conditions, but also from ventricular arrhyth-

mias, increasing the risk of sudden cardiac death.[41,44] Lastly, use of antipsychotics has been associated with increased risk of all-cause mortality, especially among the elderly, those with dementia, and those treated with first-generation antipsychotics.[45,46] While most pathophysiological aspects of antipsychotic-induced diabetes are known, the pathophysiology behind antipsychotic-induced dyslipidemia is not fully understood, although it might involve dysregulation of hepatic lipid metabolism.[47,48]

Evidence from randomized controlled trials RCTs including quetiapine and cardiovascular end points have not been conducted, likely due to the extensive number of participants and follow-up needed to capture such events. However, risk factors for cardiovascular disease (QT-prolongation or change in cholesterol-/triglyceride-levels) are commonly reported in RCTs and have been summarized in two meta-analyses. A network meta-analysis of RCTs in schizophrenia found that quetiapine, compared to placebo, increased total cholesterol-levels (MD 0.31 mmol/L, 95%CI: 0.19 to 0.42), LDL-cholesterol-levels (MD 0.17 mmol/L, 95%CI: 0.06 to 0.28), and triglyceride-levels (MD 0.32 mmol/L, 95%CI: 0.21 to 0.44), while no significant effect on HDL cholesterol-levels were seen (MD 0.01 mmol/L, 95%CI: -0.03 to 0.05)[33*]. In RCTs comparing quetiapine to placebo in various off-label indications, quetiapine was associated with significant changes in total cholesterol (MD 3.36 mg/dL, 95%CI: 0.38-6.35), HDL cholesterol-levels (MD -1.59mg/dL, 95%CI: -2.52 to -0.65), and triglyceride-levels (MD 15.3mg/dL, 95%CI: 6.7 to 24.0), while no significant effect was seen for LDL cholesterol-levels (data not reported)[34†]. Lastly, use of quetiapine has been associated with significant QT-prolongation in RCTs on treatment in schizophrenia, although not of a clinically relevant degree (average dose: MD 3.43 milliseconds, 95%CI: 0.94 to 6.00).[49]

[*] Data on dose and duration reported in the subsection **Quetiapine and diabetes**

[†] Data on dose and duration reported in the subsection **Quetiapine and diabetes**

Evidence from observational studies A considerable number of observational studies have been conducted on the association between use of antipsychotic drugs and the risk of cardiovascular

events or mortality. However, most of these studies compared first-generation with second-generation antipsychotics and do not provide specific information regarding the associated risk with use of quetiapine. Other studies were conducted early after quetiapine was approved, or were only able to include very few users and/or cardiovascular events.[50]

A US-based cohort study found use of quetiapine, compared to use of antidepressants, to be associated with an increased risk of essential hypertension (HR 1.24, 95%CI: 1.18 to 1.31), hyperlipidemia (HR 1.08, 95%CI: 1.02 to 1.15), hypertensive heart disease (HR 1.39, 95%CI: 1.07 to 1.81), coronary heart disease (HR 1.27, 95%CI: 1.10 to 1.46), and stroke (HR 1.60, 95%CI: 1.26 to 2.01).[35] This study included all quetiapine-users aged 18-64 years in the population regardless of diagnoses or dose. Additionally, it indicated a potential increase, although not statistically significant, for myocardial infarction (HR 1.15, 95%CI: 0.83 to 1.59) and transient ischemic attack (HR 1.21, 95%CI: 0.97 to 1.51).[35] A case-crossover study including 429 elderly users of quetiapine found significant increases in the risk of ischemic stroke with use of quetiapine (OR 2.7, 95%CI: 2.0-3.6).[51] However, this study did not account for dose, although doses could potentially be low as cases were $\geq$65 years and the majority (60%) were diagnosed with dementia.[51]

Increased risk of cardiovascular mortality with off-label, low-dose use of quetiapine (and olanzapine) was investigated in a recent Swedish nation-wide cohort study.[52] The cohort was confined to those filling 2 or more prescriptions for either quetiapine or olanzapine, and the follow-up was confined to treatment with prescriptions for tablet strengths $\leq$75 mg and (annual) average doses of $\leq$75 mg/day. An increased risk of death from cardiovascular causes was found with 6 to 12 months of cumulative exposure, although the number of events was low (17 events, HR 1.89, 95%CI: 1.22 to 2.92). Only pooled results for off-label, low-dose users of quetiapine and olanzapine were described, thus the study did not provide estimates for quetiapine specifically.[52]

Summary of the current evidence

Use of quetiapine has become increasingly prevalent with indications of substantial off-label use. This development might pose a significant problem, as quetiapine has also been associated with the development of diabetes, various cardiovascular diseases, and death from cardiovascular causes in population-based cohort studies. Data from randomized placebo-controlled trials or network meta-analyses of RCTs have found significant degrees of dyslipidemia with the use of quetiapine, even within relatively short follow-up, whereas the impact on blood glucose-levels is uncertain.

Altogether, this suggests that the use of quetiapine can impact cardiometabolic health as addressed in several reviews on the topic.[53–56] However, no specific data exist on the cardiometabolic safety of quetiapine when used off-label and in low doses (<100-200mg/day), and thus no answer exists to the most pressing question: is low-dose use of quetiapine safe?

Aim of the thesis

The aim of this thesis was two-fold: to map the current extent of off-label use of antipsychotics in Denmark, and to investigate safety aspects with off-label, low-dose use of quetiapine.

Study I examined the extent of and development in off-label use in Denmark between 1997 and 2018. Furthermore, it investigated characteristics of antipsychotic users without diagnoses relevant to antipsychotic treatment and compared treatment duration in different diagnostic groups.

The risk of cardio-metabolic adverse events with use of second-generation antipsychotics for treatment of severe mental disorders is well-documented, but the risk associated with use of quetiapine off-label in low doses has not been evaluated specifically.

Study II assessed the association between use of quetiapine in low doses and the risk of diabetes.

Study III assessed the association between use of quetiapine in low doses and the risk of major adverse cardiovascular events.

Study IV assessed the association between use of quetiapine in low doses and changes in blood glucose or lipids.

Methodological considerations

All four studies included in this thesis are based on Danish healthcare registers. The first part of this chapter introduces these registers, their content, and coverage. The second part of the chapter describes study-specific methods for each for the four studies, along with methodological considerations in designing each study.

Danish health care registers

Virtually all health care in Denmark is provided free-of-charge through the public health system. Information is recorded in a Danish health register each time a resident of Denmark is admitted to a hospital; visits an outpatient clinic, general practitioner, or practicing specialist; fills a prescription; or has a blood sample analyzed at a clinical laboratory. This information can be linked using the civil registration number, which allows population-based research integrating several types of data (e.g. prescriptions, diagnoses, healthcare contacts, and blood sample results). The civil registration number is a unique, personal 10-digit identifier assigned to all residents in Denmark at birth or at point of immigration by the Central Office of Civil Registration.[57] In connection to the civil registration number, the Danish Civil Registration System contains information on vital status, residence, and emi-/immigration dates for all Danish inhabitants.[57] The

following subsections describes the individual registers with emphasis on the data types used in the four studies.

The Danish National Prescription Register

The Danish National Prescription Register contains information on all prescriptions filled at Danish pharmacies since 1995.[58] Each prescription record contains information on patient identifier, product name, ATC-code, formulation, strength, amount etc. As antipsychotics are only sold on prescription in Denmark, all prescriptions for antipsychotics (and other psychotropic drugs) filled at pharmacies are captured by the Danish National Prescription Register. However, hospital use of medications is not recorded in the register (e.g. during admission or supplied from outpatient clinics). For antipsychotics, 82% of the 28,856,000 DDDs used in 2020 were dispensed at community pharmacies.[14]

The Danish National Patient Register

The Danish National Patient Register contains information on admissions to Danish hospitals from 1977 and outpatient contacts from 1995.[59] Information on admissions or outpatient contacts to psychiatric hospitals were recorded in The Danish Psychiatric Central Research Register from 1969 and 1995, respectively, but is now included in the Danish National Patient Register. Each record in the registers holds information on date of admission/visit, type of admission/visit, and associated diagnoses (both primary and secondary). From 1994, diagnoses were recorded using WHO International Statistical Classification of Disease and Health-related Problems, 10th revision, whereas the 8th revision was used prior to 1994.[59] Validity of the diagnoses may vary according to type, but were generally high for relevant diagnoses such as diabetes (positive predictive value [PPV]: $\geq$95%), acute myocardial infarction (PPV: 98-100%), and stroke (PPV: 94-97%).[60]

The Danish Cause of Death Register

Date of death is registered in the Danish Civil Registration System; but for more detailed information pertaining to manner and cause of death, information is found in the Danish Cause of Death Register.[61] Information from the latter register can be used to classify deaths as, e.g., from natural causes or by suicide, and to assess the underlying (direct) cause of death and contributory cause(s) of death. The later information is of special interest in assessing outcomes such as death from cardiovascular causes (study III).

The Danish National Laboratory Databank

Blood samples taken at hospitals, and most blood samples taken at general practitioners, are analyzed at clinical chemical laboratories which store information on analysis codes, sampling date, and results.[62,63] Each of the five administrative regions in Denmark has its own clinical laboratory information system, but since 2013-2015 data from these systems has been collected in the Danish National Laboratory Databank. The central data set contains data from before 2013/2015, but coverage might vary. Additionally, general practitioners might analyze biomarkers as HbA1c using point-of-care devices, and these results will not be transferred to this register.

The Danish National Health Service Register

In Denmark, general practitioners and (most) specialists in private practice provide free-of-charge health care according to a collaborative agreement with the administrative regions.[64] They are subsequently reimbursed by the administrative regions and the data used for this reimbursement process is recorded in the Danish National Health Service Register.[65] These data include

date of the contact, type of service, and the providers medical specialty (e.g. general practitioner, psychiatrist, neurologist, etc.). No information on diagnoses associated with the encounter is included in the register. Additionally, other information that might be recorded in connection to the encounter (e.g. body mass index, smoking status, alcohol consumption, etc.) is not collected routinely and thus not available for research based on registers.

Study specific methods

All four studies were based on prescriptions for antipsychotics or quetiapine from the Danish National Prescription Register, with various supplementation from the other registers described above. Study I is a descriptive study (a drug utilization study), while studies II-IV are cohort studies based on new users of quetiapine. An overview of study characteristics, populations, outcomes, and comparisons is provided in Table 3 (p. 39).

Table 3: Overview of study characteristics, populations, and data sources in studies I-IV

Study	Type	Population	Outcomes	Comparison
I	Drug utilization study	All users of APs 1997-2018	Overall AP use statistics, assessment of possible indications, characterization of AP users without diagnoses of interest, and treatment persistence in various subgroups	–
II	Cohort study	New users of quetiapine 1998-2017	Incidence of diabetes	New users of SSRIs
III	Cohort study	New users of quetiapine 2003-2017	Incidence of major adverse cardiovascular events (myocardial infarction, stroke, and death from cardiovascular causes)	New users of Z-drugs and SSRIs
IV	Cohort study	New users of quetiapine 2008-2018	Change in HbA1c, cholesterols, and triglycerides	Within-subject

Abbreviations: AP: antipsychotic, HbA1c: glycosylated hemoglobin A1c, SSRIs: selective serotonin reuptake-inhibitors, Z-drugs: benzodiazepine-related drugs (ATC-code N05CF, e.g. zolpiclone).

Study I: Assessment of potential indications for off-label use

This study describes the use of antipsychotics in Denmark in four dimensions: i) at population-level using various drug utilization measures, ii) at group-level categorizing users according to potential indications for antipsychotic treatment, iii) characterizing those treated outside hospitals, and iv) assessing treatment persistence in specific subgroups. The methods used for each part are described in detail in paper I[66] (appendix 1), and the following paragraph elaborates on how potential indications were assessed.

In principle, it is possible to assess indications for antipsychotic therapy, as prescription records in the Danish National Patient Register include data on the patient instruction, which occasionally includes the reason for which the prescription was issued.[58] However, for discretion, this text is often very unspecific, or euphemistic for psychotropic drugs (e.g. 'for mental illness / discomfort') and would not be sufficient to separate on-label use from off-label use or to investigate specific indications for antipsychotic treatment. To overcome this issue, the occurrence of diagnoses recorded in the Danish National Patient Register in connection to prescriptions for antipsychotic drugs in the Danish National Prescription Register was assessed. This approach was used to classify each individual who filled a prescription for an antipsychotic drug into one of the six categories described in Table 4 (p. 41). In connection to other drug use statistics (described in detail in paper I[66]), this classification was used to describe the current use of antipsychotics in Denmark, and its development from 1997 to 2018.

Table 4: Classification of individuals with antipsychotic prescriptions based on the occurrence or absence of specific diagnoses in the Danish National Patient Register

Groups*	**Diagnoses (examples)**	**Assessment window**	**Remarks**
Group 1: Severe mental disorders	Schizophrenia, other psychoses, bipolar disorder	From register inception to 6 months after the prescription	Core indications for antipsychotic treatment. The assessment period was extended to any record before the prescription to capture individuals with the diagnosis, but with no or infrequent hospital contacts.
Group 2: Chronic mental disorders	Dementia, intellectual disability, autism	From register inception to 6 months after the prescription	Conditions where antipsychotic treatment might be indicated. The assessment period was extended to any record before the prescription as these conditions are chronic but only have hospital contacts around the time of diagnosis.
Group 3: Other mental disorders	Substance abuse disorders, major depression, anxiety disorders, personality disorders	Within 6 months before or after the prescription	This group includes all psychiatric diagnoses not included in group 1 and 2. Antipsychotics are generally not approved for treatment of these conditions, except for major depression (flupentixol and quetiapine) or major depression with psychotic symptoms (most antipsychotics)

Continues on next page

Table 4 (continued)

Groups*	Diagnoses (examples)	Assessment window	Remarks
Group 4: Neurological diagnoses only	Parkinson' disease, epilepsy, sleep disorders	Do.	Antipsychotics are generally not approved for neurological conditions, except for psychosis in Parkinson's disorder (clozapine) or hyperkinesias (haloperidol and pimozide). Antipsychotics might be used in neurological conditions with psychosis, e.g. some cases of epilepsy.
Group 5: Cancer diagnoses only	Any malignant neoplasm	Do.	Antipsychotics might be used for delirium in end-of-life care or for chemotherapy induced nausea and vomiting. Individuals with records of non-melanoma skin cancer was excluded as they are not likely to be terminal or undergo chemotherapy.
Group 6: No relevant diagnosis**	–	Do.	–

Notes: *Groups were mutually exclusive and individuals were assigned to the lowest group for which they fulfilled the criteria. **No relevant diagnosis means 'in the Danish National Patient Register or the Danish Psychiatric Central Research Register' as individuals in this groups might have been diagnoses and treated for mental disorders at general practitioners or psychiatrist in private practice for e.g. major depression. Therefore, this group was further characterized using information from the Danish National Health Service Register as described in paper I.[66]

Study II/III: New-user, active comparator-controlled cohort studies

Studies II and III investigate the association between use of low-dose quetiapine, diabetes, and cardiovascular events. As such associations are likely to be confounded, both studies were based on a new-user, active-comparator design with strict inclusion and censoring criteria. Furthermore, a high-dimensional propensity score (hdPS) was used to mitigate the impact of both measured and potential unmeasured confounders. Overall, the design mimicked a hypothetical 'trial' on the safety of low-dose quetiapine compared to another relevant treatment option.

Only new users of each drug were allowed in the cohort, and individuals who had recent use of the other study drug or of another antipsychotic were excluded to avoid carry-over effects from this exposure. Eligible individuals were then followed from treatment initiation until they experienced either the outcome, died, or were censored. Reasons for censoring were twofold: 'classical' (e.g. emigration, reaching maximum follow-up, end of data availability) or events that 'shifted' individuals into another risk category (e.g. using higher doses of quetiapine, using another antipsychotic, switching from one study drug to the other, being diagnosed with a severe mental disorder).

Selective serotonin reuptake inhibitors (SSRIs) and benzodiazepine-related drugs (Z-drugs) were used as active comparators. These non-antipsychotic medications were chosen as other antipsychotics are either associated with a higher risk of metabolic adverse effects than quetiapine (e.g. olanzapine[67]) or, for those with less metabolic adverse effects, not commonly used of off-label as quetiapine (e.g., aripiprazole). Furthermore, SSRIs and Z-drugs are used in a wide range of mental disorders where quetiapine might also be used. SSRIs were chosen as comparator in study II on diabetes, as they have potentially no or little effect on the risk of diabetes.[68] However, Z-drugs were chosen as the primary comparator in study III on cardiovascular outcomes for two main reasons: i) Z-drugs have not been associated with cardiovascular

disease,[69] ii) SSRIs have platelet-inhibiting properties,[70] which might reduce the risk of thrombo-embolic events and complicate interpretation of results. Further elaboration on the choice of comparators, and their potential shortcomings, is provided in the discussion.

A high-dimensional propensity score (hdPS) was used in both studies to minimize the impact of confounding that could not be eliminated by restriction on measured confounders*.[71] In general terms, a propensity score is the individual's probability to initiate a specific treatment given a set of characteristics (e.g. age, sex, use of drug A, B, C, history of condition X, Y, Z, etc.).[72] The hdPS-algorithm proposed by Schneeweiss et al.[73] is a data-driven approach to select characteristics (e.g. diagnoses or prescriptions) with the highest potential for confounding and which allows inclusion of multiple co-variates when there are few outcomes, without the risk of small sample bias†.

* e.g. prior use of other drugs associated with the outcomes or confounding by indication (i.e. the effect of disease on outcomes).

In study II and III, 50/100 covariates selected by the hdPS-algorithm were used to predict each individuals' propensity to initiate treatment with low-dose quetiapine. The resulting propensity scores were then used: i) to create a population of comparable individuals by removing individuals in the non-overlapping regions,[75] and then ii) to 'level-out' between-group differences in the distribution of various confounders. In study II, the latter was achieved by matching on the propensity score, whereas individuals were weighted according to their propensity score in study III.

† 'The highest potential for confounding' refers to given covariate (confounder) that is positively or negatively associated with the outcome and more prevalent in one group than in the other. Such imbalance will increase the risk of bias. Therefore, the product of the association and the prevalence ratio (multiplicative bias) is used for prioritization and selection of covariates. We included 50 covariates in study II and 100 covariates in study III, as such numbers give sufficient confounder control, with only minor gains from inclusion of more covariates.[74]

In study II, the primary analysis was conducted on a propensity score-matched population as diabetes is a relatively frequent event, and any loss of individuals from matching was not likely to result in an insufficient number of events. In study III, the hdPS was used for various types of weighting. This approach was chosen over matching as cardiovascular events are less frequent than diabetes, and therefore information from as many individuals as possible was crucial.

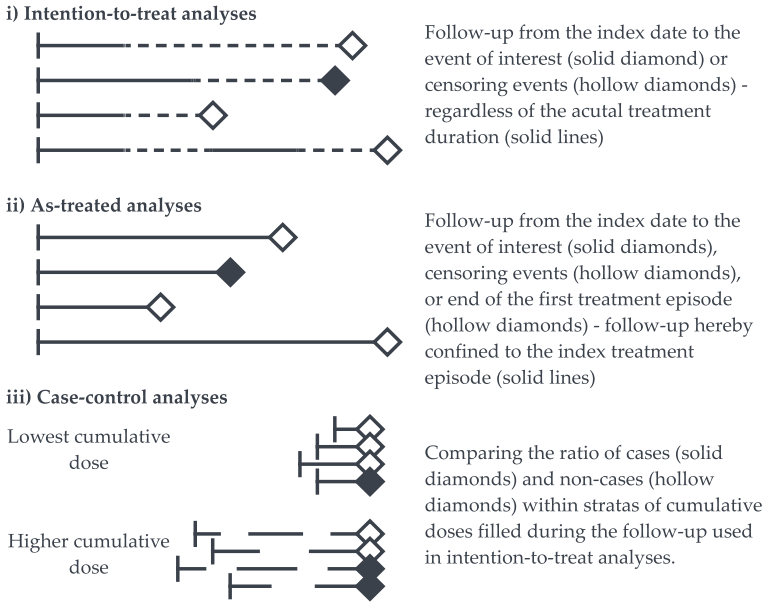


Figure 2: Various approaches to follow-up used in study II-III. See further description in the text.

The cohorts were analyzed in three different ways as depicted in Figure 2: i) using an 'as-treated' approach to follow-up; ii) using an 'intention-to-treat-like' approach to follow-up; and iii) using a nested case-control analysis. These three approaches were chosen to supplement each other as antipsychotic-induced diabetes or cardiovascular disease involves multiple pathophysiological mechanisms and might, or might not, be dependent of dose or duration. In as-treated analyses, only events that occurred in connection to the first treatment episode were considered. This approach prioritizes continuous use but does not consider events that occurred after treatment, even though they might be related to the treatment. In intention-to-treat analyses, all events between treatment initiation and end of follow-up were considered. This approach captures events that could be related to the treatment but occurred months or years after the treatment was stopped, and thus not captured in as-treated analyses. However, longer follow-up can increase the impact of other factors on cardiovascular risk. Lastly, a case-control analysis supplemented the intention-to-treat and as-treated analyses by assessing the

relation between cumulative dose and the outcomes. In this analysis, the risk of outcomes with higher cumulative dose categories were compared with the risk among those with minimal use (i.e. one prescription for quetiapine).

Study IV: New-user cohort study

Study IV used blood test results to investigate the impact of low-dose quetiapine on HbA1c, triglyceride, and cholesterol-levels. A cohort of new low-dose quetiapine-users in Denmark (2008-2018*) was constructed using the Danish National Prescription Register. From this cohort, individuals with a history of severe mental disorders or recent use of other antipsychotics were excluded. The Danish National Laboratory Databank was then used to identify all measurements of HbA1c, fasting triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol within 365 days before and after the index date† for the eligible low-dose quetiapine-users. Only individuals with measurements both before and after the index date were included in analyses.

Mixed-effects linear regression models were then used to examine the development in HbA1c-, triglyceride, and cholesterol-levels after initiation of low-dose quetiapine. Exploratory analyses found that low-dose quetiapine-users with abnormal levels before the index date were more likely to have measurements after the index date, and thus more likely to be included in the analyses. To mitigate the potential for selection bias and the vulnerability to 'regression-towards-the-mean'‡, inverse probability weights were implemented in regression models. Each participant was weighted according to the inverse of their probability to have post-initiation measurements, estimated from the individual's sex, age at initiation, calendar year of initiation, and the average level of the of the outcome in the year before the index date.

To explore effect modification, analyses were also conducted for

* In study IV, the inclusion period began in 2008 as there were no measurements of the relevant analyses available in the Danish National Laboratory Databank prior to this year.

† Similar to study II and III, follow-up after the index date was restricted to time without use of other antipsychotics, without prescription fills for quetiapine in tablet strengths $\geq$50mg, and without diagnosis of a severe mental disorder (i.e. follow-up ended if individuals received a diagnosis of e.g. schizophrenia).

‡ 'Regression towards the mean' describes the phenomenon that the value following an extreme value (e.g. very high or very low blood glucose) will most likely be less extreme (closer to the mean).

various subgroups (e.g. sex, age, or outcome level before the index date). Furthermore, two supplementary analyses were conducted i) excluding individuals with any use of antidiabetic or lipid-lowering drugs during the observation period, as such treatment might mitigate or obscure a potential effect of low-dose quetiapine on HbA1c-, triglyceride-, or cholesterol-levels; and ii) in cohorts initiating higher tablet strengths of quetiapine (100mg/>100mg vs. $\leq$50mg) to asses if the effect on outcomes was dependent on the dose of quetiapine.

This chapter introduced the data sources used in the four studies and described methodological considerations regarding central design features. The following chapter summarizes the main results from each of the four studies. General limitations and further methodological issues with these designs and their implementation are addressed in the discussion.

Summary of findings

The main results from each the four studies are presented in the following chapter. The resulting papers and their supplementary material are included at the end of the thesis as appendices I to IV.

Study I: Use of antipsychotics in Denmark

The first study explored how antipsychotics were used in Denmark in 2018 and the development in diagnostic groups from 1997 to 2018. The primary focus is the diagnoses associated with use of antipsychotics, but it also includes overall drug utilization measures, a characterization of AP-users without relevant diagnoses, and an exploration of treatment persistence in selected subgroups. The study is based on the 630,307 individuals who filled prescriptions for antipsychotic drugs at pharmacies in Denmark from 1997 to 2018.

The two largest groups, within the 127,649 individuals who filled one or more prescriptions for an antipsychotic in 2018, were those with diagnoses of severe mental disorders (34% of all users in 2018) and those without records of psychiatric, neurological, or cancer diagnoses (37%). Individuals with 'non-severe' mental disorders accounted for 27% of AP-users in 2018, with the largest groups being dementia, mental retardation (incl. autism), sub-

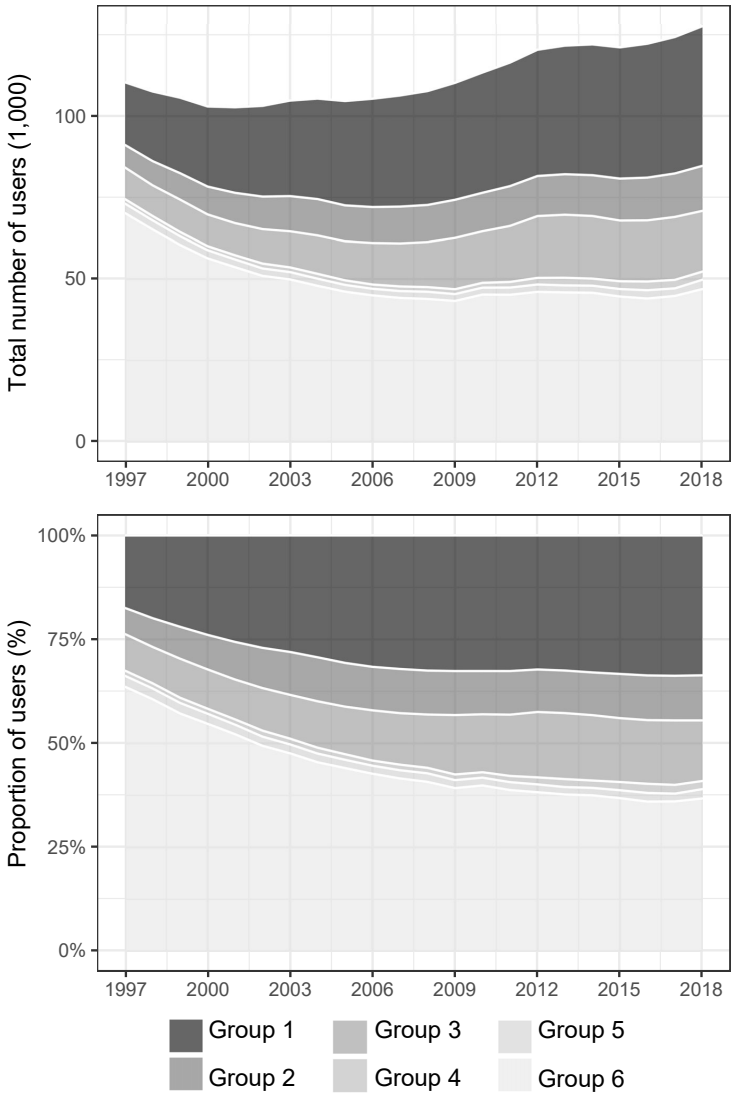


Figure 3: Total number and proportion of AP-users by diagnostic groups, Denmark 1997-2018. Group numbers correspond with table 4. Adapted from paper I.[66]

stance use disorders, major depression, and reaction to severe stress (e.g. post-traumatic stress disorder or adjustment disorder). Individuals with neurological disorders or cancer diagnoses (and no record of mental disorders) constituted only 4% of all AP-users in 2018. From 1997 to 2018, the prevalence of antipsychotic drug-use did not increase considerably (from 20.9 to 22.1 users per 1,000 inhabitants). Meanwhile, the group of AP-users without relevant diagnoses decreased from 62 to 37%, and most other groups increased in size (Figure 3).

The number of users for specific antipsychotics in 2018 are shown in Table 5. The 10 most commonly used antipsychotics accounted for 91% of the total amount sold. However, the diagnoses among users of the most commonly used antipsychotics differed considerably. Nearly all users of clozapine had diagnoses of severe mental disorders (91%), whereas most users of flupentixol had no record of relevant diagnoses (72%). For quetiapine, the proportion of users without relevant diagnoses was 42%. However, as quetiapine was the most frequently used antipsychotic, this group corresponded to 27,277 individuals in 2018.

Antipsychotic	Users
Quetiapine	64,946
Olanzapine	17,554
Risperidone	16,056
Chlorprothixene	14,028
Aripiprazole	12,357
Haloperidol	7,963
Zuclopenthixol	4,224
Levomepromazine	4,017
Flupentixol	3,809
Clozapine	3,403
Paliperidone	1,523
Ziprasidone	1,066
Amisulpride	720
Pimozide	558
Perphenazine	537
Lurasidone	371
Prochlorperazine	313
Sulpiride	311
Sertindole	247
Pipamperone	222
Melperone	198
Periciazine	170
Asenapine	25
Cariprazine	<5

Table 5: The number of users by specific antipsychotics in Denmark 2018. Adapted from paper I[66]

In the group of users without relevant diagnoses, most would fill prescriptions for small quantities ($\leq$90 DDD, 80%) during 2018. Half of users in this group would also fill prescriptions for antidepressants in connection to their first prescription (51%). Among incident users without relevant diagnoses in 2018, 12% had seen an office-based psychiatrist in the 14 days prior to their first prescription of an antipsychotic, while 65% (9,434 individuals) had only been in contact with a general practitioner.

Lastly, analyses of treatment persistence found that many AP-users would end treatment within a year after their first prescription, but also that a considerable proportion of patients with non-severe mental illnesses would continue to fill prescriptions for antipsychotics 5 years after their first prescription.

Study II: Diabetes

The second study investigated the association between off-label use of quetiapine in low doses and development of type 2 diabetes in a new-user, active-comparator cohort design. The study was based on all eligible new users of quetiapine (n=57,701) and SSRIs (n=838,584) in Denmark from 1998 to 2017. Eligible users began treatment with quetiapine in tablet strengths $\leq$50mg, had not previously used the other drug (SSRIs or quetiapine), had no recent use of other antipsychotics, had no records of diabetes or severe mental illness, had resided in Denmark >1 year before inclusion, and were $\geq$18 years at the time of their first prescription. From this cohort, a high-dimensional propensity score-matched cohort was formed including 54,616 new users of each drug. Median follow-up among low-dose quetiapine-users in the ITT-analysis was 1.3 years and common reasons for censoring were prescription fills for SSRIs or other antipsychotics.

In analyses of the full cohort, use of low-dose quetiapine was associated with a slightly higher risk of developing type 2 diabetes compared to use of SSRIs. However, in analyses of the hdPS-matched cohort there were no difference between incidence rates in the two groups (Table 6).

Lastly, increasing cumulative doses of quetiapine (as low dose treatment) was not associated with increased risk of developing type 2 diabetes. However, supplementary analyses that included higher tablet strengths of quetiapine found increasing risk of diabetes.

	Full cohort IRR (95%CI)	Matched cohort IRR (95%CI)
As-treated analysis	1.18 (1.07-1.30)	0.99 (0.87-1.13)
Intention-to-treat analysis	1.13 (1.06-1.21)	0.92 (0.84-1.00)

Abbreviations: CI, confidence interval; IRR, Incidence rate ratio.

Table 6: Association between use of low-dose quetiapine and development of type 2 diabetes. Adapted from paper II.[76]

Study III: Major adverse cardiovascular events

The third study investigated the association between off-label use of quetiapine in low doses and major adverse cardiovascular events (MACE)* in a new-user, active-comparator cohort design. The study is based on all eligible new users of quetiapine (n=60,566) and Z-drugs (n=454,567) in Denmark from 2003 to 2017. Eligibility and censoring criteria were generally similar to those used in study II, although with exclusion of individuals with history of myocardial infarction or stroke instead of diabetes. The study used various propensity score-weighting methods to adjust for baseline confounding. To minimize exposure misclassification, the intention-to-treat analyses were restricted to individuals with $\geq$1 additional prescription within 180 days after the first prescription. Median follow-up among low-dose quetiapine-users in the ITT-analysis was 2.6 years, and common reasons for censoring were use of other antipsychotics, use of quetiapine in higher doses, or use of the comparator drug.

* The term 'major adverse cardiovascular events' (MACE) has been used inconsistently in observational studies.[77] In this study, MACE was defined as similar to that in RCTs i.e. as a composite end-point of acute myocardial infarction, stroke, and death from cardiovascular causes. These events were also investigated separately.

Use of low-dose quetiapine was associated with higher risk of MACE, compared to use of Z-drugs, in both intention-to-treat analyses and as-treated analyses (Table 7). This increased risk was mainly driven by an increased risk of death from cardiovascular causes as the risk of myocardial infarction was not increased in any the analyses, and an increased risk of stroke was only found with continuous treatment (i.e. in as-treated analyses).

Table 7: Association between use of low-dose quetiapine and major adverse cardiovascular events, compared to use of Z-drug hypnotics. Adapted from paper III.[78]

	Intention-to-treat analysis* HR (95%CI)	As-treated analysis** HR (95%CI)
Major cardiovascular adverse events	1.13 (1.02-1.24)	1.52 (1.35-1.70)
Non-fatal myocardial infarction	0.91 (0.73-1.14)	0.91 (0.69-1.21)
Non-fatal ischemic stroke	0.98 (0.83-1.15)	1.37 (1.13-1.68)
Death from cardiovascular causes	1.26 (1.11-1.43)	1.90 (1.64-2.19)

Abbreviations: CI, confidence interval; HR, hazard ratio.
Notes: *Adjusted for baseline confounding using fine-stratification weights. **Adjusted for baseline confounding and selection bias using inverse probability of treatment and censoring weights.

Sensitivity analyses found similar results both using SSRIs as alternative comparator and excluding individuals with a history of hospital-treated major depression. The risk of MACE was not related with cumulative dose of quetiapine (as low dose treatment), although a sensitivity analysis including all tablet strengths of quetiapine found an increased risk of death from cardiovascular causes with cumulative doses >50,000mg compared to cumulative doses ≤2500mg (odds ratio [OR] 1.32, 95%CI: 1.09-1.60).

Study IV: Metabolic changes

The fourth study investigates whether initiation of low-dose quetiapine was associated with metabolic alterations in a new-user design.

Between 2008 and 2018, a total of 106,711 eligible new users of quetiapine were identified in the Danish National Prescription Register. Approximately 10% of this population had measurements of HbA1c, total cholesterol, LDL cholesterol, and/or HDL cholesterol before and after initiation of low-dose quetiapine. For fasting triglycerides, the proportion was even lower (approx. 1%). Exploratory analyses found that the probability of having measurements after initiation of low-dose quetiapine increased considerably if pre-initiation-levels were elevated.

Outcome	Individuals/samples, N	Coefficient (95%CI)
HbA1c	9420/33740	0.999 (0.997 to 1.002)
Total cholesterol	9905/33678	0.993 (0.989 to 0.996)
Triglycerides	1300/4195	1.049 (1.027 to 1.072)
LDL cholesterol	9220/30940	0.984 (0.977 to 0.990)
HDL cholesterol	9524/32111	0.982 (0.978 to 0.986)

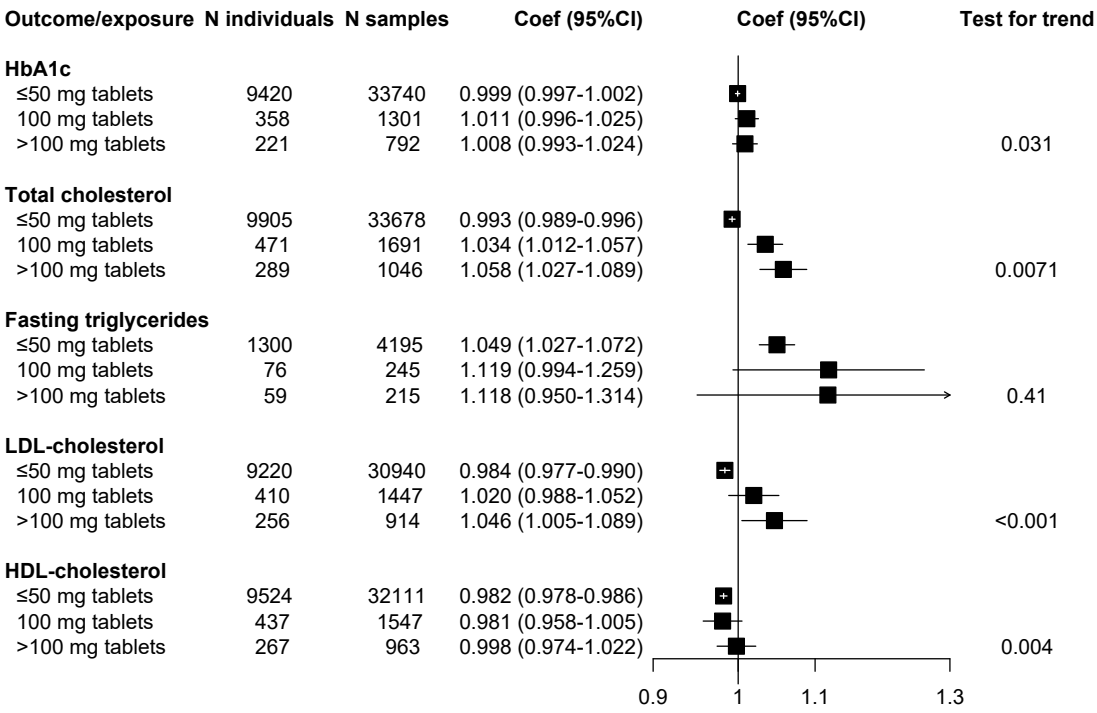
Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number.
Notes: A coefficient above 1 indicates higher levels after initiation of low-dose quetiapine relative to before initiation.

Table 8: Change in metabolic parameters after initiation of treatment with low-dose quetiapine. Adapted from paper IV.

Overall, initiation of low-dose quetiapine was associated with increases in (fasting) triglycerides; and decreases in total cholesterol, LDL-cholesterol, and HDL-cholesterol, whereas there was no indication of significant increases on HbA1c (Table 8).

However, analyses stratifying on the average level in the preceding year before initiation found that initiation of low-dose quetiapine was associated with increases in HbA1c, fasting triglycerides, total cholesterol, LDL cholesterol; and decreases in HDL cholesterol; among those with normal levels before initiation. Furthermore, supplementary analyses suggested that changes in metabolic parameters might depend on the daily dose of quetiapine, as initiating higher tablet strengths was associated with higher relative increases in the outcomes (Figure 4).

Figure 4: Change in metabolic parameters after initiation of treatment with quetiapine in various tablet strengths. (From paper IV)



Discussion

This chapter begins with a brief summary of findings in relation to the thesis aims. Hereafter follows a discussion of the need for observational studies to answer safety questions, selected methodological issues with designing such studies, and what these limitations might mean for their generalizability. Lastly, the implications for off-label use of quetiapine will be discussed.

This PhD project contributes to the evidence regarding off-label use of antipsychotics and the safety of such use. The first study provides a comprehensive, updated description of the current utilization of antipsychotics in Denmark. Additionally, the study identifies quetiapine as the most relevant antipsychotic for further study, and that a considerable proportion of antipsychotics are prescribed outside psychiatry. The remaining three studies provide evidence on the cardio-metabolic safety of quetiapine in its predominant role – used off-label in low doses. The second study found no clear association between off-label, low-dose use of quetiapine and subsequent development of type 2 diabetes, whereas the third study found that off-label use of low-dose quetiapine was associated with an increased risk of stroke and death from cardiovascular causes, but not of myocardial infarction. The fourth study found that use of quetiapine in low doses was associated with changes in both fasting triglyceride-levels and HDL cholesterol-levels, when considering all users, and in HbA1c- and total/LDL cholesterol-levels among those with normal pre-initiation levels. However, the findings must be interpreted in

light of both the strengths and limitations of observational designs, which are discussed in the following chapter. Specifically, the present chapter elaborates on the issues regarding choice of comparators, restrictions on follow-up, and external validity of the findings as a prerequisite for the conclusions regarding safety of low-dose quetiapine.

The relevance of observational studies for safety questions

A randomized controlled trial (RCT) is considered the 'gold standard' in medical research for its ability to reduce the impact of confounders, and hereby allow causal inference (i.e. does one treatment result in benefit/harm compared to another treatment). However, practical limitations with RCTs make them unfeasible to study long-term adverse effects such as diabetes and cardiovascular events.[79] In order to capture an adequate number of events, both a large number of participants and a considerable follow-up are needed. Such large-scale, long-term RCTs are costly and time consuming, which is why they are only likely to be conducted by the industry and for certain medications with a large body of users (i.e. antidiabetic drugs). Additionally, exclusion criteria related to medical comorbidities might limit the generalizability of results from RCTs.[80] Furthermore, ethical concerns regarding the potential harm of an intervention might preclude an RCT as the appropriate design to study a given question.[81]

For these reasons, observational studies on routinely collected data offer a way to answer safety questions regarding antipsychotic drugs, and the development of sophisticated analytical methods have improved their ability to reduce the impact from various confounding factors.[82] This development includes several approaches to mitigate the impact of confounding factors such as the use of new-user active-comparator designs, emulation of a target trial, and propensity score methods.[72,83,84]

Choice of comparator

The overall idea of conducting an active comparator-controlled study is to control for 'confounding by indication', i.e. to separate the effect of the drug from the effect of disease on the outcome.[83] In the present studies, it means that both mental illness/distress (and associated factors) as well as the use of quetiapine could be related to development of diabetes or cardiovascular disease. Therefore, comparison with population controls would not yield the intended causal contrast (the effect of treatment with quetiapine regarding the outcomes) but rather the combined effect of quetiapine and the condition for which it was used, and thus not providing an answer specific to quetiapine alone.

Ideally, the comparator should be as appropriate a treatment option as the drug of interest to ensure that individuals might equally well be in one group as the other (positivity).[85] However, for low dose quetiapine there is no such direct alternative. As briefly touched upon in the methods section, no other antipsychotic constitutes a suitable comparator: e.g. the second-generation olanzapine, which might be used in a similar role as quetiapine for its anxiolytic/hypnotic properties, is associated with an even higher risk of metabolic disturbances than quetiapine.[33,86] The first-generation antipsychotic chlorprothixene is commonly used in a role similar to that of low dose quetiapine, but it has recently been associated with increased risk of diabetes and stroke compared to use of low-dose quetiapine.[87] Another commonly used second-generation antipsychotic aripiprazole has less impact on metabolic parameters than quetiapine.[33] However, aripiprazole is predominantly used for treatment of severe mental disorders, and not in the same role as sedative or hypnotic as quetiapine. Lastly, metabolic disturbances could to some degree be considered a 'class effect' for second-generation antipsychotics and disqualify any second-generation antipsychotic as comparator.[88] For these reasons, the comparator had to be chosen among other psychotropic drugs

than antipsychotics, which might also be used in conditions with symptoms such as anxiety or insomnia. However, the chosen comparators (SSRIs and Z-drugs) are not ideal as they are not completely 'substitutable' with low-dose quetiapine. SSRIs are used in a variety of psychiatric disorders, e.g. anxiety disorders and major depression, whereas Z-drugs are used by a wider 'range' of individuals who are not necessarily suffering from other psychiatric symptoms than insomnia. However, prescription fills for the comparator drugs still indicate some level of psychiatric symptoms, thus providing a more suitable comparator group than the general population. On this basis, application of propensity score-methods can be used to select comparable individuals from the comparator population and to adjust for differences in the distribution of potential confounders between groups.

Restrictions on follow-up

As described in the background chapter, diabetes and cardiovascular disease have a complex pathophysiology in which exposure to antipsychotic medication is only one of many potential factors.[30,41] Several censoring criteria were applied in an attempt to isolate the effect of low-dose quetiapine-use on the outcomes. However, the use of strict censoring criteria comes at a cost: follow-up is automatically limited, as many low-dose quetiapine users will become censored after a relatively short while due to e.g. prescription fills for the comparator drug or other antipsychotics as seen in both study II and III. Therefore, the true effect of low dose quetiapine on the risk of diabetes or cardiovascular events might be underestimated with the present designs as such outcomes typically develop over years and might not be diagnosed within the follow-up period.

Extending the follow-up further would potentially increase the impact of other factors during follow-up, for which we were not able to control e.g. lifestyle-related factors or other treatments

affecting the outcomes. This was the main reason for limiting the maximum follow-up to 5 or 10 years. Furthermore, we included as-treated analyses as an aid for the interpretation of intention-to-treat analyses in both study II and III. Similar or higher risk in as-treated analyses compared to intention-to-treat analyses would imply that the extent of exposure was related to the outcomes.

External validity

An important question is if findings from the present studies can be applied to other countries or populations. Even though the common and increasing use of quetiapine has been documented in several countries around the world,[13,15,16,18,89] the specific utilization of antipsychotics is likely to be somewhat country-specific and vary with tradition, health care organization etc. For example, chlorprothixene is commonly used in the Scandinavian countries, whereas sulpiride is commonly used in some Asian countries.[89] Therefore, the results from study I are not thought to be generalizable beyond Denmark but should be used specifically to guide initiatives on the rational use of antipsychotics in Denmark.

In contrast, the results from studies II-IV regarding cardiometabolic safety might be generalizable to low-dose quetiapine-users in other countries. However, the actual study populations should be kept in mind as studies II-IV only included i) adults, ii) without severe mental illness, and iii) not concomitantly using other antipsychotics or SSRIs/Z-drugs. Therefore, the results do not allow inference about the risk of cardiometabolic safety of low-dose quetiapine in children and adolescents, who have been found to be particularly vulnerable to adverse events in relation to use of antipsychotic drugs, including diabetes.[90,91] Likewise, individuals with severe mental illness or individuals who use other psychotropic drugs concomitantly are at increased risk of cardiometabolic adverse events.[40,42] This phenomenon was, to

some extent, illustrated in study II by the higher rate of diabetes in the full cohort in comparison with the hdPS-matched cohort. Low-dose quetiapine-users not included in the hdPS-matched cohort were more likely to have recent prescriptions for e.g. mirtazapine*.

* An antidepressant with high affinity for the H1-receptors involved in the pathophysiology of diabetes[28]

Besides concerns regarding the target population, there are a number of other factors to consider in order to generalize the findings. The specific risk of cardiometabolic adverse events is likely to be differential, which was the reason to include subgroup analyses in studies II-IV. Furthermore, the question of generalizability to other populations may arise, e.g. would the use of low-dose quetiapine be associated with higher rates of diabetes in a population with higher rates of obesity? As the cohort studies addresses biological effects, these are unlikely to vary substantially by population, although some degree of effect measure modification might be present. For example, the pharmacokinetics for quetiapine can differ between various ethnicities due differences in polymorphisms.[92] Slow metabolism of quetiapine will then increase exposure and might render some ethnic groups more vulnerable to side effects than others. To elucidate the potential for effect measure modification, and to confirm the findings, the studies should be replicated in other populations.

Implications for off-label use of quetiapine

The use of quetiapine has become increasingly common over the last decades in Denmark[13] and a substantial proportion of prescriptions are issued by general practitioners.[93] This development has coincided with a decreasing use of benzodiazepines and related drugs,[94] likely due to increased attention to the adverse effects of benzodiazepines. The 'switch' from benzodiazepines towards antipsychotics with anxiolytic-sedative properties (e.g. quetiapine) might reflect a 'clinical vacuum' – that patients are in need of medications for symptoms as anxiety or

insomnia, or that non-pharmacological initiatives are not sufficient or feasible. Future initiatives to ensure the rational use of antipsychotics should therefore focus on both psychiatrists and non-psychiatrists (including general practitioners).

The crucial question is how we should perceive the safety of quetiapine when used off-label and in low doses. While quetiapine, used in this role, was not associated with an increased risk of diabetes in study II,[76] an increased risk of death from cardiovascular causes was identified in study III.[78] Furthermore, study IV found that off-label, low-dose use of quetiapine was associated with development of various metabolic disturbances, most clearly with increasing triglyceride-levels and decreasing HDL cholesterol-levels. Altogether, these findings suggests that off-label, low-dose use of quetiapine should not be perceived as harmless, and that the association with metabolic dysregulation and cardiovascular mortality should motivate the search for alternatives – ideally non-pharmacological alternatives.

However, the clinical reality is complex and off-label use of antipsychotics as quetiapine is likely to continue, even though there is evidence of adverse effects.

In this situation, the central initiative to identify and intervene with such adverse events is adequate monitoring of risk factors for cardiometabolic disease. Especially, the low level of testing and the indication of selective testing identified in study IV, draws attention to this issue. Nowadays, monitoring of cardiometabolic risk factors is considered standard of care when initiating treatment with antipsychotic medications.[95–97] However, in Denmark, monitoring of such risk factors is only mandatory when using antipsychotics in individuals with psychotic disorders.[98] Given the association with metabolic dysregulation seen with even low doses of quetiapine, such metabolic monitoring should be installed with the prescription of any antipsychotic, regardless of indication, dose, and duration.

Conclusions

The work presented has shed light on both the current utilization of antipsychotics in Denmark and provided evidence on the cardiometabolic safety of quetiapine used off-label and in low doses.

The majority of users of antipsychotic drugs did not have diagnoses of severe mental illnesses such as schizophrenia or bipolar disorder, which are the main indications to install treatment with an antipsychotic drug. Of all antipsychotics, quetiapine had the highest number of users and is thus the most relevant drug to explore further. Lastly, results from study I indicated that general practitioners were responsible for initiating treatment with antipsychotic drugs in a proportion of users.

The absence of a major risk for cardiometabolic adverse events with off-label, low-dose use of quetiapine is reassuring. Bearing in mind the target population and the limitations on follow-up, no increased risk for diabetes was found, and the risk of major adverse cardiovascular events was modest. However, in studies II and III, analyses found that both dose and duration of treatment are likely to influence the risk of cardiometabolic outcomes, and that low dose use quetiapine should not necessarily be regarded as completely safe on the basis of these studies. Furthermore, study IV found that treatment with low doses of quetiapine was associated with development of risk factors for cardiovascular disease.

Directions for future research

Future studies on antipsychotic utilization should address the reasons for using antipsychotics in non-psychotic conditions, both from the prescriber perspective and the patient perspective. An in-depth exploration of the drivers and motives for the decision to prescribe or take an antipsychotic drug off-label will provide valuable insights for future initiatives to promote rational pharmacotherapy. Even though quetiapine was the most commonly used antipsychotic drug in 2018, attention should be devoted to other commonly used antipsychotics with indications of considerable off-label use, e.g. chlorprothixene or flupentixol.

The safety studies should be replicated in other populations, and the safety of low-dose quetiapine might be investigated in further detail, e.g. in cohort studies with manually collected information on life-style factors that would allow better exploration of how other risk factors for cardiometabolic disease (e.g. lifestyle-related factors), not captured in health care registers, might influence the association with diabetes and cardiovascular disease. As cardiometabolic risk is likely to be differential, future studies might also target other populations than those included in the present studies, e.g. children and adolescents or concurrent users of other psychotropic drugs to allow inference for a larger proportion of the actual users of quetiapine.

Lastly, prescribers might benefit from a better understanding of the potential adverse events with the use of quetiapine, and further development of clinical guidelines might ensure that non-pharmacological alternatives are pursued or that adequate monitoring of risk factors is installed.

References

1. European Medicines Agency. Off-label use. URL: https://www.ema.europa.eu/en/glossary/label-use (visited on 06/07/2022).
2. Wittich CM, Burkle CM, and Lanier WL. Ten Common Questions (and Their Answers) About Off-label Drug Use. Mayo Clin Proc 2012;87:982–90.
3. Ito S. Drugs for Children. Clin Pharmacol Ther 2017;101:704–6.
4. European Medicines Agency. Summary of product characteristics: Haldol and associated names (haloperidol). URL: https://www.ema.europa.eu/en/documents/referral/haldol-article-30-referral-annex-iii_en.pdf (visited on 06/07/2022).
5. Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, and Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet 2019;393:768–77.
6. Ingenhoven TJM and Duivenvoorden HJ. Differential effectiveness of antipsychotics in borderline personality disorder: meta-analyses of placebo-controlled, randomized clinical trials on symptomatic outcome domains. J Clin Psychopharmacol 2011;31:489–96.

7. Zhou DD, Zhou XX, Lv Z, et al. Comparative efficacy and tolerability of antipsychotics as augmentations in adults with treatment-resistant obsessive-compulsive disorder: A network meta-analysis. J Psychiatr Res 2019;111:51–8.
8. Liu Xh, Xie Xh, Wang Ky, and Cui H. Efficacy and acceptability of atypical antipsychotics for the treatment of posttraumatic stress disorder: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials. Psychiatry Res 2014;219:543–9.
9. Atkin T, Comai S, and Gobbi G. Drugs for Insomnia beyond Benzodiazepines: Pharmacology, Clinical Applications, and Discovery. Pharmacol Rev 2018;70:197–245.
10. Carton L, Cottencin O, Lapeyre-Mestre M, et al. Off-Label Prescribing of Antipsychotics in Adults, Children and Elderly Individuals: A Systematic Review of Recent Prescription Trends. Curr Pharm Des 2015;21:3280–97.
11. Baandrup L and Kruse M. Incident users of antipsychotics: who are they and how do they fare? Soc Psychiatry Psychiatr Epidemiol 2016;51:505–12.
12. WHO Collaborating Centre for Drug Statistics Methodology. DDD - Definition and general considerations. URL: https://www.whocc.no/ddd/definition_and_general_considera/ (visited on 06/07/2022).
13. Højlund M, Pottegård A, Johnsen E, et al. Trends in utilization and dosing of antipsychotic drugs in Scandinavia: Comparison of 2006 and 2016. Brit J Clin Pharmacol 2019;85:1598–606.
14. Danish Health Data Authority. Danish Register of Medicinal Product Statistics. URL: https://medstat.dk/en (visited on 06/07/2022).
15. Gjerden P, Bramness JG, Tvete IF, and Slørdal L. The antipsychotic agent quetiapine is increasingly not used as such: dispensed prescriptions in Norway 2004-2015. Eur J Clin Pharmacol 2017;73:1173–9.

16. Duncan D, Cooke L, Symonds C, Gardner D, and Pringsheim T. Quetiapine use in adults in the community: a population-based study in Alberta, Canada. BMJ Open 2016;6:e010861.

17. Leslie DL, Mohamed S, and Rosenheck RA. Off-label use of antipsychotic medications in the department of Veterans Affairs health care system. Psychiatr Serv 2009;60:1175–81.

18. Hartung DM, Zerzan J, Yamashita T, Tong S, Morden NE, and Libby AM. Characteristics and trends of low-dose quetiapine use in two western state Medicaid programs. Pharmacoepidemiol Drug Saf 2014;23:87–94.

19. Olfson M, King M, and Schoenbaum M. Antipsychotic treatment of adults in the United States. J Clin Psychiatry 2015;76:1346–53.

20. U.S. Food and Drug Administration. Seroquel® (quetiapine fumarate) tablets - Prescribing information. 2013. URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020639s045s046lbl.pdf (visited on 06/07/2022).

21. European Medicines Agency. Summary of product characteristics: Seroquel, Seroquel XR and associated names (quetiapine). URL: https://www.ema.europa.eu/en/documents/referral/seroquel-seroquel-xr-associated-names-article-30-referral-annex-iii_en.pdf (visited on 06/07/2022).

22. Danish Medicines Agency. Summary of product characteristics: Seroquel (Quetiapine fumarate). URL: http://produktresume.dk/AppBuilder/search (visited on 06/07/2022).

23. U.S. Food and Drug Administration. SEROQUEL XR® (quetiapine fumarate) extended-release tablets. URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022047s033s037lbl.pdf (visited on 06/07/2022).

24. Nemeroff CB, Kinkead B, and Goldstein J. Quetiapine: preclinical studies, pharmacokinetics, drug interactions, and dosing. J Clin Psychiatry 2002;63 Suppl 13:5–11.

25. Ravindran AV, Al-Subaie A, and Abraham G. Quetiapine: novel uses in the treatment of depressive and anxiety disorders. Expert Opin Investig Drugs 2010;19:1187–204.

26. Stahl SM. Stahl's essential psychopharmacology: neuroscientific basis and practical application. 4th ed. New York: Cambridge University Press, 2013.

27. Solmi M, Murru A, Pacchiarotti I, et al. Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review. Ther Clin Risk Manag 2017;13:757–77.

28. Kroeze WK, Hufeisen SJ, Popadak BA, et al. H1-Histamine Receptor Affinity Predicts Short-Term Weight Gain for Typical and Atypical Antipsychotic Drugs. Neuropsychopharmacology 2003;28:519–26.

29. Correll C. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics. Eur Psychiatry 2010;25:S12–S21.

30. Holt RIG. Association Between Antipsychotic Medication Use and Diabetes. Curr Diab Rep 2019;19:96.

31. Whicher CA, Price HC, and Holt RIG. Mechanisms in endocrinology: Antipsychotic medication and type 2 diabetes and impaired glucose regulation. Eur J Endocrinol 2018;178:R245–R258.

32. Chen J, Huang XF, Shao R, Chen C, and Deng C. Molecular Mechanisms of Antipsychotic Drug-Induced Diabetes. Front Neurosci 2017;11:643.

33. Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. The Lancet Psychiatry 2020;7:64–77.

34. Stogios N, Smith E, Bowden S, et al. Metabolic adverse effects of off-label use of second-generation antipsychotics in the adult population: a systematic review and meta-analysis. Neuropsychopharmacology 2022;47:664–72.

35. Correll CU, Joffe BI, Rosen LM, Sullivan TB, and Joffe RT. Cardiovascular and cerebrovascular risk factors and events associated with second-generation antipsychotic compared to antidepressant use in a non-elderly adult sample: results from a claims-based inception cohort study. World Psychiatry 2015;14:56–63.

36. Kessing LV, Thomsen AF, Mogensen UB, and Andersen PK. Treatment with antipsychotics and the risk of diabetes in clinical practice. Br J Psychiatry 2010;197:266–71.

37. Yood MU, DeLorenze GN, Quesenberry CP, et al. Association between second-generation antipsychotics and newly diagnosed treated diabetes mellitus: does the effect differ by dose? BMC Psychiatry 2011;11:97.

38. Cates ME, Jackson CW, Feldman JM, Stimmel AE, and Woolley TW. Metabolic consequences of using low-dose quetiapine for insomnia in psychiatric patients. Community Ment Health J 2009;45:251–4.

39. Carr CN, Lopchuk S, Beckman ME, and Baugh TB. Evaluation of the use of low-dose quetiapine and the risk of metabolic consequences: A retrospective review. Mental Health Clinician 2016;6:308–13.

40. Holt RIG and Mitchell AJ. Diabetes mellitus and severe mental illness: mechanisms and clinical implications. Nat Rev Endocrinol 2015;11:79–89.

41. Correll CU, Detraux J, De Lepeleire J, and De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World Psychiatry 2015;14:119–36.

42. Nielsen RE, Banner J, and Jensen SE. Cardiovascular disease in patients with severe mental illness. Nat Rev Cardiol 2021;18:136–45.

43. Douglas IJ and Smeeth L. Exposure to antipsychotics and risk of stroke: self controlled case series study. BMJ 2008;337:a1227.

44. Murray-Thomas T, Jones ME, Patel D, et al. Risk of mortality (including sudden cardiac death) and major cardiovascular events in atypical and typical antipsychotic users: a study with the general practice research database. Cardiovasc Psychiatry Neurol 2013;2013:247486.

45. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 2005;353:2335–41.

46. Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, and Wang PS. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ 2007;176:627–32.

47. Oh KJ, Park J, Lee SY, et al. Atypical antipsychotic drugs perturb AMPK-dependent regulation of hepatic lipid metabolism. Am J Physiol Endocrinol Metab 2011;300:E624–632.

48. Yan H, Chen JD, and Zheng XY. Potential mechanisms of atypical antipsychotic-induced hypertriglyceridemia. Psychopharmacology (Berl.) 2013;229:1–7.

49. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet 2019;394:939–51.

50. Layton D, Harris S, Wilton LV, and Shakir SAW. Comparison of incidence rates of cerebrovascular accidents and transient ischaemic attacks in observational cohort studies of patients prescribed risperidone, quetiapine or olanzapine in general practice in England including patients with dementia. J Psychopharmacol 2005;19:473–82.

51. Shin JY, Choi NK, Jung SY, Lee J, Kwon JS, and Park BJ. Risk of ischemic stroke with the use of risperidone, quetiapine and olanzapine in elderly patients: a population-based, case-crossover study. J Psychopharmacol 2013;27:638–44.

52. Berge J, Abri P, Andell P, Movahed P, and Ragazan DC. Associations between off-label low-dose olanzapine or quetiapine and cardiometabolic mortality. J Psychiatr Res 2022;149:352–8.

53. Anderson SL and Vande Griend JP. Quetiapine for insomnia: A review of the literature. Am J Health Syst Pharm 2014;71:394–402.

54. Blaszczyk AT, McGinnis KA, Michaels HN, and Nguyen TN. Is it time to call it quits on low-dose quetiapine? Consult Pharm 2015;30:287–90.

55. Coe HV and Hong IS. Safety of Low Doses of Quetiapine When Used for Insomnia. Ann Pharmacother 2012;46:718–22.

56. Modesto-Lowe V, Harabasz AK, and Walker SA. Quetiapine for primary insomnia: Consider the risks. Cleve Clin J Med 2021;88:286–94.

57. Schmidt M, Pedersen L, and Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014;29:541–9.

58. Kildemoes HW, Sørensen HT, and Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;39:38–41.

59. Lynge E, Sandegaard JL, and Rebolj M. The Danish National Patient Register. Scand J Public Health 2011;39:30–3.

60. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, and Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449–90.

61. Helweg-Larsen K. The Danish Register of Causes of Death. Scand J Public Health 2011;39:26–9.

62. Arendt JFH, Hansen AT, Ladefoged SA, Sørensen HT, Pedersen L, and Adelborg K. Existing Data Sources in Clinical Epidemiology: Laboratory Information System Databases in Denmark. Clin Epidemiol 2020;12:469–75.

63. Danish Health Data Authority. Danish National Laboratory Databank [Den Nationale Labdatabank]. URL: https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/doedsaarsager-og-biologisk-materiale/laboratoriedatabasen (visited on 06/07/2022).

64. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol 2019;11:563–91.

65. Andersen JS, Olivarius NDF, and Krasnik A. The Danish National Health Service Register. Scand J Public Health 2011;39:34–7.

66. Højlund M, Andersen JH, Andersen K, Correll CU, and Hallas J. Use of antipsychotics in Denmark 1997–2018: a nation-wide drug utilisation study with focus on off-label use and associated diagnoses. Epidemiol Psych Sci 2021;30:e28.

67. De Hert M, Detraux J, Winkel R van, Yu W, and Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol 2012;8:114–26.

68. Barnard K, Peveler RC, and Holt RIG. Antidepressant medication as a risk factor for type 2 diabetes and impaired glucose regulation: systematic review. Diabetes Care 2013;36:3337–45.

69. Kim YH, Kim HB, Kim DH, Kim JY, and Shin HY. Use of hypnotics and the risk of or mortality from heart disease: a meta-analysis of observational studies. Korean J Intern Med 2018;33:727–36.

70. Abajo FJd. Effects of Selective Serotonin Reuptake Inhibitors on Platelet Function. Drugs Aging 2011;28:345–67.

71. Gokhale M, Stürmer T, and Buse JB. Real-world evidence: the devil is in the detail. Diabetologia 2020;63:1694–705.

72. Brookhart MA, Wyss R, Layton JB, and Stürmer T. Propensity Score Methods for Confounding Control in Non-Experimental Research. Circ Cardiovasc Qual Outcomes 2013;6:604–11.

73. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, and Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 2009;20:512–22.

74. Hallas J and Pottegård A. Performance of the High-dimensional Propensity Score in a Nordic Healthcare Model. Basic Clin Pharmacol Toxicol 2017;120:312–7.

75. Stürmer T, Wyss R, Glynn RJ, and Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. J Intern Med 2014;275:570–80.

76. Højlund M, Lund LC, Andersen K, Correll CU, and Hallas J. Association of Low-Dose Quetiapine and Diabetes. JAMA Netw Open 2021;4:e213209.

77. Bosco E, Hsueh L, McConeghy KW, Gravenstein S, and Saade E. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. BMC Medical Research Methodology 2021;21:241.

78. Højlund M, Andersen K, Ernst MT, Correll CU, and Hallas J. Use of low-dose quetiapine increases the risk of major adverse cardiovascular events: results from a nationwide active comparator-controlled cohort study. World Psychiatry 2022 (In press).

79. Black N. Why we need observational studies to evaluate the effectiveness of health care. BMJ 1996;312:1215–8.

80. Taipale H, Schneider-Thoma J, Pinzón-Espinosa J, et al. Representation and Outcomes of Individuals With Schizophrenia Seen in Everyday Practice Who Are Ineligible for Randomized Clinical Trials. JAMA Psychiatry 2022;79:210–8.

81. Franklin JM and Schneeweiss S. When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials? Cli. Pharmacol Ther 2017;102:924–33.

82. Ohlsson H and Kendler KS. Applying Causal Inference Methods in Psychiatric Epidemiology: A Review. JAMA Psychiatry 2020;77:637–44.

83. Lund JL, Richardson DB, and Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Curr Epidemiol Rep 2015;2:221–8.

84. Hernán MA and Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol 2016;183:758–64.

85. D'Arcy M, Stürmer T, and Lund JL. The importance and implications of comparator selection in pharmacoepidemiologic research. Curr Epidemiol Rep 2018;5:272–83.

86. Carnovale C, Lucenteforte E, Battini V, et al. Association between the glyco-metabolic adverse effects of antipsychotic drugs and their chemical and pharmacological profile: a network meta-analysis and regression. Psychol Med 2021;30:1–13.

87. Højlund M, Wagner CB, Wesselhoeft R, Andersen K, Fink-Jensen A, and Hallas J. Use of chlorprothixene and the risk of diabetes and major adverse cardiovascular events: a nation-wide cohort study. Basic Clin Pharmacol Toxicol 2022;130:501–12.

88. Hopkins SC, Ogirala A, Worden M, and Koblan KS. Depicting Safety Profile of TAAR1 Agonist Ulotaront Relative to Reactions Anticipated for a Dopamine D2-Based Pharmacological Class in FAERS. Clin Drug Investig 2021;41:1067–73.

89. Hálfdánarson Ó, Zoëga H, Aagaard L, et al. International trends in antipsychotic use: A study in 16 countries, 2005-2014. Eur Neuropsychopharmacol 2017;27:1064–76.

90. Galling B, Roldán A, Nielsen RE, et al. Type 2 Diabetes Mellitus in Youth Exposed to Antipsychotics: A Systematic Review and Meta-analysis. JAMA Psychiatry 2016;73:247–59.

91. Bobo WV, Cooper WO, Stein CM, et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. JAMA Psychiatry 2013;70:1067–75.

92. Zubiaur P, Fernández-Campos P, Navares-Gómez M, et al. Variants in COMT, CYP3A5, CYP2B6, and ABCG2 Alter Quetiapine Pharmacokinetics. Pharmaceutics 2021;13:1573.

93. Højlund M, Rasmussen L, Olesen M, Munk-Olsen T, and Pottegård A. Who prescribes quetiapine in Denmark? Br J Clin Pharmacol 2022.

94. Huerta C, Abbing-Karahagopian V, Requena G, et al. Exposure to benzodiazepines (anxiolytics, hypnotics and related drugs) in seven European electronic healthcare databases: a cross-national descriptive study from the PROTECT-EU Project. Pharmacoepidemiol Drug Saf 2016;25 Suppl 1:56–65.

95. Cooper SJ, Reynolds GP, Barnes T, et al. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. J. Psychopharmacol. 2016;30:717–48.

96. Stahl SM, Mignon L, and Meyer JM. Which comes first: atypical antipsychotic treatment or cardiometabolic risk? Acta Psychiatr Scand 2009;119:171–9.

97. Stahl SM, Sy S, and Maguire GA. How and when to treat the most common adverse effects of antipsychotics: Expert review from research to clinical practice. Acta Psychiatrica Scandinavica 2021;143:172–80.

98. Sundheds- og Ældreministeriet [The Danish Ministry of Health]. VEJ nr 9276: Vejledning om behandling med antipsykotiske lægemidler til personer over 18 år med psykotiske lidelser [Guideline on treatment with antipsychotic drugs in adults with psychotic disorders]. URL: https :

//www.retsinformation.dk/eli/retsinfo/2014/9276
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Use of antipsychotics in Denmark 1997–2018: a nation-wide drug utilisation study with focus on off-label use and associated diagnoses

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Abstract

Aims. Antipsychotics are primarily labelled for the treatment of severe mental illness and have documented clinical utility in certain neurological disorders or palliative care. However, off-label use of antipsychotics is common and increasing, and prior studies on antipsychotic utilisation have not specifically assessed users in neurology, palliative care or general practice. We aimed to explore diagnoses associated with antipsychotic use, treatment patterns and characteristics of users without diagnoses relevant to antipsychotic treatment.

Methods. Population-based study identifiying all users of antipsychotics in Denmark (pop 5.7 mio.) 1997–2018 in the Danish National Prescription Register (DNPR). Possible indications for antipsychotic therapy were evaluated using in- and outpatient contacts from the DNPR. Users were divided hierarchically into six groups: severe mental disorders (schizophrenia, bipolar-spectrum disorders), chronic mental disorders (dementias, mental retardation, autism), other mental disorders (depression-spectrum, anxiety and personality disorders, etc.), selected neurological diseases, cancer and antipsychotic users without any of these diagnoses. This last group was characterised regarding demographics, antipsychotic use, health care utilisation and likely antipsychotic treatment initiator in 2018.

Results. Altogether, 630 307 antipsychotic users were identified, of whom 127 649 had filled prescriptions during 2018. Users without diagnoses relevant to antipsychotic treatment comprised of the largest group (37%), followed by schizophrenia and bipolar-spectrum disorders (34%), other mental disorders (15%), dementia, autism and mental retardation (11%), cancer (2.2%) and neurological diagnoses (2.0%). Of 37 478 incident users in 2018, 39% had no diagnosis relevant to antipsychotic treatment, 7.9% had major depression, 7.7% neurotic/stress-related disorders and 7.5% dementia. Quetiapine was most commonly used, both overall (51%) and among users without diagnoses relevant to antipsychotic treatment (58%). Of 14 474 incident users in 2018 without diagnoses relevant to antipsychotic treatment, treatment was most likely initiated by a general practitioner (65%), with only 17% seeing a psychiatrist during the following year. As many as 18% of patients with adjustment disorders and 14% of those without relevant diagnoses for antipsychotic use, remained on antipsychotic treatment 5 years after their first prescription.

Conclusions. Over one-third of antipsychotic users in Denmark did not have psychiatric, neurological or cancer diagnoses as possible indications for antipsychotic therapy. Many antipsychotics are initiated or prescribed in general practice, and a concerningly large subgroup without documented diagnoses relevant for antipsychotics continued to receive them. Rational prescribing, adequate side effect monitoring and further research into reasons for the observed antipsychotic use patterns and their risk–benefit ratio are needed.

Introduction

Antipsychotics are generally labelled for treatment of severe mental disorders, such as schizophrenia, mania and bipolar depression. Other licensed indications can be insufficiently responding unipolar depression, autism and Tourette's syndrome. Furthermore, the use of antipsychotics can be clinically relevant in other psychiatric conditions that do not have a licensed indication, such as dementia, post-traumatic stress disorder or obsessive-compulsive disorder. Caution is warranted when using antipsychotics, as they are associated with a

number of potentially serious adverse effects, including fatal arrhythmias, metabolic disturbances and extrapyramidal symptoms (Solmi *et al.*, 2017; Stroup and Gray, 2018; Papola *et al.*, 2019).

However, prior drug utilisation studies have found a considerable use of antipsychotics in other psychiatric conditions for which antipsychotics do not have an indication, including dementia, anxiety disorders and insomnia (Marston *et al.*, 2014; Carton *et al.*, 2015; Baandrup and Kruse, 2016). Furthermore, antipsychotics are also used in other medical specialties than psychiatry, e.g. for delirium (Marcantonio, 2017), for psychotic symptoms in epilepsy (Agrawal and Mula, 2019), treatment of headache disorders (Siow *et al.*, 2005; Bendtsen *et al.*, 2012), as antiemetics (Walsh *et al.*, 2017) or in end-of-life care (Bush *et al.*, 2017).

The dispensed quantity of antipsychotics has remained stable in Denmark over the past 10 years, while the prevalence of antipsychotic use has increased during the same period, indicating increasing low-dose use of antipsychotics (Danish Health Data Authority). The reasons for this increase are poorly understood. However, a pronounced decrease in the use of benzodiazepine analogues has been observed over the same period (Danish Health Data Authority), which might have been replaced, at least partly, by low-dose use of antipsychotics acting as anxiolytics or hypnotics. The quite low average quantities dispensed to each user lends some support to this hypothesis (Højlund *et al.*, 2019).

Studies addressing the underlying drivers of antipsychotic utilisation are scarce (Olfson *et al.*, 2012; Baandrup and Kruse, 2016), and prior studies on overall antipsychotic utilisation commonly lack information on associated diagnoses (Hálfdánarson *et al.*, 2017; Højlund *et al.*, 2019), or were confined to patients with psychiatric diagnoses or contacts (Olfson *et al.*, 2012; Baandrup and Kruse, 2016). Thus, these studies did not assess the entire population of users treated in general practice, private psychiatric practice or other medical specialties than psychiatry.

The aim of this study was to analyse current patterns and long-term trends in antipsychotic utilisation, including associated diagnoses, treatment persistence and characteristics of users without diagnoses relevant to antipsychotic treatment.

Method

Study design and data sources

We conducted a nation-wide drug utilisation study to explore current patterns and long-term trends in antipsychotic use by identifying all Danish residents who filled a prescription for an antipsychotic between 1 January 1997 and 31 December 2018 in the Danish Register of Medicinal Product Statistics (DRMPS) (Pottegård *et al.*, 2017). Antipsychotics were defined as all medications within the World Health Organization (WHO) Anatomical Therapeutic Chemical Classification (ATC) group N05A (WHOCC-ATC/DDD Index), excluding lithium (ATC N05AN01). Preparations within ATC-group N05A are only available on prescription, and all dispensing at community pharmacies is recorded in the DRMPS.

Prescription data were then linked, using civil registration numbers, to information on psychiatric diagnoses from the Danish National Patient Register (DNPR) (Lynge *et al.*, 2011) and the Danish Psychiatric Central Research Register (DPCRR) (Mors *et al.*, 2011), and to information on health care utilisation from the National Health Insurance Services Register (NHISR) (Andersen *et al.*, 2011). DRMPS contains information on all prescriptions dispensed at Danish community pharmacies from 1995 onwards. DNPR contains information on hospital contacts and diagnoses from all admissions or outpatient contacts to Danish hospitals since 1977 and 1995 respectively. DPCRR contains information on admissions to psychiatric hospitals from 1970 and outpatient contacts to psychiatric facilities from 1995. NHISR contains information on all contacts to general practitioners and practicing specialists from 1990 onwards and is based on invoices to the region health administrations. Virtually, all health care in Denmark is publicly funded, and thus captured in these registers. An overview of the underlying data sources is provided in online Supplementary Appendix 1.

Outcome measures and statistical analysis

We analysed the data in four dimensions: (1) overall drug use statistics, (2) diagnoses associated with antipsychotic use, (3) characterisation of users without diagnoses relevant to antipsychotic treatment and (4) treatment persistence for selected subgroups.

Overall drug use statistics

We calculated 1-year prevalence as the total number of users divided by the population base, and incidence as the number of new antipsychotic users (i.e. users without antipsychotic prescriptions in the preceding year) divided by the population base. Mean dose was calculated as the total amount of antipsychotic sold divided by the number of users for that antipsychotic divided by 365 days per year, resulting in the average daily dose for all users of that antipsychotic (unit: DDD/user/day). To assess overall differences in treatment duration, we calculated a duration index as $P/(1-P) \times I$ (where P is the prevalence and I is the incidence for the specific antipsychotic) (Hallas and Støvring, 2006). Prevalent users were defined as users with antipsychotic prescriptions in the preceding year and incident users as users without prescriptions in the preceding year. High duration indices above 1 indicate a retention of users (i.e. continuous or recurrent treatment). To assess skewness in antipsychotic consumption, we calculated 1st and 50th percentiles as the proportion of antipsychotic sales accounted for by the 1 and 50% most intensive users (Hallas and Støvring, 2006).

Diagnoses associated with antipsychotic use

Antipsychotic users were divided into six groups based on occurrence of in- or outpatient diagnoses in the DNPR/DPCRR. We used an appropriateness hierarchy based on main indications for antipsychotic therapy, followed by other relevant chapters of the WHO International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) (see online Supplementary Appendix 2 for specific codes):

- Group 1 'Severe mental disorders': users diagnosed with schizophrenia, schizoaffective disorder, other delusional disorders, mania or bipolar affective disorder.
- Group 2 'Chronic mental disorders': users diagnosed with dementias, mental retardation, autism and no record of diagnoses in group 1.
- Group 3 'Other mental disorders': users with other psychiatric diagnoses (e.g. major depression, anxiety disorders or personality disorders) and no record of diagnoses in groups 1 and 2.
- Group 4 'Neurological diagnoses only': users with selected neurological diagnoses where antipsychotic treatment might

be relevant (e.g. Parkinson's disease), and no record of diagnoses in groups 1–3.
- Group 5 'Cancer diagnoses only': users with diagnosis of a malignant neoplasm and no record of diagnoses in groups 1–4 suggesting use in palliative care.
- Group 6 'No relevant diagnosis': users with no record of diagnoses in groups 1–5.

Users were assigned to group 1 or 2 if they had any occurrence of these diagnoses in registers between register inception (1997 for inpatient diagnoses and 1995 for outpatient diagnoses, see online Supplementary Appendix 1) and their first antipsychotic prescription that year. All other users were assigned to a group based on occurrence of diagnoses within 6 months before or after their first antipsychotic prescription that year. We used a 6-month window to allow subsequent diagnoses to be associated with the current prescription in incident users, and to capture outpatient visits that were separated in time from prescription redemptions. The groups (and subgroups) were hierarchical, such that an individual would be assigned as belonging to the lowest possible group (or subgroup) number. For all years in the study period, we defined prevalent users as users with antipsychotic prescriptions in the preceding calendar year and incident users as users without prescriptions in the preceding year. Additionally, we conducted a sensitivity analysis extending the assessment period from 1 to 2 and 5 years, respectively, before 2018 to explore the proportion of 'intermittent users'.

Characterisation of antipsychotic uses without diagnoses relevant to antipsychotic treatment

Users in group 6 were characterised in terms of demographics, antipsychotics used, number of prescriptions, number of antipsychotics used, total amount redeemed, concurrent use of psychotropic medications, somatic comorbidity, first prescriber (incident users only) and health care utilisation (incident users only). The use of other psychotropic medications was assessed as prescriptions of drugs listed in online Supplementary Appendix 3 within 3 months before or after the first antipsychotic prescription in 2018. Somatic co-morbidities were assessed as any occurrence of the diagnoses or prescriptions listed in online Supplementary Appendix 3 before the first antipsychotic prescription in 2018. Incident users without hospital contacts were linked with NHISR to assess health care use outside the hospital system. To assess the likely first prescriber, we evaluated health care contacts in NHISR 14 days prior to the first antipsychotic prescription as most patients will fill prescriptions within few days after the prescription was issued (Pottegård *et al.*, 2014). We categorised health care contacts as 'general practitioner', 'psychiatrist' and 'neurologist'. If the user had been in contact with both a general practitioner and a specialist within this 14-day period, conservatively, the latter was assigned as the likely first prescriber. Health care utilisation in general was assessed as any contact in NHISR during 2018 with a psychiatrist, neurologist or a general practitioner only.

Treatment persistence for selected subgroups

We estimated persistence of antipsychotic use for individuals with schizophrenia/schizoaffective disorder, dementias, adjustment disorders and no relevant diagnoses using 'proportion of patients covered' (PPC) as described by Rasmussen *et al.* (2018). These groups were chosen, as they are expected to represent different treatment patterns, e.g. long-term treatment in schizophrenia, episodic treatment in dementia and short-term treatment in adjustment disorders. Treatment persistence was calculated as the proportion of new users within subgroup who were covered by their latest prescription, conservatively assuming the use of one tablet per day. In contrast to traditional drug survival analyses the PPC-approach allows patients to re-enter in analyses as treated when they redeem new prescriptions. Thereby, PPC is less sensitive to assumptions about the treatment period that should be assigned to a single prescription (Rasmussen *et al.*, 2018).

Other

Data management and analyses were conducted with STATA MP release 15.1 (StataCorp, College Station, TX, USA). Approval for data access was obtained from the Danish Health Data Authority. According to Danish law, no ethical approval or informed consent is needed for purely register-based studies.

Results

We identified a total of 19 092 613 antipsychotic prescriptions in the DRMPS from 1997 to 2018, filled by 630 307 individuals. The median number of prescriptions per individual was 4 (total range: 1–2465, interquartile range: 1–24), and the proportion of individuals with >1 antipsychotic prescription was 71%. The prevalence of antipsychotic use increased by 5.3% from 20.9 users/1000 inhabitants in 1997 to 22.1 users/1000 inhabitants in 2018.

Overall antipsychotic use statistics

In 2018, the ten most prescribed antipsychotics (in terms of users) accounted for 91% of the total volume sold: quetiapine (51% of all users), olanzapine (14%), risperidone (13%), chlorprothixene (11%), aripiprazole (9.7%), haloperidol (6.2%), zuclopenthixol (3.3%), levomepromazine (3.1%), flupentixol (3.0%) and clozapine (2.7%) (Table 1). The highest rates of new users were observed for quetiapine and haloperidol with 3.92 and 1.22 new users per 1000 inhabitants, respectively. The highest 50th percentiles were observed for haloperidol, quetiapine, levomepromazine, risperidone and chlorprothixene, whereas the highest duration indices were observed for sulpiride, clozapine, perphenazine, sertindole and zuclopenthixol (Table 1).

Diagnoses associated with antipsychotic use

Since 1997, the proportion of users with severe mental disorders increased and the proportion of users without relevant diagnoses decreased (Fig. 1). The proportion of users in 2018 without severe mental disorders was 66% (84 716, Table 2).

Antipsychotic use in chronic mental disorders accounted for 11% (13 836) of all users in 2018, with 69% (2809) of incident users in this group being individuals with dementia (Table 2). Antipsychotic use in other mental disorders was the third largest group among all users with 15% (18 594), and the second largest group among incident users in 2018 with 26% (9850, Table 2). Especially, the number of incident antipsychotic users belonging to other mental disorders increased considerably from 1997 onwards. Increasing antipsychotic use in affective disorders (excluding bipolar disorder) and neurotic or stress-related disorders was the underlying driver for this increase among both incident and prevalent users (online Supplementary Figs 1–3).

Table 1. Drug statistics for all marketed antipsychotic drugs in Denmark in 2018 (population base: 5 781 190 inhabitants)

Antipsychotic drug (ATC)	DDD (oral use, mg)	Total number of users	One-year prevalence (users/1000 inhabitants)	Incidence rate (users/1000 inhabitants/year)	Volume sold (1000 DDD)	Mean dose (DDD/user/day)	Duration index[a]	1st percentile[b] (% of total volume)	50th percentile[b] (% of total volume)
All antipsychotics	–	127 649	22.08	6.48	21 286	0.46	3.5	10.0	94.5
Quetiapine (N05AH04)	400	64 946	11.23	3.92	6033	0.25	2.9	11.1	93.3
Olanzapine (N05AH03)	10	17 554	3.04	0.94	5293	0.83	3.3	5.5	88.8
Risperidone (N05AX08)	5	16 056	2.78	0.95	1906	0.33	2.9	7.1	90.7
Chlorprothixene (N05AF03)	300	14 028	2.43	0.85	613	0.12	2.8	10.3	89.7
Aripiprazole (N05AX12)	15	12 357	2.14	0.66	2808	0.62	3.3	4.3	85.0
Haloperidol (N05AD01)	8	7963	1.38	1.22	505	0.17	1.1	20.0	96.6
Zuclopenthixol (N05AF05)	30	4224	0.73	0.10	767	0.50	7.5	6.4	87.8
Levomepromazine (N05AA02)	300	4017	0.69	0.19	118	0.08	3.7	15.2	92.8
Flupentixol (N05AF01)	6	3809	0.66	0.15	282	0.20	4.3	18.8	87.9
Clozapine (N05AH02)	300	3403	0.59	0.06	1113	0.90	9.2	3.3	76.9
Paliperidone (N05AX13)	6	1523	0.26	0.07	587	1.06	4.0	3.4	78.2
Ziprasidone (N05AE04)	80	1066	0.18	0.03	441	1.13	7.3	4.0	81.6
Amisulpride (N05AL05)	400	720	0.13	0.03	176	0.67	3.6	4.8	86.4
Pimozide (N05AG02)	4	558	0.10	0.01	103	0.51	7.0	7.6	83.3
Perphenazine (N05AB03)	30	537	0.09	0.01	253	1.29	9.1	5.2	73.2
Lurasidone (N05AE05)	60	371	0.06	0.05	65	0.48	1.4	6.1	89.3
Prochlorperazine (N05AB04)	100	313	0.05	0.02	7	0.06	3.0	8.2	85.2
Sulpiride (N05AL01)	800	311	0.05	<0.01	75	0.67	17.4	5.0	77.8
Pipamperone (N05AD05)	200	222	0.04	0.01	26	0.32	4.7	7.8	88.4
Sertindole (N05AE03)	16	247	0.04	0.01	72	0.80	8.3	3.1	73.9

Melperone (N05AD03)	300	198	0.03	0.01	9	0.13	2.8	8.0	85.5	
Periciazine (N05AC01)	50	170	0.03	<0.01	21	0.34	6.2	7.2	87.8	
Asenapine (N05AH05)	20	25	<0.01	<0.01	4	0.47	5.7	–	–	
Cariprazine (N05AX15)	3	(<5)	<0.01	<0.01	<1	0.04	–	–	–	

ATC, Anatomic Therapeutic Chemical Classification System (who.int/classifications/atcddd/en); DDD, World Health Organization defined daily dose; ICD-10, World Health Organization International Statistical Classification of Diseases and Related Health Problems 10th revision (icd.who.int/browse10/2019/en).
[a]Duration index represents ratio between numbers of prevalent users and incident users.
[b]1st and 50th percentiles describe the total amount (in percent) consumed by the 1 and 50% of users with the highest annual consumption, e.g. 50% of quetiapine users consume 93% of the dispensed amount of quetiapine, and the remaining 50% of users consumes 7%.

Overall, antipsychotic use in individuals with neurological or cancer diagnoses accounted only for a minor proportion of all users (2.0 and 2.2%, respectively, corresponding to 2494 and 2869 individuals). However, the proportion of incident users was considerably higher with 3.7 and 5.9% of all incident users, respectively (1386 and 2217 individuals, Table 2). In 2018, antipsychotic use in sleep disorders was the largest subgroup among neurological disorders, followed by use in Parkinson's disease, epilepsy and headache disorders. The antipsychotic use in sleep disorders increased from 28 individuals in 1997 to 1015 in 2018, whereas the number of antipsychotic users in other neurological disorders remained relatively stable (online Supplementary Figs 1–3).

Extending the assessment period for 'incident use' to 2 and 5 years prior to 2018, reduced the number of incident users in all categories, suggesting a subgroup of intermittent users in every category (online Supplementary Table 1). Overall, 21% of the 'incident users' in 2018 have had prescriptions of antipsychotics within the preceding 5 years. Individuals with severe mental disorders had the largest proportion of users with prior prescriptions of antipsychotics within 5 years (47%), whereas this proportion was 3–21% for the remaining groups (online Supplementary Table 1). Importantly, the proportion of users without diagnoses relevant to antipsychotic treatment remained the same (79%), but the absolute number was lower when extending the assessment period to 5 years (11 482 *v.* 14 474 users without prior antipsychotic prescriptions within 5 years and 1 year, respectively).

Diagnoses associated with use of specific antipsychotics

In 2018, antipsychotics, such as clozapine, zuclopenthixol, aripiprazole and olanzapine, were predominantly used by individuals with severe mental illness (61–91% of users), while flupentixol, levomepromazine, chlorprothixene and quetiapine had high proportions of antipsychotic users without relevant diagnoses (47–72% of users). The proportion of users in each diagnostic group by commonly used antipsychotics can be seen in Fig. 2, and the total number of users is displayed in online Supplementary Table 2.

Characteristics of users without diagnoses relevant to antipsychotic use

In this group, quetiapine was the most commonly used antipsychotic (58% of users) followed by chlorprothixene (14%). Most users in this group would use only one antipsychotic (93%), fill three or more prescriptions (60%) and use ⩽90 DDD (80%) (online Supplementary Table 3).

Of the 14 474 incident antipsychotic users in this group during 2018, only 12% had seen a practicing psychiatrist in the 14 days preceding their use of an antipsychotic. Furthermore, only 17% had seen a practicing psychiatrist at any time during 2018, and most antipsychotic users in this group (80%) had only been in contact with a general practitioner and had no relevant diagnosis in hospital registers within 6 months before or after their first antipsychotic prescription (online Supplementary Table 3).

A general practitioner was the initial prescriber in 65% of incident antipsychotic users in this group without diagnoses relevant to antipsychotic use (online Supplementary Table 3). For quetiapine users, this proportion was 68% and for chlorprothixene users it was 72%, whereas the numbers were considerably lower for users of other antipsychotics (online Supplementary Table 4).

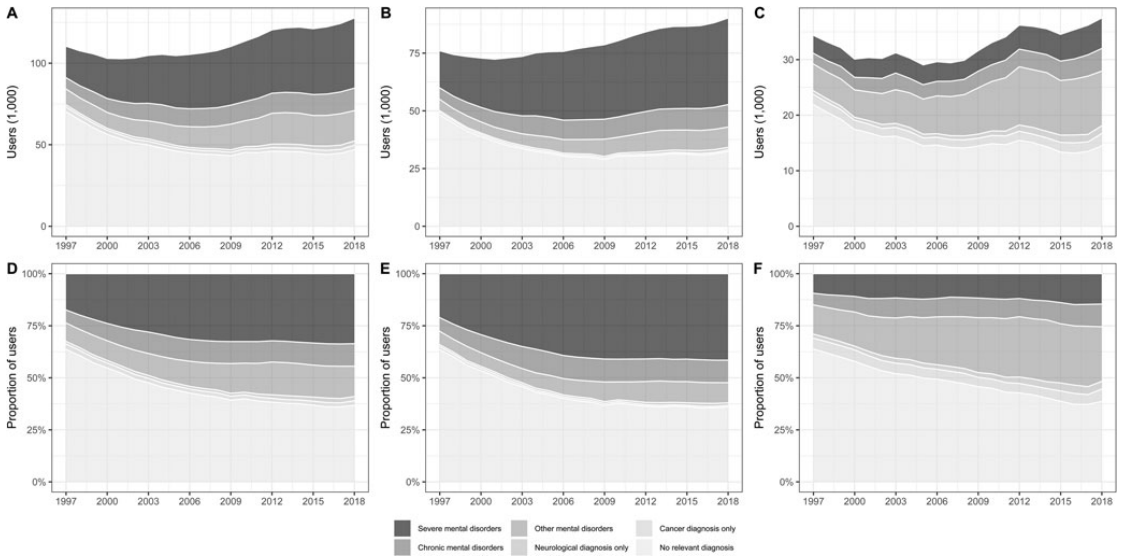

Fig. 1. Development in total number of users by diagnostic groups and the proportion of users by diagnostic groups, 1997–2018 for all (A + D), prevalent (B + E) and incident users (C + F).

Haloperidol use in this group was predominantly by those aged 80 or more (72%), and for short-term use (70% with only one prescription) (online Supplementary Table 4). Median starting years early in the study period, indicating long-term use, was seen for flupentixol, levomepromazine and zuclopenthixol (2003, 2003 and 1995 respectively) (online Supplementary Table 4).

Treatment persistence

Most antipsychotic users stopped their treatment within 6 months of first prescription. However, 57% of patients with dementia were still in treatment after 1 year, and 41% were still in treatment after 5 years. Among patients with adjustment disorders and those without relevant diagnoses, 18 and 14%, respectively, remained on antipsychotic treatment 5 years after their first prescription (Fig. 3).

Discussion

The main findings of this nation-wide, 22-year antipsychotic utilisation study in 630 307 individuals filling 19 092 613 antipsychotic prescriptions are: (1) off-label antipsychotic use was highly prevalent; (2) most incident users were either diagnosed with non-severe mental illness or had no record of diagnoses relevant to antipsychotic treatment; (3) both overall and among patients without relevant diagnoses for antipsychotic use, quetiapine, used at low doses, was most frequently prescribed; (4) general practitioners most likely initiated antipsychotic treatment in users without relevant diagnoses for antipsychotic use and (5) long-term antipsychotic treatment was common in individuals with dementia, adjustment disorders and those without relevant diagnoses for antipsychotic use.

The increasing prevalence of antipsychotic use was driven by an increasing number of users in most diagnostic groups, although the number of users without relevant diagnoses for antipsychotic use decreased from 1997 to 2018. The finding of a considerable use of antipsychotics outside severe mental disorders is in line with prior drug utilisation studies from Denmark, France, the United Kingdom and the United States (Olfson *et al.*, 2012; Marston *et al.*, 2014; Baandrup and Kruse, 2016; Montastruc *et al.*, 2018). The main addition of this study is the comprehensive evaluation of diagnoses associated with the use of antipsychotics in psychiatry as well as other medical specialties, including general practice.

One notable finding is that the number of incident users with non-severe mental disorders increased considerably over the study period. Some of these individuals might have diagnoses that, at some point, may benefit from off-label use of antipsychotics (e.g. anxiety disorders, borderline personality disorder, obsessive compulsive disorder and post-traumatic stress disorder) (Ingenhoven and Duivenvoorden, 2011; Liu *et al.*, 2014; Slee *et al.*, 2019; Zhou *et al.*, 2019), or be in the process of psychiatric evaluation and eventually are diagnosed with severe mental illness. However, the substantial number of individuals and the variety of associated psychiatric diagnoses could suggest that the threshold for prescribing antipsychotics has decreased during the study period. A related finding is the large proportion of users without any record of psychiatric, neurological or cancer diagnoses in the registers. Here, evaluation of health care contacts found that most new users had not been evaluated by a psychiatrist or been in contact with a psychiatric emergency room. This finding suggests that the antipsychotic treatment was most likely initiated by a general practitioner for a condition that did not require specialised psychiatric evaluation or treatment.

A considerable proportion of users with dementia diagnoses continued long-term antipsychotic treatment, although this practice is not recommended due to e.g. increased risk of stroke and death (Douglas and Smeeth, 2008; Kales *et al.*, 2012). The same pattern, although for a smaller proportion of patients, was

Table 2. Diagnoses associated with antipsychotic use in Denmark, 2018

	All users			Prevalent users			Incident users			
ICD-10 diagnosis	*N*	% (all users)	% (sub-group)	*N*	% (all users)	% (sub-group)	*N*	% (all users)	% (sub-group)	Duration index[a]
All users	127 649	100	.	90 171	100	.	37 478	100	.	3.5
Severe mental disorders	42 933	34	100	37 464	42	100	5469	15	100	7.9
Schizophrenia and schizoaffective disorder (F20 + 25)	22 931	18	53	20 789	23	55	2142	5.7	39	10.8
Other delusional disorders (F22–24, 26–29)	10 859	8.5	25	8883	9.9	24	1976	5.3	36	5.5
Mania and bipolar affective disorder (F30–31)	9143	7.2	21	7792	8.6	21	1351	3.6	25	6.8
Chronic mental disorders	13 836	11	100	9754	11	100	4082	11	100	3.4
Dementia (F00–03, G30–31)	7292	5.7	53	4483	5	46	2809	7.5	69	2.6
Mental retardation and autism (F70–79 + 84)	6544	5.1	47	5271	5.8	54	1273	3.4	31	5.2
Other mental disorders[b]	18 594	15	100	8744	9.7	100	9850	26	100	1.9
Organic mental orders (excl. dementia) (F04–09)	1638	1.3	8.8	480	0.53	5.5	1158	3.1	12	1.4
Psychoactive substance use (F10–19)	4014	3.1	22	2243	2.5	26	1771	4.7	18	2.3
Schizotypal disorder (F21)	536	0.42	2.9	306	0.34	3.5	230	0.61	2.3	2.3
Psychotic depression (F32.3, 33.3)	459	<1	2.5	202	<1	2.3	257	<1	2.6	1.8
Depressive episode (F32.0-0.2)	2172	1.7	12	701	<1	8	1471	3.9	15	1.5
Recurrent depressive episode (F33.0-0.2)	2714	2.1	15	1535	1.7	18	1179	3.1	12	2.3
Phobias and other anxiety disorders (F40–41)	1792	1.4	9.6	772	0.86	8.8	1020	2.7	10	1.8
Obsessive-compulsive disorder (F42)	250	0.2	1.3	126	0.14	1.4	124	0.33	1.3	2.0
Reaction to severe stress (F43)	2927	2.3	16	1238	1.4	14	1689	4.5	17	1.7
Acute stress reaction (F43.0)	302	0.24	1.6	94	0.1	1.1	208	0.55	2.1	1.5
Post-traumatic stress disorder (F43.1)	987	0.77	5.3	531	0.59	6.1	456	1.2	4.6	2.2
Adjustment disorders (F43.2)	1048	0.82	5.6	398	0.44	4.6	650	1.7	6.6	1.6
Dissociative disorders (F44)	21	<0.1	0.11	16	<0.1	0.18	5	<0.1	<0.1	4.2
Somatoform disorders (F45)	60	<0.1	0.32	32	<0.1	0.37	28	<0.1	0.28	2.1
Eating disorders (F50)	158	0.12	0.85	84	<0.1	0.96	74	0.2	0.75	2.1
Nonorganic sleep disorders (F51)	52	<0.1	0.28	19	<0.1	0.22	33	<0.1	0.34	1.6
Specific and mixed personality disorders (F60–61)	960	0.75	5.2	563	0.62	6.4	397	1.1	4	2.4
Hyperkinetic disorder (F90)	377	0.3	2	191	0.21	2.2	186	0.5	1.9	2.0
Selected neurological diagnoses only[b]	2494	2	100	1108	1.2	100	1386	3.7	100	1.8
Encephalitis (G04–05)	9	<0.1	0.36	0	–	–	9	<0.1	0.65	.
Huntington's disease (G10)	11	<0.1	0.44	11	<0.1	0.99	0	–	–	.

(*Continued*)

Table 2. (*Continued.*)

ICD-10 diagnosis	All users			Prevalent users			Incident users			Duration index[a]
	N	% (all users)	% (sub-group)	*N*	% (all users)	% (sub-group)	*N*	% (all users)	% (sub-group)	
Parkinson's disease (G20)	370	0.29	15	211	0.23	19	159	0.42	11	2.3
Multiple sclerosis (G35)	95	<0.1	3.8	59	<0.1	5.3	36	<0.1	2.6	2.6
Epilepsy (G40–41)	288	0.23	12	143	0.16	13	145	0.39	10	2.0
Migraine and other headache syndromes (G43–44)	311	0.24	12	136	0.15	12	175	0.47	13	1.8
Cerebrovascular disease (G45–46)	128	0.1	5.1	68	<0.1	6.1	60	0.16	4.3	2.1
Sleep disorders (G47)	1015	0.8	41	385	0.43	35	630	1.7	45	1.6
Hydrocephalus (G91)	47	<0.1	1.9	17	<0.1	1.5	30	<0.1	2.2	1.6
Cancer diagnosis only	2869	2.2	.	652	0.72	.	2217	5.9	.	1.3
No relevant diagnosis	46 923	37	.	32 449	36	.	14 474	39	.	3.3

ICD-10, World Health Organization International Statistical Classification of Diseases and Related Health Problems 10th revision (icd.who.int/browse10/2019/en).
[a]Duration index represents ratio between prevalent users and incident users.
[b]Categories with few users have been left out due to confidentiality issues. Therefore, the displayed categories or subcategories does not necessarily add up to totals.

observed for users with adjustment disorders or no diagnosis relevant for antipsychotic use in the registers. This pattern might reflect the use of antipsychotics as anxiolytics or hypnotics instead of benzodiazepines or benzodiazepine-related medications (Anderson and Vande Griend, 2014; Gjerden *et al.*, 2017). However, the reasons for such continuous use and the relevance of deprescribing efforts should be investigated further.

The predominant use of quetiapine is important for several reasons: it is by far the most commonly prescribed antipsychotic in Denmark in 2018 filled by 51% of all users. In 2018, 42% of all quetiapine users had no record of diagnoses relevant to antipsychotic treatment, which were 27 447 individuals in total. Of these, 82% would redeem small quantities of quetiapine (<90 DDD/year) indicating low-dose/off-label use. This wide-spread use of quetiapine might be problematic as safety is not thoroughly evaluated with the use of quetiapine in low dose. However, prior observational studies have indicated increased risk of metabolic disturbances (Carr *et al.*, 2016), fall-related injuries (Tapiainen *et al.*, 2020), stroke (Correll *et al.*, 2015) and all-cause mortality (Gerhard *et al.*, 2020; Reutfors *et al.*, 2020) with the use of quetiapine in individuals without severe mental disorders.

A major strength of the current study is its data sources, which are nation-wide and allow long-term follow-up. In Denmark, virtually all health care is publicly funded, especially for the investigated specialties (psychiatry, neurology, oncology and general practice), and thus captured in the DNPR or NHISR. Furthermore, all prescriptions filled at community pharmacies are recorded in DRMPS and use at long-term care facilities (e.g. nursing homes) are also included and individually referable.

Limitations of the current analyses must be acknowledged: first, the specific indication for antipsychotic therapy is not recorded in registers. This point is especially relevant for users treated in general practice or by specialists who do not report diagnostic information in the reimbursement process. Regarding the latter group, there are about 150–200 office-based psychiatrists (including child and adolescent psychiatrists) in Denmark who treat approximately 20% of the patients with psychiatric disorders (Mors *et al.*, 2011). However, psychiatric disorders that require antipsychotic treatment are generally not treated solely by such practitioners and will likely generate in- or outpatient diagnoses in hospital registers. An exception from this rule could be individuals with bipolar affective disorder, depression or obsessive-compulsive disorder. To strengthen the appropriateness evaluation, we extended the evaluation of diagnoses in groups 1 and 2 to any occurrence between register inception and 6 months after the first prescription of an antipsychotic. Otherwise, individuals with e.g. schizophrenia, bipolar affective disorder, dementia or intellectual disabilities and no recent hospital contacts would lead to overestimation of other groups. Still, the possibility remains that some individuals would only have records of diagnoses in group 1 or 2 before DNPR inception in 1977/1995, that we were thus not able to evaluate (e.g. individuals with bipolar affective disorder on maintenance treatment with antipsychotics treated in office-based psychiatry). Second, the use of a 6-month window in the classification process is somewhat arbitrary. A wider window could direct attention away from the disorder associated with the relevant antipsychotic prescription (especially, for incident users), whereas a narrower window could ignore relevant information and result in overestimation of group 6. Third, we have to acknowledge that all diagnostic codes have imperfect sensitivity, i.e. we may have overlooked some conditions that would justify the use of antipsychotics e.g.

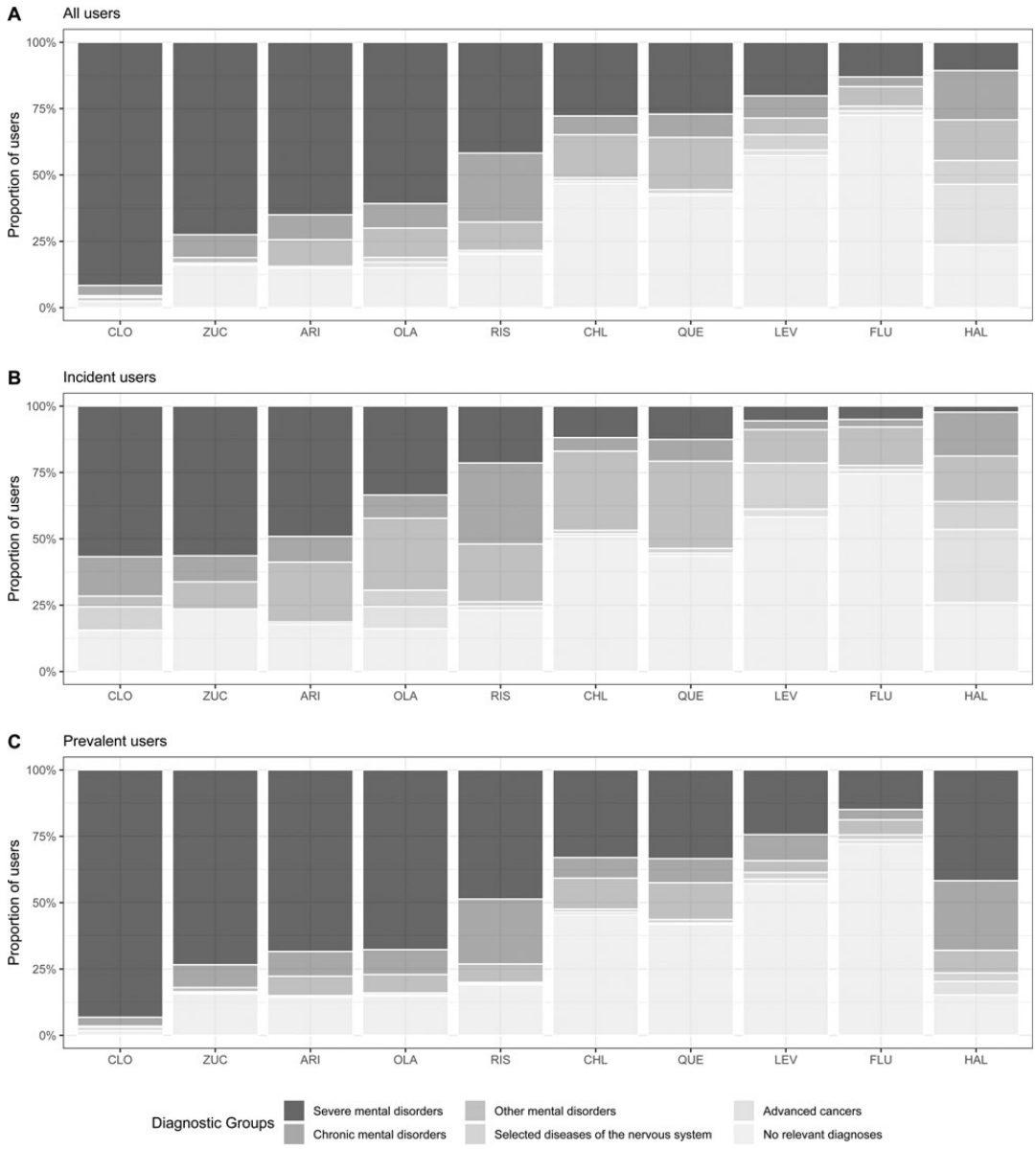

Fig. 2. Proportion of users by diagnostic subgroups for commonly used antipsychotics, Denmark 2018.

that antipsychotic treatment was initiated in office-based psychiatry where diagnostic information is not accessible, or on the basis of advice from a specialist to e.g. a general practitioner. However, diagnoses of severe mental disorders as schizophrenia will most likely lead to hospital contacts at some point and high validity have been demonstrated for the schizophrenia diagnosis in Danish registers (Uggerby *et al*., 2013). Fourth, we had no data on which other non-pharmacologic or pharmacologic treatments were tried first and which may have failed. Fifth, prescribed daily doses are not available in the registers. Sixth, exact prescribed daily doses are not available in the registers and the utilised DDD method does not ensure fully equivalent dose levels for each individual antipsychotic. Finally, results are limited to Denmark, and may not generalise to other countries and health care settings.

Despite these limitations, results from this relatively large descriptive study indicate that a considerable number of users have no clear indication for antipsychotic therapy. Although off-label use might be warranted in some cases, attention should be given to enhance the rational use of antipsychotics that can

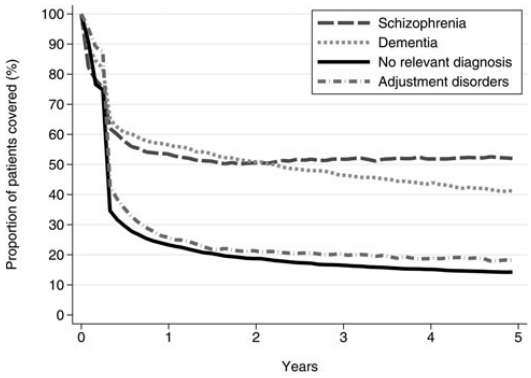

Fig 3. Duration of antipsychotic treatment measured by 'PPC' for selected subgroups.

have considerable adverse effects (Solmi *et al.*, 2017; Papola *et al.*, 2019). Initiatives which focus on rational prescribing and deprescribing should also include antipsychotics. Especially, instead of using antipsychotics for their sedative-hypnotic properties in anxiety and adjustment disorders and insomnia, non-pharmacological interventions or use of antihistamines could serve as better alternatives and should be tried first. Furthermore, deprescribing efforts seem especially relevant, given the high proportion of long-term users with diagnoses of dementia, adjustment disorders, and no relevant diagnoses for antipsychotic use. Finally, continuous side effect monitoring during antipsychotic treatment is standard of care in psychiatry and should apply to all antipsychotic users. Therefore, monitoring should be directed to the group of users in other medical specialties and those treated in primary care, consisting of 41% of antipsychotic-treated individuals in 2018, and 49% of new antipsychotic users. Given the substantial number of off-label users, the potential side-effects of antipsychotics become even more relevant. Consequences of off-label and/or low-dose use of antipsychotics should be investigated, especially of quetiapine, which was by far the most used antipsychotic regardless of the diagnostic group.

In conclusion, antipsychotic use has increased in both severe and non-severe mental disorders in Denmark over the past two decades. More than one-third of all antipsychotic users had no psychiatric, neurological or cancer diagnoses as possible indications for antipsychotic therapy. Health insurance data indicate that a considerable proportion of antipsychotics is prescribed in general practice and that long-term prescribing for adjustment disorders and patients without relevant indications for antipsychotic use occurs in a concerningly large subgroup. Reasons for the considerable off-label use and its risk–benefit ratio warrant further investigation.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S2045796021000159

Data. The data used for this study are not publicly available, but can be obtained by application to The Danish Health Data Authority (www.sundhedsdatastyrelsen.dk).

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Ethical standards. The authors assert that all procedures contributing to this study comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

Agrawal N and Mula M (2019) Treatment of psychoses in patients with epilepsy: an update. *Therapeutic Advances in Psychopharmacology* **9**, 1–10.

Andersen JS, Olivarius NDF and Krasnik A (2011) The Danish national health service register. *Scandinavian Journal of Public Health* **39**(7 Suppl), 34–37.

Anderson SL and Vande Griend JP (2014) Quetiapine for insomnia: a review of the literature. *American Journal of Health-System Pharmacy* **71**, 394–402.

Baandrup L and Kruse M (2016) Incident users of antipsychotics: who are they and how do they fare? *Social Psychiatry and Psychiatric Epidemiology* **51**, 505–512.

Bendtsen L, Birk S, Kasch H, Aegidius K, Sørensen PS, Thomsen LL, Poulsen L, Rasmussen MJ, Kruuse C and Jensen R (2012) Reference programme: diagnosis and treatment of headache disorders and facial pain. Danish Headache Society, 2nd Edition. *The Journal of Headache and Pain* **13**(Suppl 1), 1–29.

Bush SH, Tierney S and Lawlor PG (2017) Clinical assessment and management of delirium in the palliative care setting. *Drugs* **77**, 1623–1643.

Carr CN, Lopchuk S, Beckman ME and Baugh TB (2016) Evaluation of the use of low-dose quetiapine and the risk of metabolic consequences: a retrospective review. *Mental Health Clinician* **6**, 308–313.

Carton L, Cottencin O, Lapeyre-Mestre M, Geoffroy PA, Favre J, Simon N, Bordet R and Rolland B (2015) Off-label prescribing of antipsychotics in adults, children and elderly individuals: a systematic review of recent prescription trends. *Current Pharmaceutical Design* **21**, 3280–3297.

Correll CU, Joffe BI, Rosen LM, Sullivan TB and Joffe RT (2015) Cardiovascular and cerebrovascular risk factors and events associated with second-generation antipsychotic compared to antidepressant use in a non-elderly adult sample: results from a claims-based inception cohort study. *World Psychiatry* **14**, 56–63.

Danish Health Data Authority. *Danish Register of Medicinal Product Statistics* (http://medstat.dk/en). Accessed 15 October 2020.

Douglas IJ and Smeeth L (2008) Exposure to antipsychotics and risk of stroke: self controlled case series study. *BMJ* **337**, a1227.

Gerhard T, Stroup TS, Correll CU, Setoguchi S, Strom BL, Huang C, Tan Z, Crystal S and Olfson M (2020) Mortality risk of antipsychotic augmentation for adult depression. *PLoS One* **15**, e0239206.

Gjerden P, Bramness JG, Tvete IF and Slørdal L (2017) The antipsychotic agent quetiapine is increasingly not used as such: dispensed prescriptions in Norway 2004–2015. *European Journal of Clinical Pharmacology* **73**, 1173–1179.

Hálfdánarson Ó, Zoëga H, Aagaard L, Bernardo M, Brandt L, Fusté AC, Furu K, Garuoliené K, Hoffmann F, Huybrechts KF, Kalverdijk LJ, Kawakami K, Kieler H, Kinoshita T, Litchfield M, López SC, Machado-Alba JE, Machado-Duque ME, Mahesri M, Nishtala PS, Pearson SA, Reutfors J, Saastamoinen LK, Sato I, Schuiling-Veninga CCM, Shyu YC, Skurtveit S, Verdoux H, Wang LJ, Yahni CZ and Bachmann CJ (2017) International trends in antipsychotic use: a study in 16 countries, 2005–2014. *European Neuropsychopharmacology* **27**, 1064–1076.

Hallas J and Støvring H (2006) Templates for analysis of individual-level prescription data. *Basic & Clinical Pharmacology & Toxicology* **98**, 260–265.

Højlund M, Pottegård A, Johnsen E, Kroken RA, Reutfors J, Munk-Jørgensen P and Correll CU (2019) Trends in utilization and dosing of antipsychotic drugs in Scandinavia: comparison of 2006 and 2016. *British Journal of Clinical Pharmacology* **85**, 1598–1606.

Ingenhoven TJM and Duivenvoorden HJ (2011) Differential effectiveness of antipsychotics in borderline personality disorder: meta-analyses of placebo-controlled, randomized clinical trials on symptomatic outcome domains. *Journal of Clinical Psychopharmacology* **31**, 489–496.

Kales HC, Kim HM, Zivin K, Valenstein M, Seyfried LS, Chiang C, Cunningham F, Schneider LS and Blow FC (2012) Risk of mortality among individual antipsychotics in patients with dementia. *The American Journal of Psychiatry* **169**, 71–79.

Liu XH, Xie XH, Wang KY and Cui H (2014) Efficacy and acceptability of atypical antipsychotics for the treatment of post-traumatic stress disorder: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials. *Psychiatry Research* **219**, 543–549.

Lynge E, Sandegaard JL and Rebolj M (2011) The Danish National Patient Register. *Scandinavian Journal of Public Health*, **39**(7 Suppl), 30–33.

Marcantonio ER (2017) Delirium in hospitalized older adults. *The New England Journal of Medicine* **377**, 1456–1466.

Marston L, Nazareth I, Petersen I, Walters K and Osborn DPJ (2014) Prescribing of antipsychotics in UK primary care: a cohort study. *BMJ Open* **4**, e006135.

Montastruc F, Bénard-Laribière A, Noize P, Pambrun E, Diaz-Bazin F, Tournier M, Bégaud B and Pariente A (2018) Antipsychotics use: 2006–2013 trends in prevalence and incidence and characterization of users. *European Journal of Clinical Pharmacology* **74**, 619–626.

Mors O, Perto GP and Mortensen PB (2011) The Danish psychiatric central research register. *Scandinavian Journal of Public Health*, **39**(7 Suppl), 54–57.

Olfson M, Blanco C, Liu S-M, Wang S and Correll CU (2012) National trends in the office-based treatment of children, adolescents, and adults with antipsychotics. *Archives of General Psychiatry* **69**, 1247–1256.

Papola D, Ostuzzi G, Gastaldon C, Morgano GP, Dragioti E, Carvalho AF, Fusar-Poli P, Correll CU, Solmi M and Barbui C (2019) Antipsychotic use and risk of life-threatening medical events: umbrella review of observational studies. *Acta Psychiatrica Scandinavica* **140**, 227–243.

Pottegård A, Christensen R dePont, Houji A, Christiansen CB, Paulsen MS, Thomsen JL and Hallas J (2014) Primary non-adherence in general practice: a Danish register study. *European Journal of Clinical Pharmacology* **70**, 757–763.

Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J and Schmidt M (2017) Data resource profile: the Danish national prescription registry. *International Journal of Epidemiology* **46**, 798–798f.

Rasmussen L, Pratt N, Hansen MR, Hallas J and Pottegård A (2018) Using the 'proportion of patients covered' and the Kaplan–Meier survival analysis to describe treatment persistence. *Pharmacoepidemiology and Drug Safety* **27**, 867–871.

Reutfors J, Brenner P, Brody B, Heather W, Andersen M and Brandt L (2020) A post-authorization safety study of quetiapine as antidepressant treatment in Sweden: nested case-control analyses of select outcomes. *Drug Safety* **43**, 135–145.

Siow HC, Young WB and Silberstein SD (2005) Neuroleptics in headache. *Headache* **45**, 358–371.

Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z and Freemantle N (2019) Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. *Lancet* **393**, 768–777.

Solmi M, Murru A, Pacchiarotti I, Undurraga J, Veronese N, Fornaro M, Stubbs B, Monaco F, Vieta E, Seeman MV, Correll CU and Carvalho AF (2017) Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review. *Therapeutics and Clinical Risk Management* **13**, 757–777.

Stroup TS and Gray N (2018) Management of common adverse effects of antipsychotic medications. *World Psychiatry* **17**, 341–356.

Tapiainen V, Lavikainen P, Koponen M, Taipale H, Tanskanen A, Tiihonen J, Hartikainen S and Tolppanen AM (2020) The risk of head injuries associated with antipsychotic use among persons with Alzheimer's disease. *Journal of the American Geriatrics Society* **68**, 595–602.

Uggerby P, Østergaard SD, Røge R, Correll CU and Nielsen J (2013) The validity of the schizophrenia diagnosis in the Danish psychiatric central research register is good. *Danish Medical Journal* **60**, A4578.

Walsh D, Davis M, Ripamonti C, Bruera E, Davies A and Molassiotis A (2017) 2016 updated MASCC/ESMO consensus recommendations: management of nausea and vomiting in advanced cancer. *Supportive Care in Cancer* **25**, 333–340.

WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index. Available from: https://www.whocc.no/atc_ddd_index/ (Accessed 15 October 2020).

Zhou DD, Zhou XX, Lv Z, Chen XR, Wang W, Wang GM, Liu C, Li DQ and Kuang L (2019) Comparative efficacy and tolerability of antipsychotics as augmentations in adults with treatment-resistant obsessive-compulsive disorder: a network meta-analysis. *Journal of Psychiatric Research* **111**, 51–58.

SUPPLEMENTARY MATERIAL

Use of Antipsychotics in Denmark 1997-2018: A Nation-wide Drug Utilization Study with Focus on Off-label Use and Associated Diagnoses

Højlund M, Andersen JH, Andersen K, Correll CU, Hallas J. 2021

Contents

Appendix 1: Overview of data sources

Data source	Coverage	Content	Obtained information	Notes
Danish Register of Medical Product Statistics (DRMPS)	From 1995	Information on all prescriptions dispensed at Danish community pharmacies, including preparation, amount, and strength.	Prescriptions for antipsychotics. Prescriptions for other psychotropic medications. Prescriptions for other drugs for assessment of non-psychiatric comorbidities.	In-hospital use is not covered by DRMPS. Indications not recorded in DRMPS.
Danish National Patient Register (DNPR)	Admissions: From 1977 Outpatient contacts: From 1995	Information on admissions and outpatient contacts to all public Danish hospitals.	Diagnoses of psychiatric or neurological disorders. Diagnoses of malignant neoplasms. Diagnoses of other medical conditions for assessment of co-morbidities.	Private hospitals only accounts for a negligible proportion of health care in the included disease categories.
National Health Insurance Service Register (NHISR)	From 1990	Information on all contacts to general practitioners and practicing specialists (e.g. practicing psychiatrists). Based on invoices to regional health administrations (date and type of service).	Health care contacts to: - General practitioners - Office-based psychiatrists - Office-based neurologists	Private practitioners only accounts for a negligible proportion of health care in the included disease categories.
Danish Civil Registration Register (DCRS)	Established in 1968 (covers the entire population)	Information on vital status and civil registration numbers for residents in Denmark.	Civil registration number for register-linkage	Unique identifier (civil registration number) assigned to all Danish residents upon birth or immigration allowing linkage of registers.

Appendix 2: ICD-codes used for diagnostic classification

Group	Subgroups	Codes
Severe or chronic mental disorders (group 1)	Schizophrenia and schizoaffective disorder	ICD-10: F20, 25 ICD-8: 295.xx
	Mania and bipolar affective disorder	ICD-10: F30-31 ICD-8: 296.xx
	Other psychotic disorders	ICD-10: F22-24, 26-29 ICD-8: 297.xx-299.xx
Chronic mental disorders (group 2)	Dementias	ICD-10: F00-03, G30-31 ICD-8: 290.xx
	Mental retardation and autism	ICD-10: F70-79, 84 ICD-8: 311.xx-315.xx
Other mental disorders (group 3)	Organic mental disorders (excl. dementia)	F04-09
	Psychoactive substance use	F10-19
	Schizotypal disorder	F21
	Affective disorders (excl. bipolar affective disorder)	F32-33, 34, 39
	Neurotic or stress-related disorders	F40-49
	Other behavioral disorders	F50-59
	Disorder of adult personality and behavior	F60-69
	Developmental disorders (excl. autism)	F80-83, 85-89
	Behavioral and emotional disorders (e.g. hyperkinetic disorder)	F90-98
	Unspecified mental disorder	F99
Selected diseases of the nervous system (group 4)	Encephalitis, myelitis, and encephalomyelitis	G04-05
	Huntington disease	G10
	Parkinson disease	G20
	Multiple sclerosis	G35
	Episodic and paroxysmal disorders (e.g. epilepsy, migraine, sleep disorders)	G40-47
	Other disorders of the nervous system (e.g. hydrocephalus)	G90-99
Diagnosis of cancer (group 5)	Malignant neoplasms (excl. non-melanoma skin cancer)	C00-43, 45-97

ICD: World Health Organization International Statistical Classification of Diseases and Related Health Problems 8th/10th revision (10th revision: icd.who.int/browse10/2019/en)

Appendix 3: ICD-10 and ATC codes used for covariate assessment in group 6

Co-medications	
Anti-dementia drugs	ATC: N06D
Antidepressants	ATC: N06A
Anxiolytics	ATC: N05B
Drugs used in alcohol dependence	ATC: N07BB
Drugs used in opioid dependence	ATC: N07BC
Hypnotics	ATC: N05C
Mood stabilizers	ATC: N03AX, N05AN01
Psychostimulants	ATC: N06B
Co-morbidities	
Chronic obstructive pulmonary disease	ICD-10: J40-44 ATC: R03
Hypertension	ICD-10: I10-15, H350H, I674, O10 ATC: C03A, C08C, C09A
Alcoholism-related disease	ICD-10: E244, E529A, F10, G312, G405, G621, G721, I426, K292, K70, K860, O354, P043, T519, Z502, Z714, Z721 ATC: N07BB
Ischemic heart disease	ICD-10: I200-201, I208-214, I219, I22-23, I241, I252 ATC: N02BA, C01DA
Diabetes	ICD-10: E10-14, E891, G590, G632, G730, G990C, H280, H360, I729A, M142, N083, O240-243 ATC: A10

ATC: Anatomic Therapeutic Chemical Classification System (who.int/classifications/atcddd/en), ICD-10: World Health Organization International Statistical Classification of Diseases and Related Health Problems 10th revision (icd.who.int/browse10/2019/en)

Supplementary Table 1: Sensitivity analysis extending the assessment period for incident users

	Assessment window					
	1 year		2 years		5 years	
ICD-10 diagnosis	**N**	**%[a]**	**N**	**%[a]**	**N**	**%[a]**
All incident users	37,478	100	33,868	100	29,634	100
Severe mental disorders	5,469	15	4,246	13	2,917	9.8
Chronic mental disorders	4,082	11	3,778	11	3,452	12
Other mental disorders	9,850	26	9,268	27	8,353	28
Selected diseases of the nervous system	1,386	3.7	1,335	3.9	1,278	4.3
Advanced cancers	2,217	5.9	2,190	6.5	2,152	7.3
No relevant diagnoses	14,474	39	13,051	39	11,482	39

Notes: [a]Percentage of all incident users.
Abbreviations: ICD-10: World Health Organization International Statistical Classification of Diseases and Related Health Problems 10th revision (icd.who.int/browse10/2019/en).

Supplementary Table 2: Users by commonly used antipsychotics and diagnostic groups, Denmark, 2018

ARI: Aripiprazole, CHL: Chlorprothixene, CLO: Clozapine, FLU: Flupentixol, HAL: Haloperidol, LEV: Levomepromazine, OLA: Olanzapine, QUE: Quetiapine, RIS: Risperidone, ZUC: Zuclopenthixol.

	CLO	ZUC	ARI	OLA	RIS	CHL	QUE	LEV	FLU	HAL
All users										
All groups	3,403 (100)	4,224 (100)	12,357 (100)	17,554 (100)	16,056 (100)	14,028 (100)	64,946 (100)	4,017 (100)	3,809 (100)	7,963 (100)
Severe mental disorders	3,113 (91)	3,061 (72)	8,033 (65)	10,671 (61)	6,707 (42)	3,895 (28)	17,578 (27)	811 (20)	497 (13)	848 (11)
Chronic mental disorders	130 (3.8)	364 (8.6)	1,159 (9.4)	1,624 (9.3)	4,175 (26)	994 (7.1)	5,720 (8.8)	337 (8.4)	140 (3.7)	1,482 (19)
Other mental disorders	21 (.62)	87 (2.1)	1,236 (10)	1,937 (11)	1,714 (11)	2,276 (16)	12,786 (20)	251 (6.2)	281 (7.4)	1,219 (15)
Neurological diagnosis only	52 (1.5)	14 (.33)	77 (.62)	318 (1.8)	138 (.86)	169 (1.2)	962 (1.5)	234 (5.8)	69 (1.8)	714 (9)
Cancer diagnosis only	-	16 (.38)	5 (.04)	370 (2.1)	103 (.64)	144 (1)	453 (.7)	82 (2)	61 (1.6)	1,816 (23)
No relevant diagnosis	81 (2.4)	679 (16)	1,843 (15)	2,634 (15)	3,219 (20)	6,550 (47)	27,447 (42)	2,302 (57)	2,761 (72)	1,884 (24)
Prevalent users										
All groups	3,253 (100)	3,987 (100)	10,167 (100)	13,983 (100)	11,976 (100)	10,519 (100)	45,037 (100)	3,119 (100)	3,076 (100)	1,683 (100)
Severe mental disorders	3,029 (93)	2,929 (73)	6,959 (68)	9,474 (68)	5,832 (49)	3,477 (33)	15,069 (33)	761 (24)	460 (15)	703 (42)
Chronic mental disorders	108 (3.3)	341 (8.6)	947 (9.3)	1,312 (9.4)	2,929 (24)	815 (7.7)	4,091 (9.1)	307 (9.8)	119 (3.9)	442 (26)
Other mental disorders	15 (.46)	63 (1.6)	743 (7.3)	968 (6.9)	827 (6.9)	1,230 (12)	6,240 (14)	138 (4.4)	175 (5.7)	143 (8.5)
Neurological diagnosis only	39 (1.2)	14 (.35)	59 (.58)	96 (.69)	68 (.57)	122 (1.2)	605 (1.3)	78 (2.5)	57 (1.9)	54 (3.2)
Cancer diagnosis only	-	16 (.4)	5 (.049)	73 (.52)	40 (.33)	110 (1)	252 (.56)	55 (1.8)	50 (1.6)	86 (5.1)
No relevant diagnosis	58 (1.8)	624 (16)	1,454 (14)	2,060 (15)	2,280 (19)	4,765 (45)	18,780 (42)	1,780 (57)	2,215 (72)	255 (15)
Incident users										
All groups	150 (100)	237 (100)	2,190 (100)	3,571 (100)	4,080 (100)	3,509 (100)	19,909 (100)	898 (100)	733 (100)	6,280 (100)
Severe mental disorders	84 (56)	132 (56)	1,074 (49)	1,197 (34)	875 (21)	418 (12)	2,509 (13)	50 (5.6)	37 (5)	145 (2.3)
Chronic mental disorders	22 (15)	23 (9.7)	212 (9.7)	312 (8.7)	1,246 (31)	179 (5.1)	1,629 (8.2)	30 (3.3)	21 (2.9)	1,040 (17)
Other mental disorders	6 (4)	24 (10)	493 (23)	969 (27)	887 (22)	1,046 (30)	6,546 (33)	113 (13)	106 (14)	1,076 (17)
Neurological diagnosis only	13 (8.7)	-	18 (.82)	222 (6.2)	70 (1.7)	47 (1.3)	357 (1.8)	156 (17)	12 (1.6)	660 (11)
Cancer diagnosis only	-	-	-	297 (8.3)	63 (1.5)	34 (.97)	201 (1)	27 (3)	11 (1.5)	1,730 (28)
No relevant diagnosis	23 (15)	55 (23)	389 (18)	574 (16)	939 (23)	1,785 (51)	8,667 (44)	522 (58)	546 (74)	1,629 (26)

Supplementary Table 3: Characteristics of antipsychotic users without psychiatric, neurological or cancer diagnoses in Denmark 2018 (n=46,923)

Characteristic	N	%
Age		
0-12 years	65	0.1
13-17 years	236	0.5
18-24 years	2,286	4.9
25-44 years	11,759	25.1
45-64 years	17,669	37.7
65-79 years	9,445	20.1
80+ years	5,463	11.6
Sex		
Female	26,917	57.4
Antipsychotic drugs		
Quetiapine	27,447	58.5
Chlorprothixene	6,550	14.0
Risperidone	3,219	6.9
Flupentixol	2,761	5.9
Olanzapine	2,634	5.6
Levomepromazine	2,302	4.9
Haloperidol	1,884	4.0
Aripiprazole	1,843	3.9
Zuclopenthixol	679	1.4
Clozapine	81	0.2
Number of antipsychotic prescriptions		
1	13,368	28.5
2	5,433	11.6
3-5	14,415	30.7
>5	13,707	29.2
Number of antipsychotic drugs		
1	43,620	93.0
2	3,009	6.4
>2	294	0.6
Total amount redeemed		
≤90 DDD	37,640	80.2
91-180 DDD	4,635	9.9
181-365 DDD	2,984	6.4
>365 DDD	1,633	3.5
Concurrent use of psychotropic co-medication		
Antidepressants (N06A)	24,064	51.3
Hypnotics (N05C)	8,793	18.7
Mood stabilizers (N03AX+N05AN01)	7,499	16.0
Anxiolytics (N05B)	5,804	12.4
Psychostimulants (N06B)	2,535	5.4
Drugs for alcohol dependence (N07BB)	829	1.8
Drugs for opioid dependence (N07BC)	591	1.3
Anti-dementia drugs (N06D)	270	0.6
Somatic comorbidity		
Chronic obstructive pulmonary disease	20,999	44.8
Hypertension	19,853	42.3
Alcoholism-related disease	9,199	19.6
Ischemic heart disease	8,142	17.4
Diabetes	5,793	12.3
First prescriber*		
Psychiatrist	1,721	11.9
General practitioner	9,434	65.2
Other practicing specialist	134	0.9
Hospital	467	3.2
Psychiatric hospital	247	1.7
No information	2,718	18.8
Healthcare utilization*		
Contact with GP only	11,527	79.6
Contact with practicing psychiatrist	2,383	16.5
Contact with other practicing specialist	309	2.1
No information	255	1.8

*Among incident users in 2018 (n = 14,474)

Supplementary Table 4: Characteristics of antipsychotic users without psychiatric, neurological or cancer diagnoses in Denmark 2018 for the 10 most commonly used antipsychotics

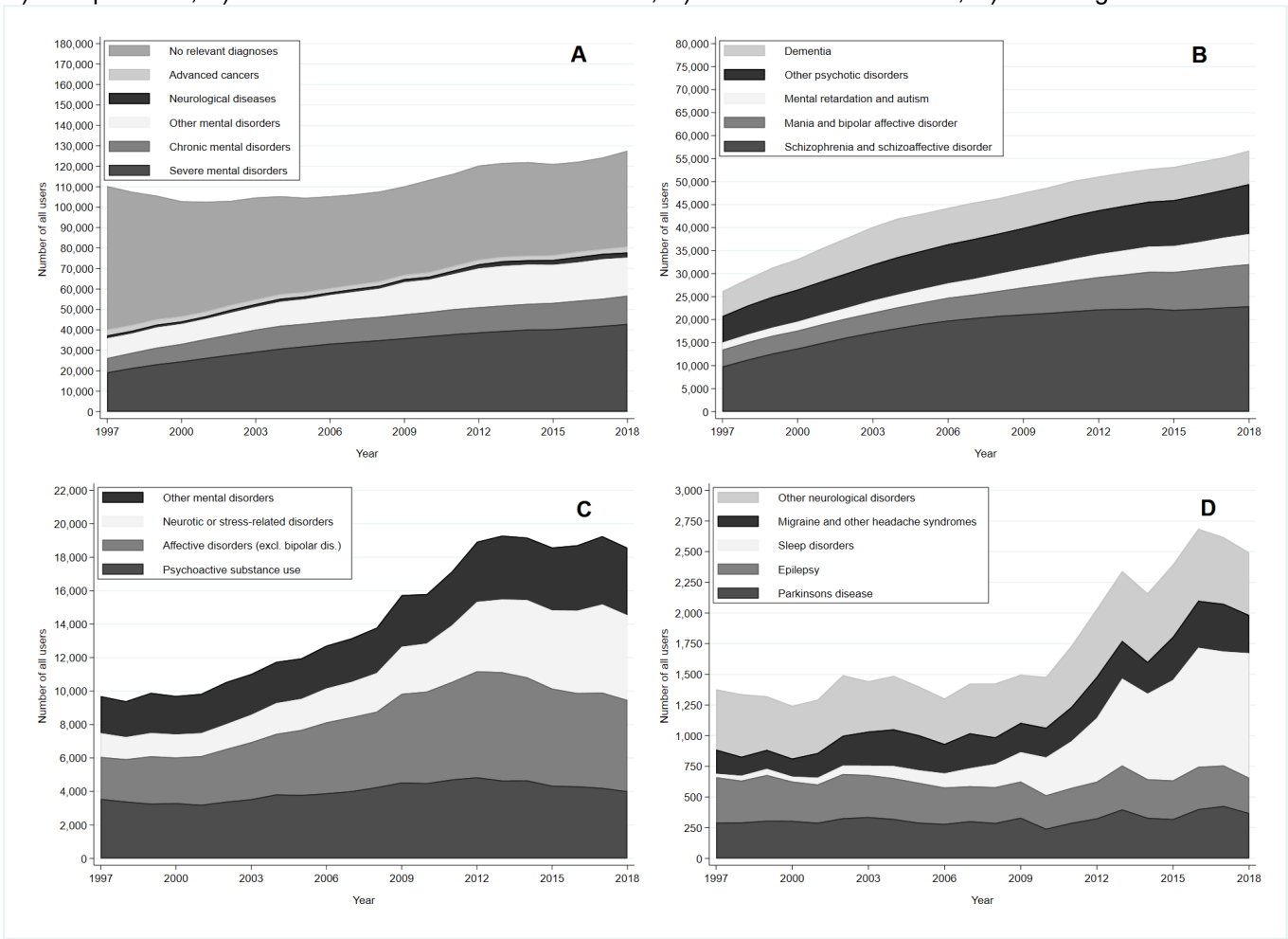
ARI: Aripiprazole, CHL: Chlorprothixene, CLO: Clozapine, FLU: Flupentixol, HAL: Haloperidol, LEV: Levomepromazine, OLA: Olanzapine, QUE: Quetiapine, RIS: Risperidone, ZUC: Zuclopenthixol. (Cells filled with – means few or zero observations and have been blinded due to confidentiality issues).

	QUE	**OLA**	**RIS**	**CHL**	**ARI**
	n = 27,447	n = 2,634	n = 3,219	n = 6,550	n = 1,843
Age, median (IQR)	50 (38-62)	58 (46-72)	59 (43-79)	54 (43-66)	44 (30-56)
Sex					
Female	15,485 (56.4%)	1,288 (48.9%)	1,677 (52.1%)	3,684 (56.2%)	1,018 (55.2%)
Starting year, median (IQR)	2014 (2009-2017)	2011 (2003-2016)	2013 (2005-2017)	2010 (2003-2015)	2012 (2006-2016)
Number of antipsychotic prescriptions					
1	7,581 (27.6%)	372 (14.1%)	517 (16.1%)	1,835 (28.0%)	200 (10.9%)
2	3,317 (12.1%)	263 (10.0%)	348 (10.8%)	706 (10.8%)	197 (10.7%)
3-5	8,827 (32.2%)	729 (27.7%)	738 (22.9%)	1,755 (26.8%)	552 (30.0%)
>5	7,722 (28.1%)	1,270 (48.2%)	1,616 (50.2%)	2,254 (34.4%)	894 (48.5%)
Total amount redeemed					
≤90 DDD	22,575 (82.2%)	982 (37.3%)	2,203 (68.4%)	5,475 (83.6%)	648 (35.2%)
91-180 DDD	2,365 (8.6%)	628 (23.8%)	539 (16.7%)	552 (8.4%)	538 (29.2%)
181-365 DDD	1,593 (5.8%)	553 (21.0%)	350 (10.9%)	316 (4.8%)	388 (21.1%)
>365 DDD	900 (3.3%)	466 (17.7%)	122 (3.8%)	201 (3.1%)	264 (14.3%)
First prescriber					
Psychiatrist	1,161 (13.4%)	119 (20.7%)	143 (15.2%)	174 (9.7%)	182 (46.8%)
General practitioner	5,848 (67.5%)	287 (50.0%)	512 (54.5%)	1,284 (71.9%)	81 (20.8%)
Hospital	100 (1.2%)	53 (9.2%)	45 (4.8%)	8 (0.4%)	-
Healthcare utilization					
Contact with GP only	6,775 (78.2%)	412 (71.8%)	734 (78.2%)	1,429 (80.1%)	167 (42.9%)
Contact with practicing psychiatrist	1,624 (18.7%)	145 (25.3%)	181 (19.3%)	288 (16.1%)	203 (52.2%)

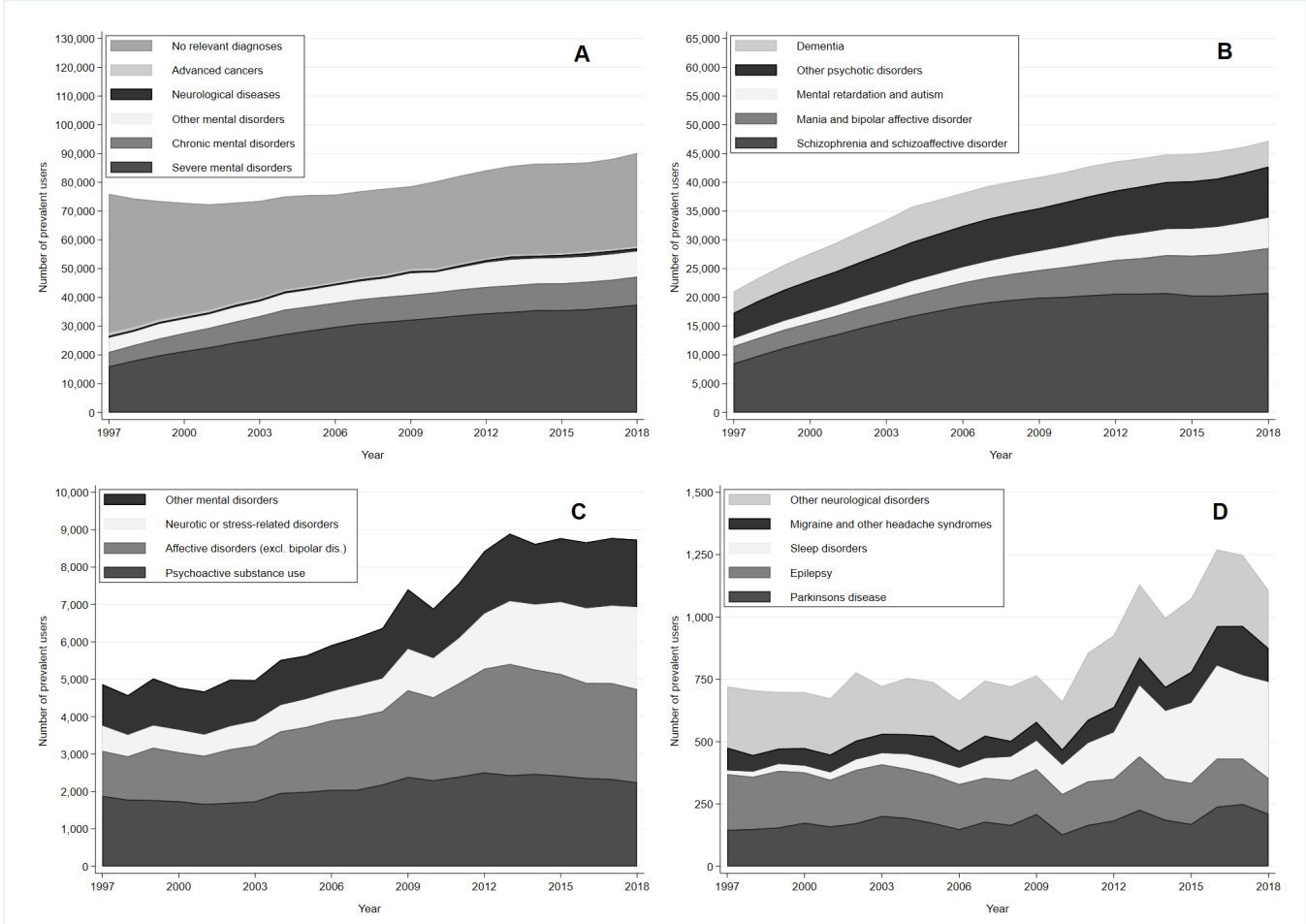
Supplementary Table 4 (cont.)

	HAL	ZUC	LEV	FLU	CLO
	n = 1,884	n = 679	n = 2,302	n = 2,761	n = 81
Age, median (IQR)	87 (79-93)	67 (56-76)	67 (58-76)	66 (53-76)	71 (56-77)
Sex					
Female	1,128 (59.9%)	1,547 (67.2%)	425 (62.6%)	1,929 (69.9%)	36 (44.4%)
Starting year, median (IQR)	2018 (2018-2018)	2003 (1995-2014)	1995 (1995-2002)	2003 (1995-2013)	2013 (2002-2017)
Number of antipsychotic prescriptions					
1	1,316 (69.9%)	656 (28.5%)	64 (9.4%)	608 (22.0%)	17 (21.0%)
2	263 (14.0%)	274 (11.9%)	48 (7.1%)	296 (10.7%)	15 (18.5%)
3-5	174 (9.2%)	687 (29.8%)	255 (37.6%)	1,181 (42.8%)	23 (28.4%)
>5	131 (7.0%)	685 (29.8%)	312 (45.9%)	676 (24.5%)	26 (32.1%)
Total amount redeemed					
≤90 DDD	1,707 (90.6%)	2,131 (92.6%)	464 (68.3%)	2,410 (87.3%)	59 (72.8%)
91-180 DDD	91 (4.8%)	81 (3.5%)	103 (15.2%)	247 (8.9%)	7 (8.6%)
181-365 DDD	52 (2.8%)	46 (2.0%)	69 (10.2%)	78 (2.8%)	9 (11.1%)
>365 DDD	30 (1.6%)	41 (1.8%)	40 (5.9%)	24 (0.9%)	6 (7.4%)
First prescriber					
Psychiatrist	-	18 (3.4%)	7 (12.7%)	109 (20.0%)	-
General practitioner	1,043 (64.0%)	305 (58.4%)	26 (47.3%)	368 (67.4%)	10 (43.5%)
Hospital	261 (16.0%)	21 (4.0%)	-	-	-
Healthcare utilization					
Contact with GP only	1,562 (95.9%)	397 (76.1%)	43 (78.2%)	393 (72.0%)	18 (78.3%)
Contact with practicing psychiatrist	5 (0.3%)	28 (5.4%)	10 (18.2%)	140 (25.6%)	-

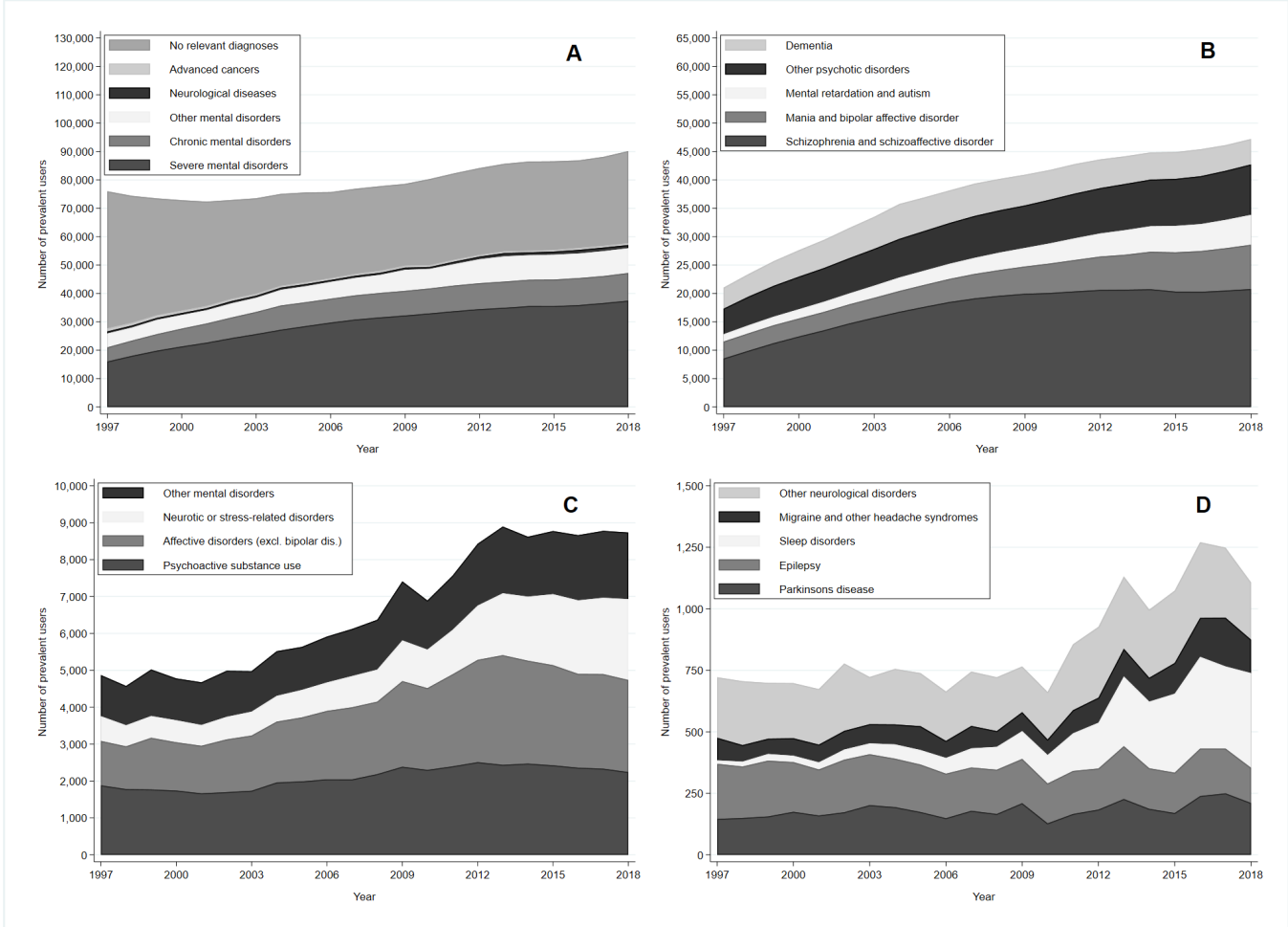
Supplementary Figure 1: Development in all users overall and by diagnostic subgroups, Denmark 1997-2018
A) Groups 1 to 6, B) Severe and chronic mental disorders, C) Other mental disorders, D) Neurological disorders



Supplementary Figure 2: Development in prevalent users overall and by subgroups, Denmark 1997-2018
A) Groups 1 to 6, B) Severe and chronic mental disorders, C) Other mental disorders, D) Neurological disorders



Supplementary Figure 3: Development in incident users overall and by subgroup, Denmark 1997-2018
A) Groups 1 to 6, B) Severe and chronic mental disorders, C) Other mental disorders, D) Neurological disorders



Paper II: Diabetes

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Original Investigation | Psychiatry

Association of Low-Dose Quetiapine and Diabetes

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Abstract

IMPORTANCE Quetiapine has been associated with increased risk of type 2 diabetes when used in medium or high doses for the treatment of severe mental disorders. It is not known whether low doses, commonly used off-label for sedative-hypnotic purposes, are also associated with increased risk of type 2 diabetes.

OBJECTIVE To investigate whether there is an association between prescription of low-dose quetiapine and the risk of type 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS This cohort study examined nationwide Danish health registers for data regarding new users of quetiapine (n = 185 938) or selective serotonin reuptake inhibitors (SSRIs) (n = 1 031 920) who were aged 18 years or older between January 1, 1998, and December 31, 2018. Individuals with schizophrenia or bipolar disorder were excluded. Quetiapine-initiators were matched 1:1 with initiators of SSRIs, using a high-dimensional propensity score (hdPS). Maximum follow-up was 5 years. Association with cumulative dose was investigated, using a case-control approach nested among quetiapine users. Data analysis was performed from May to September 2020.

EXPOSURES Dispensing of quetiapine or SSRIs. Quetiapine prescriptions were limited to tablet strengths of 25 mg and 50 mg to focus on low-dose use.

MAIN OUTCOMES AND MEASURES Incident type 2 diabetes was defined as first filling of an antidiabetic medication, first register diagnosis of type 2 diabetes or first hemoglobin A_{1C} measurement greater than or equal to 6.4% (≥48 mmol/mol). Incidence rates (IRs), incidence rate ratios (IRRs), and number-needed-to-harm (NNH) were calculated for full and matched cohorts using as-treated and intention-to-treat approaches. Odds ratios (ORs) were calculated for the association with cumulative quetiapine dose.

RESULTS Altogether, 896 285 patients were included in the full cohort; 538 164 (60%) were female and the median (interquartile range) age was 47 (33-67) years. There were 57 701 low-dose quetiapine initiators and 838 584 SSRI initiators. The matched cohort consisted of 54 616 pairs. In as-treated analyses, the incidence of type 2 diabetes during treatment with low-dose quetiapine (425 cases) was 9.59 cases/1000 person-years (PY) (95% CI, 8.72-10.5/1000 PY), which was slightly higher than for SSRI users (8462 cases; IR, 8.13/1000 PY; 95% CI, 7.96-8.30/1000 PY), resulting in a significant IRR of 1.18 (95% CI, 1.07-1.30) and NNH of 684 (95% CI, 418-1873). However, the between-group difference was nonsignificant in the hdPS-matched cohort (IR, 9.49 vs IR, 9.58; IRR, 0.99; 95% CI, 0.87-1.13). The case-control analysis found no dose-response association of low-dose quetiapine with diabetes (OR for doubling of the cumulative dose: 1.02; 95% CI, 0.95-1.09; P = .54), but in sensitivity analyses higher daily doses were associated with diabetes (all tablet strengths: OR, 1.08; 95% CI, 1.03-1.13).

(continued)

Key Points

Question Is the use of quetiapine in low doses associated with increased risk of diabetes?

Findings In this nationwide cohort study that included 57 701 new users of quetiapine in low doses and without severe mental illness, the incidence of diabetes was approximately 9 cases per 1000 person-years, similar to that of a reference population treated with selective serotonin reuptake inhibitors for other psychiatric disorders.

Meaning Quetiapine used in low doses was not associated with an increased risk of diabetes among individuals with nonsevere mental illness in comparison with use of selective serotonin reuptake inhibitors.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE In this cohort study, use of low-dose quetiapine was not associated with excess risk of type 2 diabetes in comparison with SSRIs.

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Introduction

Quetiapine is a second-generation antipsychotic medication labeled for treatment of schizophrenia, bipolar affective disorder, and as adjunctive treatment in major depression.[1,2] Its use has increased worldwide, with quetiapine now being the most commonly prescribed antipsychotic medication among adults aged 20 to 64 years in 10 of 14 countries.[3] In 2010, the 1-year prevalence of quetiapine use among publicly insured adults in the US was as high as 3 users per 100 inhabitants.[3] Furthermore, several drug utilization studies have documented considerable use of quetiapine in conditions other than labeled indications, such as anxiety disorders and insomnia.[4-7]

Quetiapine is associated with a moderate risk of metabolic disturbances in comparison with other second-generation antipsychotic medications,[8,9] and it has been linked to an increased risk of type 2 diabetes in both adolescents[10] and adults.[11,12] An observational study in new users of quetiapine in relatively low doses (≤200mg/d) found significant increases in fasting blood glucose with long-term treatment.[13]

Histaminergic and serotonergic antagonism plays a central role in antipsychotic-induced hyperglycemia,[9] and quetiapine has a considerable affinity for both the H_1- and 5-HT_{2C}-receptors involved.[14] Antipsychotic medications with high affinity of these receptors, including quetiapine, have also been associated with type 2 diabetes on the basis of adverse drug reaction reports.[15]

As quetiapine occupies H_1- and 5-HT_{2C}-receptors extensively at low doses, which are typically used for the treatment of anxiety and insomnia,[16] we hypothesized that even low doses of quetiapine might induce metabolic disturbances leading to type 2 diabetes. An association of type 2 diabetes with low doses of quetiapine would be of particular concern given the widespread use for nonpsychotic conditions, such as insomnia. Our aim was thus to investigate the association between the prescription of low-dose quetiapine and type 2 diabetes in a controlled epidemiological design.

Methods

Study Design

We conducted a register-based cohort study to assess the association between prescription of quetiapine in low doses and the risk of type 2 diabetes. Access to deidentified data was approved by the Danish Health Data Authority. According to Danish legislation, no ethical approval or informed consent is needed for register-based studies. This study followed the Reporting of Studies Conducted Using Observational Routinely Collected Data for Pharmacoepidemiological Research (RECORD-PE) reporting guideline[17] (eTable 1 in Supplement), which is an extension of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

As mental illness, or psychological distress in general, is associated with type 2 diabetes through a multitude of mechanisms,[18,19] we applied an active-comparator design to minimize confounding-by-indication. New users of selective serotonin reuptake inhibitors (SSRIs) were chosen as reference population, as SSRIs are frequently prescribed in nonpsychotic psychiatric conditions where low-dose quetiapine might also be used. Furthermore, SSRIs have not been associated with type 2 diabetes to the same extent as quetiapine.[11,20]

Because the effect of antipsychotics on type 2 diabetes risk may be either direct on pancreatic beta-cells, or mediated through weight gain, we analyzed the cohort in 3 ways: (1) using an as-treated (AT) approach to estimate the association with type 2 diabetes while being treated, (2) using an intention-to-treat (ITT) approach to estimate the association with type 2 diabetes among all who initiated treatment, but might stop because of other side effects (eg, sedation, lipid disturbances), while still being subject to weight gain or pancreatic dysfunction from the drug, and (3) analyzing the association of cumulative dose with type 2 diabetes, using a nested case-control approach (eTable 1 in Supplement).

Data Sources

We collected data from 4 different Danish health care data sources with nationwide coverage. Data on prescription of quetiapine, SSRIs, and other medications were obtained from the Danish Register of Medicinal Product Statistics (DRMPS).[21] Data on inpatient and outpatient diagnoses for outcome and comorbidity assessment were obtained from the Danish National Patient Register.[22] Glycated hemoglobin A_{1C} (HbA_{1C}) values were obtained from the Danish Laboratory Databank, which collects laboratory results from both primary care clinics and hospitals. Vital status and migration data were obtained from the Danish Civil Register.[23] Virtually all health care in Denmark is tax-funded and freely available to all citizens, which results in near-complete coverage from these data sources.[24] In Denmark, antipsychotic medications are only available via prescription, which means that all prescriptions from outpatient services and primary care are captured in DRMPS. Altogether, 99% of SSRI and 92% of quetiapine use is accounted for by this data source, the remainder being dispensed in hospitals.[25]

Study Population and Exposure

We identified prescriptions of low-dose quetiapine or SSRIs in the DRMPS between January 1, 1998, and December 31, 2018, and the date of first prescription was used as the index date. We pragmatically defined low-dose quetiapine use as filling of prescriptions for 25-mg or 50-mg tablets. These tablet strengths are typically used for sedative or hypnotic purposes, and we excluded individuals who filled prescriptions for higher tablet strengths (≥100 mg) on the index date to focus on low-dose use.

Individuals who filled prescriptions for both study drugs on the index date were also excluded, together with individuals without continuous register coverage, use of other antipsychotic medications, or use of the other study drug within 365 days before the index date. Lastly, individuals with diabetes, severe mental illness, or age younger than 18 years at index date were excluded. Cohort selection is depicted in eFigure 1 in the Supplement and codes for the inclusion and exclusion criteria in eTable 1 in the Supplement.

Outcome Definition

Incident type 2 diabetes was the defined outcome. It was defined with onset as (1) first prescription for an antidiabetic medication (Anatomical Therapeutic Chemical code [ATC]: A10), (2) first diagnosis of type 2 diabetes in registers (E10-14 in *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10]*), or (3) first HbA_{1C} measurement of greater than or equal to 6.4% (≥48 mmol/mol).

Statistical Analysis

Covariates

We used logistic regression to estimate each individual's propensity to fill prescriptions for low-dose quetiapine. The regression model included age, sex, starting year, and the 50 most influential prescriptions or diagnoses (eTable 2 in Supplement). The latter was selected using a high-dimensional propensity score (hdPS) algorithm[26] assessing all prescriptions and diagnoses recorded

within 365 days before the index date. Hereafter, individuals were matched 1:1 using nearest-neighbor matching, allowing a caliper of 0.02 and without trimming the propensity score distribution (eFigure 2 in Supplement). For subgroup analyses, we assessed HbA_{1C} measurements within 183 days before and 7 days after the index date. Standardized mean differences (SMD) were used to assess covariate balance, with SMD less than or equal to 0.1 indicating adequate balance.[27]

Intention-to-Treat and As-Treated Analyses

In ITT analyses, all individuals were followed from filling of the first prescription to outcome, death, or censoring. Reasons for censoring were (1) use of higher tablet strengths of quetiapine (≥100 mg), (2) use of other antipsychotic medications, (3) use of the other study drug, (4) diagnosis of severe mental illness (eTable 1 in Supplement), (5) diagnosis of type 1 diabetes, (6) emigration, or (7) reaching 5 years of follow-up.

For as-treated (AT) analyses, follow-up was confined to the first treatment episode or censoring as described above, whichever occurred first. Treatment episodes were constructed by assigning a duration to each prescription equivalent of the number of tablets filled (assuming use of 1 tablet/d), adding a grace period of 90 days between prescriptions to account for irregular use. Gaps exceeding 90 days were considered a gap in treatment. Furthermore, we added 90 days of observation to the last prescription to capture development of type 2 diabetes occurring shortly after treatment cessation and to avoid immortal time bias.[28]

We calculated crude incidence rate ratios (IRR) and incidence rate differences (IRD) with 95% CIs for both full and hdPS-matched cohorts from the number of events per 1000 person-years of follow-up in each group. Furthermore, we calculated the number-needed-to-harm (NNH) for low-dose quetiapine-initiation as the inverse of the IRD.

Case-Control Analysis

To investigate the association between cumulative quetiapine dose and type 2 diabetes, we conducted a case-control analysis nested among all low-dose quetiapine users. See eMethods in the Supplement.

Subgroup and Sensitivity Analyses

We conducted subgroup analyses stratified on sex, age group (<65 years or ≥65 years), and presence of prediabetes at baseline (as defined in eTable 1 in the Supplement).

To test the impact of the analytical choices on the results, we conducted a number of sensitivity and supplementary analyses: (1) varying the grace period in AT analyses, (2) extending the washout window, (3) extending the maximum follow-up time, (4) excluding individuals with recurrent depression, (5) using inverse probability of censoring weights, (6) using standardized mortality ratio weights as an alternative to hdPS-matching, (8) inclusion of 100-mg quetiapine tablets, (9) inclusion of all strengths of quetiapine tablets, (10) using Z-drugs as a comparator, and (11) using olanzapine as an active assay sensitivity control exposure. For further description and rationale for these analyses, see eMethods in the Supplement.

The significance threshold was set at $P < .05$. Statistical analyses were performed using Stata/MP version 16.1 (StataCorp) from May to September 2020.

Results

The full cohort included 896 285 patients; 538 164 were female (60%), and the median (interquartile range [IQR]) age was 47 (33-67) years. We identified 57 701 eligible new users of low-dose quetiapine (median [IQR] age, 45 [30-64] years; 29 141 female patients [51%]) and 838 584 eligible new users of SSRIs (median [IQR] age, 47 [33-67] years; 509 023 female patients [61%]) in the DRMPS between January 1, 1998, and December 31, 2018 (**Figure 1**). The matched cohort consisted of 54 616 pairs with covariate balance (SMD < 0.1) on relevant characteristics, except for

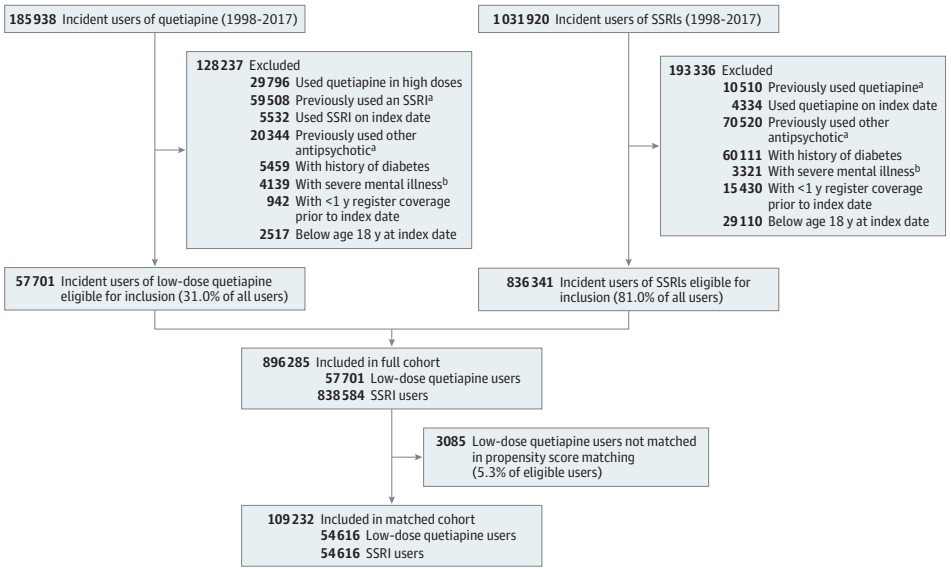
alcohol-related disorders and depression (**Table 1**). The unmatched low-dose quetiapine users were more likely to be diagnosed with depression, have alcohol-related disorders, and use mirtazapine concurrently (eTable 3 in Supplement).

Median (IQR) follow-up time in the full cohort was 1.3 (0.3-3.3) years for low-dose quetiapine users and 5.0 (2.4-5.0) years for SSRI users. For AT analyses, the median (IQR) follow-up time was 0.5 (0.3-0.8) years for low-dose quetiapine users and 0.7 (0.4-1.5) years for SSRI users. The median (IQR) number of prescriptions was 1 (1-3) for low-dose quetiapine users and 3 (1-8) for SSRI users. Among low-dose quetiapine users, 20% filled 5 or more prescriptions during their first treatment episode, and most (99%) used quantities corresponding to less than 0.25 defined daily dose (DDD) per day as calculated by the World Health Organization (eTable 4 in the Supplement). For further details on follow-up, censoring, and outcome assessment, see eTable 4, eTable 5, and eTable 6 in the Supplement.

Cumulative incidence of type 2 diabetes was relatively stable in both the full and matched cohorts during the follow-up period (**Figure 2**). Use of low-dose quetiapine was associated with a slightly elevated risk of type 2 diabetes compared with SSRIs (IRR for AT, 1.18; 95% CI, 1.07-1.30; IRR for ITT, 1.13; 95% CI, 1.06-1.21) (**Table 2**). However, this increased risk of type 2 diabetes was not present in the hdPS-matched cohort (IRR for AT, 0.99; 95% CI, 0.87-1.13; IRR for ITT, 0.92; 95% CI, 0.84-1.00) (Table 2).

In AT analysis of the full cohort, the IR of type 2 diabetes was 9.59/1000 person-years (95% CI, 8.72/1000 person-years to 10.5/1000 person-years) for those treated with low-dose quetiapine (n = 425) and 8.13/1000 person-years (95% CI, 7.96/1000 person-years to 8.30/1000 person-years) for those treated with SSRIs (n = 8462), resulting in an IRD of 1.46 (95% CI, 0.53-2.39). In the matched cohort, there were no differences in IRs for low-dose quetiapine users compared with SSRI users (IR = 9.49 vs 9.58, respectively). NNH for use of low-dose quetiapine was high in both AT and

Figure 1. Flow Diagram of Cohort Selection



SSRI indicates selective serotonin reuptake inhibitor.

[a] Within 1 year of cohort entry.

[b] Severe mental illness includes schizophrenia, schizoaffective disorder, and bipolar affective disorder.

ITT analyses (NNH for AT of full cohort = 684 [95% CI, 418-1873]; NNH for ITT of full cohort = 1038 [95% CI, 664-2378]) (Table 2).

There was no clear association between cumulative dose of quetiapine (as low-dose treatment) and risk of type 2 diabetes. The OR for each doubling of the cumulative dose was 1.02 (95% CI, 0.95-1.09; *P* = .54). Furthermore, a posthoc analyses of clinically relevant dose strata found no significant increases in type 2 diabetes risk with increasing cumulative doses, and confidence intervals were overlapping for all strata (eTable 7 in Supplement).

The IR of type 2 diabetes among individuals treated with low-dose quetiapine varied considerably across subgroups. In subgroup analyses of the matched cohort, female sex, age between 18 and 64 years, and prediabetes at baseline were each associated with higher IRs of type 2 diabetes than for the entire sample (**Figure 3**). A similar pattern was observed for SSRI users.

Table 1. Baseline Characteristics of Incident Users of Low-Dose Quetiapine and Selective Serotonin Reuptake-Inhibitors in Denmark From January 1998 to December 2018

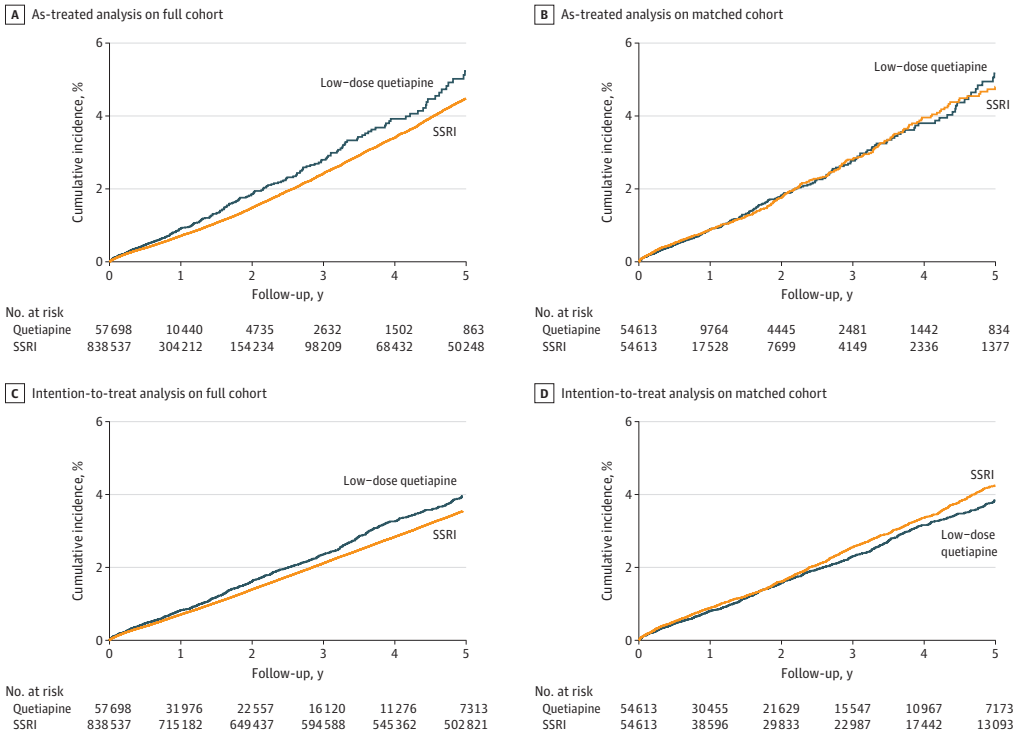
	Full cohort			hdPS-matched cohort		
	Participants, No. (%)			Participants, No. (%)		
	Low-dose quetiapine	SSRI	SMD	Low-dose quetiapine	SSRI	SMD
All	57 701	838 584		54 616	54 616	
Sex						
Female	29 141 (51)	509 023 (61)	0.21	27 383 (50)	26 237 (48)	0.04
Male	28 560 (49)	329 561 (39)		27 233 (50)	28 379 (52)	
Age, y						
Median (IQR)	45 (30-64)	47 (33-67)	<0.01	45 (29-65)	46 (29-68)	<0.01
18-64	43 349 (75)	610 368 (73)	0.05	40 898 (75)	39 357 (72)	0.06
65-79	7626 (13)	135 632 (16)	0.08	7226 (13)	8492 (16)	0.07
≥80	6726 (12)	92 584 (11)	0.02	6492 (12)	6767 (12)	0.02
Year of cohort entry						
1998-2002	83 (<1)	228 019 (27)	0.86	83 (<1)	260 (<1)	0.06
2003-2007	3622 (6)	249 081 (30)	0.64	3616 (7)	3430 (6)	0.01
2008-2012	12 820 (22)	219 460 (26)	0.09	12 622 (23)	12 358 (23)	0.01
2013-2018	41 176 (71)	142 460 (17)	1.31	38 295 (70)	38 568 (71)	0.01
Comorbidities						
Hypertension	11 835 (21)	163 686 (20)	0.02	11 095 (20)	11 981 (22)	0.04
COPD	7701 (13)	100 860 (12)	0.04	7183 (13)	6801 (12)	0.02
Heart failure	1369 (2)	22 458 (3)	0.02	1300 (2)	1482 (3)	0.02
Obesity	3504 (6)	25 383 (3)	0.15	3183 (6)	2841 (5)	0.03
Alcohol-related disorders	14 922 (26)	117 139 (14)	0.30	14 077 (26)	10 373 (19)	0.16
Major depression	12 300 (21)	47 471 (6)	0.47	10 818 (20)	5320 (10)	0.29
Recurrent depression	6225 (11)	11 905 (1)	0.40	5275 (10)	1503 (3)	0.29
Drugs used in the past year						
Digoxin	1003 (2)	22 276 (3)	0.06	967 (2)	1005 (2)	0.01
Thiazide diuretics	4292 (7)	81 780 (10)	0.08	4066 (7)	4178 (8)	0.01
Beta-blockers	6207 (11)	92 691 (11)	0.01	5802 (11)	6090 (11)	0.02
Statins	6387 (11)	75 838 (9)	0.07	5991 (11)	6237 (11)	0.01
Oral glucocorticoids	3925 (7)	58 132 (7)	0.01	3654 (7)	3795 (7)	0.01
Mirtazapine	9640 (17)	44 189 (5)	0.37	8383 (15)	8000 (15)	0.02
Antihistamines	6068 (11)	60 647 (7)	0.12	5576 (10)	4686 (9)	0.06
Hemoglobin A_{1C} at baseline						
Normal	7075 (12)	28 669 (3)	0.33	6521 (12)	8104 (15)	0.09
Prediabetes	2344 (4)	9671 (1)	0.18	2127 (4)	2552 (5)	0.04
Missing	48 282 (84)	800 244 (95)	0.39	45 968 (84)	43 960 (80)	0.10

Abbreviations: COPD, chronic obstructive pulmonary disease; hdPS, high-dimensional propensity score; IQR, interquartile range; SMD, standardized mean difference; SSRI, selective serotonin reuptake inhibitor.

Prediabetes at baseline was associated with the highest IRs observed for both users of low-dose quetiapine (33.8-34.5 cases/1000 person-years) and SSRIs (32.8-33.2 cases/1000 person-years).

Including higher tablet strengths in the exposure definition for quetiapine increased the association with type 2 diabetes, although most markedly when including tablets up to 400 mg (eFigure 3 in the Supplement). A similar association was also found in supplementary case-control analyses including higher tablet strengths (doubling of dose: OR, 1.08; 95% CI, 1.03-1.13) (eTable 7 in Supplement). Varying the grace period in AT analyses, extending washout period or maximum follow-up, or excluding individuals with recurrent depression was not associated with different results from the main analysis (eFigure 4 in the Supplement). Application of inverse probability of censoring weights and standardized mortality ratio weights in the main analysis did not suggest a considerable impact on the results from informative censoring or unmatched individuals, respectively (eTable 8 and eTable 9 in Supplement). Using Z-drugs as an alternative comparator did not prove useful, as individuals treated with Z-drugs were found to have an unexpectedly high rate of type 2 diabetes (eFigure 5 in Supplement). Finally, the use of olanzapine as an active control exposure was associated with assay sensitivity by detecting increased risk of diabetes among olanzapine users compared with SSRI users (eFigure 6 in the Supplement).

Figure 2. Cumulative Incidence of Diabetes After Initiation of Treatment With Low-Dose Antipsychotic or Selective Serotonin Reuptake Inhibitors (SSRIs)



Discussion

In this nationwide cohort study, we did not find an increased risk of developing type 2 diabetes with prescription of low-dose quetiapine compared with a psychiatrically ill reference population being prescribed SSRIs.

Considering all low-dose quetiapine users, we found an increased risk of type 2 diabetes associated with use of low-dose quetiapine compared with use of SSRIs (IRR = 1.18). However, this association was not present in analyses of the hdPS-matched cohort (IRR = 0.99). This difference in results likely represents an increased risk for developing type 2 diabetes among the subgroup of quetiapine users, who could not be matched to the reference population, and was unlikely attributable to the use of low-dose quetiapine itself. Individuals in this group were more likely to have a history of major depression, recurrent depression, obesity, or use of mirtazapine or antihistamines, each characteristics that are likely to increase the risk for type 2 diabetes.

Incidence rates of type 2 diabetes were higher among both low-dose quetiapine and SSRI users than in the general Danish population. Here the incidence rate was 6.1/1000 inhabitants/y among those aged 45 to 54 years in 2011[29] in comparison with the IR of approximately 9/1000 PY observed for both low-dose quetiapine and SSRIs. There are several explanations for this increased incidence, First, the risk of developing type 2 diabetes might be higher among individuals with psychiatric morbidity, such as depression, in which both quetiapine and SSRIs are used. Second, both medications might carry a similar, increased risk of inducing type 2 diabetes. The first explanation is supported by an increased incidence of type 2 diabetes in individuals with depression.[30] Regarding the second explanation, both SSRIs and quetiapine have been associated with development of type 2 diabetes, but the evidence for SSRIs is conflicting and the association is probably modest.[9,20,31,32] In direct comparison with antidepressant use, quetiapine (regardless of dosage) was associated with a moderately increased risk of type 2 diabetes (HR = 1.36).[11]

Prediabetes at baseline was associated with the highest IRs observed for both users of low-dose quetiapine (33.8-34.5 cases/1000 PY) and SSRIs (32.8-33.2 cases/1000 PY). This finding must be interpreted cautiously as the number of individuals with HbA_{1C} measurements at baseline was low in both groups. Furthermore, there was no clear difference between users of low-dose quetiapine and SSRIs and the high IR more likely reflects a natural progression from prediabetes to type 2 diabetes,[33] regardless of exposure to medications.

Table 2. Risk of Diabetes Associated With Use of Low-Dose Quetiapine Compared With SSRIs

	Exposed, No.	Follow-up, 1000 PY	Diabetes, No.	Incidence rate, cases/1000 PY (95% CI)	Incidence rate ratio (95% CI)	Incidence rate difference (95% CI)	NNH (95% CI)
As-treated analysis							
Full cohort							
Low-dose quetiapine	57 701	44	425	9.59 (8.72 to 10.54)	1.18 (1.07 to 1.30)	1.46 (0.53 to 2.39)	684 (418 to 1873)
SSRI	838 584	1041	8462	8.13 (7.96 to 8.30)	NA	NA	NA
PS matched							
Low-dose quetiapine	54 616	42	397	9.49 (8.60 to 10.47)	0.99 (0.87 to 1.13)	−0.09 (−1.32 to 1.14)	−11537 (−760 to 876)
SSRI	54 616	58	553	9.58 (8.81 to 10.41)	NA	NA	NA
Intention-to-treat analysis							
Full cohort							
Low-dose quetiapine	57 701	110	895	8.16 (7.64 to 8.71)	1.13 (1.06 to 1.21)	0.96 (0.42 to 1.51)	1038 (664 to 2378)
SSRI	838 584	3158	22 718	7.19 (7.10 to 7.29)	NA	NA	NA
PS matched							
Low-dose quetiapine	54 616	105	837	7.97 (7.45 to 8.53)	0.92 (0.84 to 1.00)	−0.70 (−1.43 to 0.02)	−1423 (−700 to 41600)
SSRI	54 616	141	1223	8.67 (8.20 to 9.17)	NA	NA	NA

Abbreviations: NA, not applicable; NNH, number needed to harm; PS, propensity score; PY, person-years; SSRI, selective serotonin reuptake inhibitor.

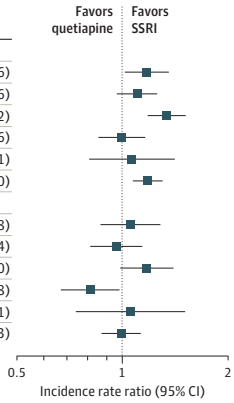
We found no association of increased type 2 diabetes risk with increasing cumulative dose, when exposure was confined to use of small tablets alone. However, there was a clear association between use of higher cumulative doses and risk of diabetes, when considering higher tablet strengths as proxy for higher daily doses (OR, 1.44; 95% CI, 1.13-1.84). Therefore, the daily dose is likely to be a more important risk factor than cumulative dose alone.

This study benefits from several design characteristics: The high number of individuals allowed us to perform appropriate propensity-score matching and yield results with reasonably high confidence. Furthermore, the application of an empirically driven matching procedure, using all prescriptions and hospital contacts, ensured a high degree of confounder control, which is a major issue in observational studies of diseases with multifactorial etiology, such as type 2 diabetes. The outcome definition was improved by including HbA_{1C} measurements, when available. Lastly, we conducted multiple supplementary and sensitivity analyses to test the influence of critical analytic decisions on the results and the robustness of our primary data analysis strategy.

Figure 3. Subgroup Analysis of Association Between Diabetes and Use of Low-Dose Quetiapine or Selective Serotonin Reuptake Inhibitors (SSRIs)

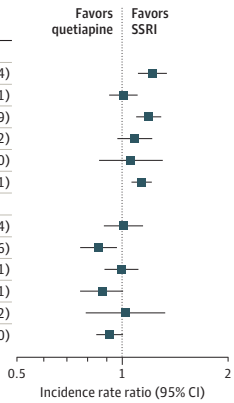
A As-treated analysis

Source	Quetiapine Events	Quetiapine Incidence rate	SSRI Events	SSRI Incidence rate	Incidence rate ratio (95% CI)
Full cohort					
Women	192	8.13	4605	6.93	1.17 (1.02-1.36)
Men	233	11.24	3858	10.22	1.10 (0.96-1.26)
Age 18-64 y	255	8.17	4504	6.11	1.34 (1.18-1.52)
Age ≥65 y	170	12.98	3958	13.04	1.00 (0.85-1.16)
Prediabetes	57	35.18	326	33.06	1.06 (0.80-1.41)
Overall	425	9.59	8462	8.13	1.18 (1.07-1.30)
hdPS-matched cohort					
Women	178	8.04	224	7.64	1.05 (0.87-1.28)
Men	219	11.12	329	11.59	0.96 (0.81-1.14)
Age 18-64 y	232	7.93	274	6.75	1.17 (0.99-1.40)
Age ≥65 y	165	13.15	279	16.26	0.81 (0.67-0.98)
Prediabetes	50	34.49	74	32.75	1.05 (0.74-1.51)
Overall	397	9.49	553	9.58	0.99 (0.87-1.13)



B Intention-to-treat analysis

Source	Quetiapine Events	Quetiapine Incidence rate	SSRI Events	SSRI Incidence rate	Incidence rate ratio (95% CI)
Full cohort					
Women	440	7.85	12705	6.45	1.22 (1.11-1.34)
Men	455	8.48	10013	8.43	1.01 (0.92-1.11)
Age 18-64 y	592	6.76	14083	5.69	1.19 (1.09-1.29)
Age ≥65 y	303	13.71	8635	12.65	1.08 (0.97-1.22)
Prediabetes	102	33.17	633	31.39	1.06 (0.86-1.30)
Overall	895	8.16	22718	7.19	1.13 (1.06-1.21)
hdPS-matched cohort					
Women	413	7.74	529	7.70	1.01 (0.88-1.14)
Men	424	8.21	694	9.61	0.85 (0.76-0.96)
Age 18-64 y	547	6.54	712	6.58	0.99 (0.89-1.11)
Age ≥65 y	290	13.61	511	15.57	0.87 (0.76-1.01)
Prediabetes	94	33.84	141	33.19	1.02 (0.79-1.32)
Overall	837	7.97	1223	8.67	0.92 (0.84-1.00)



Prediabetes at baseline is defined as one glycated hemoglobin measurement of 5.7% to 6.3% (39-47 mmol/mol) within 6 months before and 7 days after cohort entry (only available for 9419 low-dose quetiapine users [16%] and 38 340 SSRI users [5%] in the full cohort and for 8648 low-dose quetiapine users [16%] and 10 656 SSRI users [20%] in the hdPS-matched cohort). hdPS denotes high-dimensional propensity score.

To our knowledge, this is the first study to examine the risk of type 2 diabetes with low-dose quetiapine treatment, specifically, using a large, nationwide cohort and sophisticated data analytic methods. Using this design, we found that the risk of type 2 diabetes with use of low-dose quetiapine is not higher than among SSRI-treated controls, although it is higher than in the general population. The exclusion of a substantial type 2 diabetes risk with low-dose quetiapine is important, given the increasing number of low-dose quetiapine users worldwide.[3,34] Many years of critical attention to the long-term use of benzodiazepines and hypnotics is a possible driver of this increase, and could have created a new public health problem, if low-dose quetiapine were associated with considerable type 2 diabetes risk. However, the high NNH (684) suggests that this risk is likely not important for the individual user or from a public health perspective, as it will not result in a substantial number of new type 2 diabetes cases. This finding does not mean that metabolic monitoring is not important with antipsychotic treatment at any dose, as some individuals will develop type 2 diabetes during treatment and as type 2 diabetes is more prevalent in the psychiatric population than in the general population. It is also important to note that our results and conclusion pertain to use of low-dose quetiapine alone and cannot be generalized, such as to higher daily doses or concomitant use with other antipsychotics or antidepressants. These populations should be the aim of future studies and continuous monitoring of metabolic risk factors, such as body mass index, blood glucose, blood pressure and lipids, should apply to all individuals treated with antipsychotics regardless of dose or indication to identify and intervene in patients with metabolic disturbances. The high proportion of new users without HbA_{1C} measurements at the treatment initiation indicates that this screening has been insufficient, as described before.[35-37] Moreover, it is unclear to what degree data from this study generalize to other countries and cultures, which is why these results should be tested in other samples.

Limitations

Some important limitations must be acknowledged. There is no obvious comparator with low-dose quetiapine. Other antipsychotic medications commonly used in low doses, such as olanzapine or risperidone, are also associated with metabolic disturbances,[38] and not used off-label to the same extent as quetiapine.[6,34] SSRIs are not an ideal comparator because of their association with weight gain[39] and metabolic disturbances.[32,40] However, these associations are likely to be inflated from population-based comparisons and not solely represent the potential obesogenic or diabetogenic effect of SSRIs.[31] A recent study[41] on type 2 diabetes risk in children and adolescents who initiated SSRIs compared with psychotherapy found only small increases in type 2 diabetes risk, which adds to the acceptability of SSRI as a useful and valid comparator in an adult population, as children and adolescents have a higher risk of drug-induced type 2 diabetes compared with adults.[10,42,43] Furthermore, we tested the use of Z-drugs as an alternative comparator but found it to be unfeasible because of increased type 2 diabetes risk results. Overall, using SSRIs as a comparator allowed us to investigate the risk of quetiapine in a population with nonsevere mental illness, and to some degree separate the association with type 2 diabetes risk from psychiatric disorder/lifestyle and that of the medication. Another limitation is the low number of HbA_{1C} measurements at baseline, which limits the value of this subgroup analysis and a cautious interpretation of these results are needed. Also, information on body mass index was not available in the data sources. Inpatient or outpatient diagnoses of obesity were included in the propensity score model to take this important risk factor into account. Finally, the overall median exposure and follow-up time was still modest and longer-term observations would have further increased the confidence in our findings.

Conclusions

The results of this cohort study suggest that there is not a significant excess risk of type 2 diabetes with use of low-dose quetiapine in comparison with SSRIs. As this study focused on low-dose quetiapine alone, future studies should focus on higher doses or concomitant use with other antipsychotics or antidepressants.

ARTICLE INFORMATION

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Correction: This article was corrected on June 15, 2021, to remove a redundant version of eFigure 1 in the Supplement.

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Author Contributions: Drs Højlund and Lund had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Højlund, Andersen, Correll, Hallas.

Acquisition, analysis, or interpretation of data: Højlund, Lund, Andersen, Correll.

Drafting of the manuscript: Højlund.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Højlund, Lund.

Obtained funding: Højlund, Andersen.

Administrative, technical, or material support: Andersen.

Supervision: Andersen, Correll, Hallas.

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REFERENCES

1. U.S. Food and Drug Administration. SEROQUEL XR® (quetiapine fumarate) extended-release tablets. Accessed March 23, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022047s043lbl.pdf

2. European Medicines Agency. Seroquel, Seroquel XR and associated names (quetiapine) - summary of product characteristics. Accessed March 23, 2020. https://www.ema.europa.eu/en/documents/referral/seroquel-seroquel-xr-associated-names-article-30-referral-annex-iii_en.pdf

3. Hálfdánarson Ó, Zoëga H, Aagaard L, et al. International trends in antipsychotic use: a study in 16 countries, 2005-2014. *Eur Neuropsychopharmacol*. 2017;27(10):1064-1076. doi:10.1016/j.euroneuro.2017.07.001

4. Pringsheim T, Gardner DM. Dispensed prescriptions for quetiapine and other second-generation antipsychotics in Canada from 2005 to 2012: a descriptive study. *CMAJ Open*. 2014;2(4):E225-E232. doi:10.9778/cmajo.20140009

5. Duncan D, Cooke L, Symonds C, Gardner D, Pringsheim T. Quetiapine use in adults in the community: a population-based study in Alberta, Canada. *BMJ Open*. 2016;6(3):e010861. doi:10.1136/bmjopen-2015-010861

6. Marston L, Nazareth I, Petersen I, Walters K, Osborn DPJ. Prescribing of antipsychotics in UK primary care: a cohort study. *BMJ Open*. 2014;4(12):e006135. doi:10.1136/bmjopen-2014-006135

7. Gjerden P, Bramness JG, Tvete IF, Slørdal L. The antipsychotic agent quetiapine is increasingly not used as such: dispensed prescriptions in Norway 2004-2015. *Eur J Clin Pharmacol*. 2017;73(9):1173-1179. doi:10.1007/s00228-017-2281-8

8. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol*. 2011;8(2):114-126. doi:10.1038/nrendo.2011.156

9. Holt RIG. Association Between Antipsychotic Medication Use and Diabetes. *Curr Diab Rep*. 2019;19(10):96. doi:10.1007/s11892-019-1220-8

10. Bobo WV, Cooper WO, Stein CM, et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. *JAMA Psychiatry*. 2013;70(10):1067-1075. doi:10.1001/jamapsychiatry.2013.2053

11. Correll CU, Joffe BI, Rosen LM, Sullivan TB, Joffe RT. Cardiovascular and cerebrovascular risk factors and events associated with second-generation antipsychotic compared to antidepressant use in a non-elderly adult sample: results from a claims-based inception cohort study. *World Psychiatry*. 2015;14(1):56-63. doi:10.1002/wps.20187

12. Ulcickas Yood M, Delorenze GN, Quesenberry CP Jr, et al. Association between second-generation antipsychotics and newly diagnosed treated diabetes mellitus: does the effect differ by dose? *BMC Psychiatry*. 2011;11(1):197. doi:10.1186/1471-244X-11-197

13. Carr CN, Lopchuk S, Beckman ME, Baugh TB. Evaluation of the use of low-dose quetiapine and the risk of metabolic consequences: A retrospective review. *Ment Health Clin*. 2016;6(6):308-313. doi:10.9740/mhc.2016.11.308

14. Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics. *Eur Psychiatry*. 2010;25(suppl 2):S12-S21. doi:10.1016/S0924-9338(10)71701-6

15. Montastruc F, Palmaro A, Bagheri H, Schmitt L, Montastruc J-L, Lapeyre-Mestre M. Role of serotonin 5-HT2C and histamine H1 receptors in antipsychotic-induced diabetes: a pharmacoepidemiological-pharmacodynamic study in VigiBase. *Eur Neuropsychopharmacol*. 2015;25(10):1556-1565. doi:10.1016/j.euroneuro.2015.07.010

16. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application.* 4th ed. Cambridge University Press; 2013.

17. Langan SM, Schmidt SA, Wing K, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). *BMJ*. 2018;363:k3532. doi:10.1136/bmj.k3532

18. Holt RIG, Mitchell AJ. Diabetes mellitus and severe mental illness: mechanisms and clinical implications. *Nat Rev Endocrinol*. 2015;11(2):79-89. doi:10.1038/nrendo.2014.203

19. Pouwer F, Kupper N, Adriaanse MC. Does emotional stress cause type 2 diabetes mellitus? a review from the European Depression in Diabetes (EDID) Research Consortium. *Discov Med*. 2010;9(45):112-8.

20. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World Psychiatry*. 2015;14(2):119-136. doi:10.1002/wps.20204

21. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7)(suppl):38-41. doi:10.1177/1403494810394717

22. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39(7)(suppl):30-33. doi:10.1177/1403494811401482

23. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7)(suppl):22-25. doi:10.1177/1403494810387965

24. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563-591. doi:10.2147/CLEP.S179083

25. The Danish Health Data Authority. Medstat.dk (Register of Medicinal Product Statistics). Accessed February 19, 2020. https://medstat.dk/en

26. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology*. 2009;20(4):512-522. doi:10.1097/EDE.0b013e3181a663cc

27. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083-3107. doi:10.1002/sim.3697

28. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol*. 2008;167(4):492-499. doi:10.1093/aje/kwm324

29. Flachs E, Eriksen L, Koch M, et al *Sygdomsbyrden i Danmark - Sygdomme* [Burden of Disease in Denmark]. Danish Health Authority; 2015.

30. Campayo A, Gómez-Biel CH, Lobo A. Diabetes and depression. *Curr Psychiatry Rep*. 2011;13(1):26-30. doi:10.1007/s11920-010-0165-z

31. Barnard K, Peveler RC, Holt RIG. Antidepressant medication as a risk factor for type 2 diabetes and impaired glucose regulation: systematic review. *Diabetes Care*. 2013;36(10):3337-3345. doi:10.2337/dc13-0560

32. Salvi V, Grua I, Cerveri G, Mencacci C, Barone-Adesi F. The risk of new-onset diabetes in antidepressant users - a systematic review and meta-analysis. *PLoS One*. 2017;12(7):e0182088. doi:10.1371/journal.pone.0182088

33. Manu P, Correll CU, van Winkel R, Wampers M, De Hert M. Prediabetes in patients treated with antipsychotic drugs. *J Clin Psychiatry*. 2012;73(4):460-466. doi:10.4088/JCP.10m06822

34. Højlund M, Pottegård A, Johnsen E, et al. Trends in utilization and dosing of antipsychotic drugs in Scandinavia: comparison of 2006 and 2016. *Br J Clin Pharmacol*. 2019;85(7):1598-1606. doi:10.1111/bcp.13945

35. Ndukwe HC, Nishtala PS. Glucose monitoring in new users of second-generation antipsychotics in older people. *Arch Gerontol Geriatr*. 2017;70:136-140. doi:10.1016/j.archger.2017.01.006

36. Hinds A, Coulter L, Hudson J, Seaton V. Screening for diabetes in patients receiving second-generation atypical antipsychotics. *Am J Health Syst Pharm*. 2015;72(17)(suppl 2):S70-S73. doi:10.2146/ajhp150150

37. Connolly JG, Toomey TJ, Schneeweiss MC. Metabolic monitoring for youths initiating use of second-generation antipsychotics, 2003-2011. *Psychiatr Serv*. 2015;66(6):604-609. doi:10.1176/appi.ps.201400222

38. Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2020;7(1):64-77. doi:10.1016/S2215-0366(19)30416-X

39. Gafoor R, Booth HP, Gulliford MC. Antidepressant utilisation and incidence of weight gain during 10 years' follow-up: population based cohort study. *BMJ*. 2018;361:k1951. doi:10.1136/bmj.k1951

40. Yao S, Li J, Fan X, Liu Q, Lian J. The effect of selective serotonin re-uptake inhibitors on risk of type II diabetes mellitus and acute pancreatitis: a meta-analysis. *Biosci Rep*. 2018;38(5):BSR20180967. doi:10.1042/BSR20180967

41. Sun JW, Hernández-Díaz S, Haneuse S, et al. Association of selective serotonin reuptake inhibitors with the risk of type 2 diabetes in children and adolescents. *JAMA Psychiatry*. 2021;78(1):91-100. doi:10.1001/jamapsychiatry.2020.2762

42. Galling B, Roldán A, Nielsen RE, et al. Type 2 Diabetes Mellitus in Youth Exposed to Antipsychotics: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2016;73(3):247-259. doi:10.1001/jamapsychiatry.2015.2923

43. Rubin DM, Kreider AR, Matone M, et al. Risk for incident diabetes mellitus following initiation of second-generation antipsychotics among Medicaid-enrolled youths. *JAMA Pediatr*. 2015;169(4):e150285-e150285. doi:10.1001/jamapediatrics.2015.0285

SUPPLEMENT.

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Supplemental Online Content

Højlund M, Lund LC, Andersen K, Correll CU, Hallas J. Association of low-dose quetiapine and diabetes. *JAMA Netw Open.* 2021;4(5):e213209. doi:10.1001/jamanetworkopen.2021.3209

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods: Description of case-control, sensitivity, and supplementary analyses

Case-control analysis

The case-control analysis aimed to investigate the association between cumulative doses of quetiapine, used as low-dose treatment, and type 2 diabetes mellitus (T2DM). The case-control analysis was nested among low-dose quetiapine users and, thus, did not include a comparator group. Each T2DM case was matched on age and sex with ten controls, using risk set sampling. The observation period for each low-dose quetiapine user was similar to the follow-up period used in ITT-analyses, i.e., follow-up was confined to use of low-dose quetiapine alone and did not include time with use of SSRIs, other antipsychotics, or higher strengths of quetiapine tablets than equivalents of 25 mg or 50 mg per day.

We calculated odds ratios (ORs) for the association between cumulative quetiapine dose and T2DM, using conditional logistic regression in two ways:

1) Using cumulative quetiapine doses transformed by the binary logarithm as the independent variable. In this analysis, the OR represents the increase in risk for each doubling of the cumulative dose (pre-planned analysis).
2) Using predefined strata of cumulative dose (6.26-12.5/12.51-25/25.01-50/100.01-200/>200 DDD) as the independent variable.

Use of ≤6.25 DDD was used as reference in both approaches, as this amount is equivalent to 100 tablets of 25mg quetiapine – the smallest package marketed in Denmark.

Sensitivity analyses

To test the impact of analytical choices on the observed association between use of low-dose quetiapine and T2DM, we conducted the following six sensitivity analyses (reported in eFigures 3-4 and eTables 8-9):

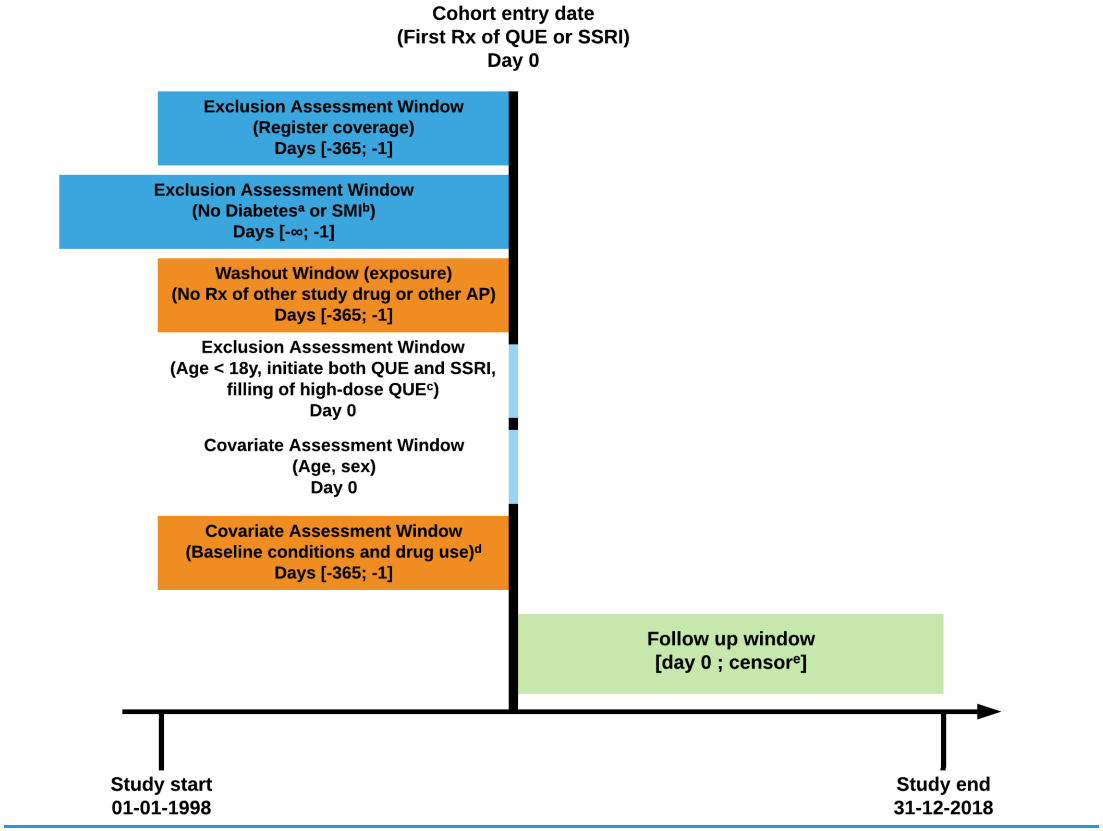
1) The grace period was varied from 90 to 60 and 120 days in as-treated analyses to test the impact of grace period definition on incidence rate estimates.
2) The washout window was extended from one to five years (applying to prior use of quetiapine, SSRIs, or other antipsychotics), to assess the impact of previous use of these drugs on T2DM risk.
3) The maximum follow-up period was extended from five to 10 years, to assess if a potential long-term risk existed beyond our initial follow-up window.
4) Exclusion of individuals with history of recurrent depression from cohort entry, to assess the impact of long-term depression on T2DM risk.
5) Using inverse probability of censoring weights (IPCW) in the main analysis, to explore the magnitude of selection bias due to potential informative censoring (e.g., using higher doses quetiapine or being diagnosed with a severe mental illness). To construct ICPWs, time was partitioned into 90-day periods, and the probability of being uncensored at the beginning of each period was estimated using logistic regression analysis. The regression model included treatment status, calendar time, and all covariates from the hdPS-model (as measured at baseline). Stabilized ICPWs were then calculated as the cumulative probability of remaining uncensored, conditional on treatment status and calendar time, divided by the cumulative probability of remaining uncensored on treatment status, calendar time and baseline covariates (in the hdPS-model). We then obtained IPCW-weighted hazard ratios using pooled logistic regression analyses.
6) Using standardized mortality ratio weights (SMRW) in a Cox proportional hazards regression model as an alternative to propensity score (PS) matching. Users of low-dose quetiapine were given a weight of 1, and SSRI-users were weighted according to their PS with a weight equal to PS/(1-PS).

Supplementary analyses

To test the impact of different exposures or comparator, and to test assay sensitivity, we conducted the following four supplementary analyses:

1) Extending the exposure definition to include 100 mg quetiapine tablets. This alternative exposure definition was tested in both AT- and ITT-analyses as well as the case-control analysis of the association with cumulative dose (eFigure 3 and eTable 7).
2) Extending the exposure definition to include all strengths of quetiapine tablets. This alternative exposure definition was tested in both AT- and ITT-analyses as well as the case-control analysis of the association with cumulative dose (eFigure 3 and eTable 7).
3) Using Z-drugs as active comparator to assess the appropriateness of choosing SSRIs as the comparator in the main analyses (eFigure 5).
4) Using olanzapine as alternative exposure to test assay sensitivity of the main analyses (eFigure 6).

eFigure 1: Graphical representation of baseline assessment and follow-up



Notes: a) History of diabetes was assessed as prescriptions for antidiabetic medications, hospital diagnoses of diabetes, or blood levels of glycosylated hemoglobin above reference values, b) History of severe mental illness was defined hospital diagnoses of schizophrenia, schizoaffective disorder, or bipolar affective disorder, c) High-dose quetiapine was defined as filling of prescriptions with tablet strengths >50mg, d) Baseline covariates for the propensity score model included prescriptions and hospital diagnoses from the prior 365 days, e) Follow-up ended at the earliest of diabetes, death, emigration, end of study, five years of follow-up, or censoring for meeting baseline exclusion criteria (i.e. diagnosis of SMI, use of high-dose QUE, use of other study drug, use of other AP, or new diagnosis of type 1 diabetes mellitus).
Abbreviations: AP: Antipsychotic, Rx: Prescription, SMI: Serious Mental Illness, SSRI: Selective Serotonin Reuptake-inhibitor, QUE: Quetiapine.

eTable 1: ICD and ATC codes for exposure and outcome variables

Study drugs	
Quetiapine	ATC: N05AH04
SSRIs	ATC: N06AB
Outcome	
Diabetes (T2DM)	ATC: A10 ICD-10: E10-14[a], G590, G632, G990, H280, H360, M142, N083, O240-243. HbA1c ≥ 6.4% or ≥ 48mmol/mol
Exclusion criteria	
Severe mental illness	ICD-10: F20, 25, 30-31
Other antipsychotics	ATC: N05A (excl. N05AH04 and N05AN01)
History of diabetes	Defined as above
Comorbidities	
Hypertension	ICD-10: I10-13,15 ATC: C02, C08-09
COPD	ICD-10: J40-44 ATC: R03
Heart failure	ICD-10: I098-99, I110, I130, I132, I255, I420, I425-29, I43, I50
Obesity	ICD-10: E65-66
Alcohol-related disorders	ICD-10: I426, F10, K292, K70, K852, K860, T51, Y911-913, Z502, Z721 ATC: N07BB
Major depression	ICD-10: F32-33
Recurrent depression	ICD-10: F33
Other medications	
Digoxin	ATC: C01AA
Thiazide diuretics	ATC: C03A
Beta-blockers	ATC: C07
Statins	ATC: C10
Oral glucocorticoids	ATC: H02AB
Other antipsychotics	ATC: N05A (excl. N05AH04 and N05AN01)
Mirtazapine	ATC: N06AX11
Antihistamines	ATC: R06A
Hemoglobin A1c (HbA1c)	
Prediabetes (covariate)	HbA1c: 5.7-6.3% or 39-47 mmol/mol

a) Individuals with new diagnosis type 1 diabetes mellitus (T1DM) during follow-up were censored and were not classified as having the outcome of interest - if they had solely E10-diagnoses and prescriptions for insulin in registers, as this was considered incident T1DM. Occurrences of both E10 and other E1x-diagnoses or use of other antidiabetic medications than insulin was classified as T2DM due to the potential low validity of the T1DM-diagnosis. ATC: World Health Organization Anatomical Therapeutic Chemical classification, HbA1c: Glycosylated Hemoglobin A1c, ICD-10: World Health Organization International Classification of diseases, 10th revision.

eTable 2: Covariates included in high-dimensional propensity score model

The 50 most common prescriptions and hospital diagnoses among the included low-dose quetiapine or SSRI-users within 12 months before cohort entry. Use of drugs or occurrence of hospital diagnoses are divided into three groups: At least one occurrence, sporadic use (i.e., more than the median number of prescriptions/hospital contacts in the cohort), and frequent use (i.e., more than the 75th percentile of prescriptions/hospital contacts in the cohort).

ATC-group or ICD-10 diagnosis	Frequency	Low-dose Quetiapine, N (%)	SSRI, N (%)	RR (cd)	RR (ce)	Multiplica-tive bias
Statins (C10AA)	One or more	5852 (10)	68270 (8)	2.37	0.73	1.025
Other special examinations and investigations (Z01, outpatient)	One or more	16242 (28)	158853 (19)	1.25	1.13	1.022
Proton pump inhibitors (A02BC)	One or more	11224 (19)	119379 (14)	1.43	1.11	1.021
Proton pump inhibitors (A02BC)	Median or more	5474 (9)	53234 (6)	1.52	1.23	1.016
Obesity (E66, outpatient)	One or more	442 (1)	3403 (0)	4.51	1.35	1.012
Other antiepileptics (N03AX)	One or more	5637 (10)	16697 (2)	1.15	3.02	1.012
Other opioids (N02AX)	One or more	8092 (14)	87408 (10)	1.33	1.42	1.012
NSAIDs (M01AE)	One or more	11797 (20)	142569 (17)	1.36	1.14	1.012
Paracetamol (N02BE)	One or more	15885 (28)	133001 (16)	1.09	1.30	1.011
Statins (C10AA)	Median or more	2278 (4)	25816 (3)	2.21	0.86	1.010
Inhaled adrenergics with corticosteroids (R03AK)	One or more	2364 (4)	23276 (3)	1.63	1.01	1.008
Non-selective monoamine reuptake inhibitors (N06AA)	One or more	3271 (6)	21024 (3)	1.26	3.28	1.008
Sleep disorders (G47, outpatient)	One or more	423 (1)	2258 (0)	2.62	1.32	1.007
Other opioids (N02AX)	Median or more	3686 (6)	34916 (4)	1.31	1.64	1.007
Medical observation (Z03, outpatient)	One or more	6459 (11)	64957 (8)	1.20	1.02	1.007
Non-selective monoamine reuptake inhibitors (N06AA)	Median or more	1959 (3)	9875 (1)	1.30	4.87	1.007
Penicillin with beta-lactamase inhibitor (J01CR)	One or more	1778 (3)	9435 (1)	1.34	1.03	1.007
Other antidepressants (N06AX)	Third quartile or more	7536 (13)	10053 (1)	1.05	13.76	1.006
Proton pump inhibitors (A02BC)	Third quartile or more	2690 (5)	28312 (3)	1.50	1.40	1.006
Other antiepileptics (N03AX)	Median or more	2887 (5)	7467 (1)	1.15	3.49	1.006
Medical observation (Z03, inpatient)	One or more	6829 (12)	64946 (8)	1.14	1.42	1.006
Drugs used in erectile dysfunction (G04BE)	One or more	1452 (3)	10703 (1)	1.45	1.20	1.006
Obesity (E66, inpatient)	One or more	325 (1)	3295 (0)	4.00	1.25	1.005
Other opioids (N02AX)	Third quartile or more	2414 (4)	21397 (3)	1.29	1.75	1.005
Beta-lactamase resistant penicillins (J01CF)	One or more	2930 (5)	29595 (4)	1.29	1.25	1.004
NSAIDs (M01AE)	Third quartile or more	2591 (4)	30257 (4)	1.52	1.27	1.004

(eTable 2 continued on next page)

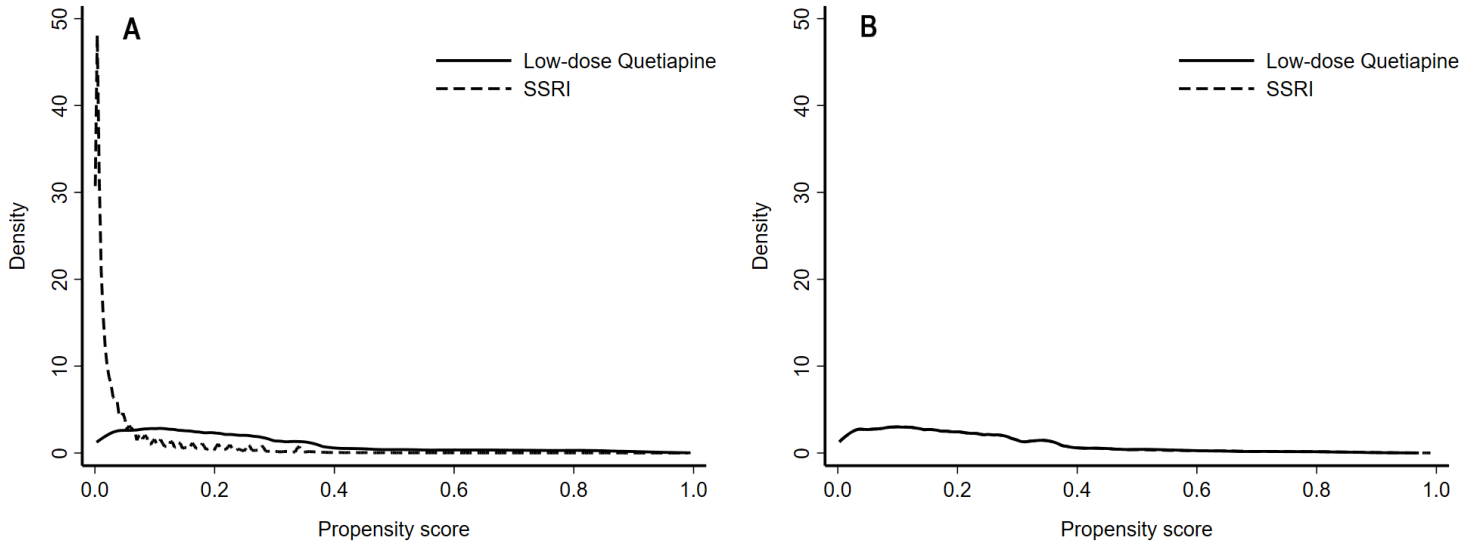
eTable 2: Covariates included in high-dimensional propensity score model (continued)

ATC-group or ICD-10 diagnosis	Frequency	Low-dose Quetiapine, N (%)	SSRI, N (%)	RR (cd)	RR (ce)	Multiplica-tive bias
Other examinations and investigations (Z01, outpatient)	Third quartile or more	2307 (4)	20821 (2)	1.28	1.11	1.004
Non-selective monoamine reuptake inhibitors (N06AA)	Third quartile or more	1096 (2)	4405 (1)	1.27	6.50	1.004
Angiotensin II antagonists (C09CA)	One or more	2252 (4)	28962 (3)	1.81	0.75	1.004
ACE inhibitors and diuretics (C09BA)	One or more	917 (2)	10962 (1)	2.20	0.81	1.003
Dihydropyridine derivatives (C08CA)	One or more	4256 (7)	58068 (7)	1.78	0.79	1.003
Persons encountering health services (Z71, outpatient)	One or more	652 (1)	5250 (1)	1.65	1.15	1.003
Paracetamol (N02BE)	Median or more	7111 (12)	61083 (7)	1.06	1.38	1.003
Other antidepressants (N06AX)	Median or more	11224 (19)	19674 (2)	1.02	9.65	1.003
Natural opium alkaloids (N02AA)	One or more	3757 (7)	32659 (4)	1.11	1.28	1.003
Drugs used in opioid dependence (N07BC)	One or more	775 (1)	2875 (0)	1.30	4.10	1.003
Other antiepileptics (N03AX)	Third quartile or more	1558 (3)	3862 (0)	1.13	3.77	1.003
Benzodiazepine related drugs (N05CF)	Third quartile or more	2849 (5)	24687 (3)	1.14	2.44	1.003
Angiotensin II antagonists and diuretics (C09DA)	One or more	1251 (2)	15834 (2)	2.03	0.77	1.003
Inhaled adrenergics with corticosteroids (R03AK)	Median or more	995 (2)	10246 (1)	1.56	0.93	1.003
Statins (C10AA)	Third quartile or more	792 (1)	9247 (1)	2.04	1.09	1.003
Natural opium alkaloids (N02AA)	Third quartile or more	1062 (2)	7728 (1)	1.30	1.71	1.003
Beta blocking agents, selective (C07AB)	Median or more	2139 (4)	28583 (3)	1.88	0.90	1.003
Benzodiazepine related drugs (N05CF)	Median or more	4747 (8)	46010 (5)	1.09	2.20	1.003
Beta blocking agents, selective (C07AB)	Third quartile or more	1182 (2)	14452 (2)	1.72	0.96	1.002
Imidazole and triazole derivatives (D01AC)	One or more	3944 (7)	49061 (6)	1.23	1.12	1.002
Hormonal contraceptives (G03AB)	One or more	223 (0)	8766 (1)	0.69	0.89	1.002
Use of tobacco (F17, inpatient)	One or more	213 (0)	1271 (0)	1.91	1.58	1.002
Muscle relaxants (M03BB)	One or more	1184 (2)	12217 (1)	1.33	1.16	1.002
Anticholinergics (R03BB)	One or more	1137 (2)	12992 (2)	1.46	0.88	1.002

ATC: Anatomical Therapeutic Chemical Classification, ICD-10: World Health Organization International Classification of diseases, 10th revision, RR(cd): Association between confounder and outcome as relative risk, RR(ce): Association between confounder and exposure as relative risk, SSRI: Selective Serotonin Reuptake-inhibitors.

eFigure 2: Propensity score distribution before and after matching

A: Before propensity score matching, B: After propensity score matching (without trimming).



eTable 3: Characteristics of unmatched individuals

	Individuals not included in the hdPS-matched cohort		
	Low-dose Quetiapine	**SSRI**	**SMD**
All	3,085	783,968	.
Sex, N (%)			.
Female	1,758 (57.0)	482,786 (61.6)	0.09
Age, N (%)			.
Median (IQR)	47 (36-60)	47 (33-67)	<0.01
18-64 years	2,451 (79.4)	571,011 (72.8)	0.16
65-79 years	400 (13.0)	127,140 (16.2)	0.09
80+ years	234 (7.6)	85,817 (10.9)	0.12
Year of cohort entry, N (%)			.
1998-2002	0	227,759 (29.1)	0.90
2003-2007	6 (0.2)	245,651 (31.3)	0.95
2008-2012	198 (6.4)	207,102 (26.4)	0.56
2013-2017	2,135 (69.2)	89,531 (11.4)	1.46
Comorbidities, N (%)			.
Hypertension	736 (23.9)	151,562 (19.3)	0.11
COPD	516 (16.7)	93,853 (12.0)	0.14
Heart failure	69 (2.2)	20,972 (2.7)	0.03
Obesity	307 (10.0)	21,878 (2.8)	0.30
Alcohol-related disorders	836 (27.1)	106,441 (13.6)	0.34
Major depression	1,467 (47.6)	41,996 (5.4)	1.09
Recurrent depression	941 (30.5)	10,342 (1.3)	0.87
Drugs used in the past year, N (%)			.
Digoxin	36 (1.2)	21,271 (2.7)	0.11
Thiazide diuretics	226 (7.3)	77,530 (9.9)	0.09
Beta-blockers	402 (13.0)	86,500 (11.0)	0.06
Statins	396 (12.8)	69,573 (8.9)	0.13
Oral glucocorticoids	270 (8.8)	54,261 (6.9)	0.07
Mirtazapine	1,251 (40.6)	36,097 (4.6)	0.95
Antihistamines	488 (15.8)	55,787 (7.1)	0.28
Hemoglobin A1c at baseline			.
Normal	554 (18.0)	20,565 (2.6)	0.52
Prediabetes	217 (7.0)	7,119 (0.9)	0.32
Missing	2,314 (75.0)	756,284 (96.5)	0.64

COPD: Chronic obstructive pulmonary disease, hdPS: High-dimensional propensity score, IQR: Interquartile range, SMD: Standardized mean difference, SSRI: selective serotonin reuptake inhibitor.

eTable 4: Characteristics of follow-up in full and hdPS-matched cohort

	Full cohort		hdPS-matched cohort	
	Low-dose Quetiapine	**SSRI**	**Low-dose Quetiapine**	**SSRI**
	N = 57,701	N = 838,584	N = 54,616	N = 54,616
As-treated analysis				
Median follow-up, years (IQR)	0.5 (0.3-0.8)	0.7 (0.4-1.5)	0.5 (0.3-0.7)	0.6 (0.4-1.3)
Number of prescriptions, N (%)				
Median (IQR)	1.0 (1.0-3.0)	3.0 (1.0-8.0)	1.0 (1.0-3.0)	3.0 (1.0-6.0)
Range	1-240	1-259	1-240	1-259
1 prescription	31,147 (54)	244,649 (29)	29,791 (55)	18,570 (34)
2-4 prescriptions	15,176 (26)	249,805 (30)	14,244 (26)	17,941 (33)
5-9 prescriptions	5,308 (9)	158,321 (19)	4,937 (9)	9,682 (18)
10+ prescriptions	6,070 (11)	185,809 (22)	5,644 (10)	8,423 (15)
Average daily dose, DDD/day				
Median (IQR)	0.04 (0.03-0.07)	0.62 (0.38-0.94)	0.04 (0.03-0.07)	0.67 (0.52-1.03)
<0.25, N (%)	57,001 (99)	120,522 (14)	53,976 (99)	3,447 (6)
0.25-0.49, N (%)	671 (1)	171,168 (20)	616 (1)	9,671 (18)
0.50-0.99, N (%)	27 (0)	369,823 (44)	22 (0)	27,156 (50)
1.00+, N (%)	(n<5)	176,130 (21)	(n<5)	14,283 (26)
Intention-to-treat analysis				
Median follow-up, years (IQR)	1.3 (0.3-3.3)	5.0 (2.4-5.0)	1.3 (0.3-3.4)	2.3 (0.8-4.8)

Abbreviations: DDD: WHO Defined Daily Dose, hdPS: High-dimensional propensity score, IQR: Interquartile range, N: Number, SSRI: Selective serotonin reuptake-inhibitor.

eTable 5: Reasons for censoring in full and hdPS-matched cohort

	Full cohort		hdPS-matched cohort	
	Low-dose Quetiapine	**SSRI**	**Low-dose Quetiapine**	**SSRI**
	N = 57,701	N = 838,584	N = 54,616	N = 54,616
As-treated analysis				
Death	3,422 (6)	59,603 (7)	3,302 (6)	3,511 (6)
Emigration	112 (0)	3,508 (0)	107 (0)	241 (0)
New diagnosis of T1DM	(n<5)	69 (0)	(n<5)	(n<5)
New diagnosis of SMI	752 (1)	3,119 (0)	703 (1)	233 (0)
Use of high-dose quetiapine	4,373 (8)	1,135 (0)	4,015 (7)	148 (0)
Switching to other study drug	6,540 (11)	12,625 (2)	6,322 (12)	2,261 (4)
Prescription of another AP	4,653 (8)	40,370 (5)	4,399 (8)	2,336 (4)
End of follow-up	860 (1)	50,165 (6)	831 (2)	1,371 (3)
End of study (31dec2018)	7,080 (12)	31,861 (4)	6,333 (12)	10,745 (20)
End of first treatment episode	29,484 (51)	627,736 (75)	28,207 (52)	33,217 (61)
Intention-to-treat analysis				
Death	4,906 (9)	98,489 (12)	4,745 (9)	5,064 (9)
Emigration	420 (1)	12,780 (2)	406 (1)	741 (1)
New diagnosis of T1DM	7 (0)	170 (0)	7 (0)	9 (0)
New diagnosis of SMI	1,082 (2)	6,536 (1)	1,013 (2)	413 (1)
Use of high-dose quetiapine	4,898 (8)	2,442 (0)	4,515 (8)	257 (0)
Switching to other study drug	9,863 (17)	24,615 (3)	9,568 (18)	3,564 (7)
Prescription of another AP	6,764 (12)	78,364 (9)	6,418 (12)	3,707 (7)
End of follow-up	7,293 (13)	502,546 (60)	7,154 (13)	13,064 (24)
End of study (31dec2018)	21,573 (37)	89,924 (11)	19,953 (37)	26,574 (49)

Abbreviations: AP: Antipsychotic drug, hdPS: High-dimensional propensity score, T1DM: Type 1 Diabetes mellitus, SMI: Severe mental illness (i.e., schizophrenia, schizoaffective disorder, and bipolar disorder), SSRI: Selective serotonin reuptake-inhibitor.

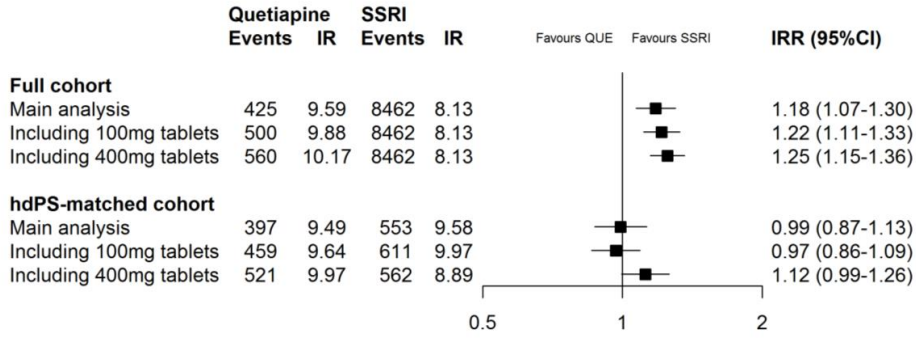
eTable 6: Outcome distribution for full and hdPS-matched cohort

	Full cohort		hdPS-matched cohort	
	Low-dose Quetiapine	**SSRI**	**Low-dose Quetiapine**	**SSRI**
	N = 57,701	N = 838,584	N = 54,616	N = 54,616
As-treated analysis				
Incident T2DM	425	8,462	397	553
New diagnosis of DM	84 (20)	2,743 (32)	82 (21)	109 (20)
First prescription of antidiabetic medication	134 (32)	4,347 (51)	125 (31)	191 (35)
First measurement of elevated HbA1c	207 (49)	1,372 (16)	190 (48)	253 (46)
Intention-to-treat analysis				
Incident T2DM	895	22,718	837	1,223
New diagnosis of DM	147 (16)	6,503 (29)	144 (17)	207 (17)
First prescription of antidiabetic medication	316 (35)	12,345 (54)	296 (35)	476 (39)
First measurement of elevated HbA1c	432 (48)	3,870 (17)	397 (47)	540 (44)

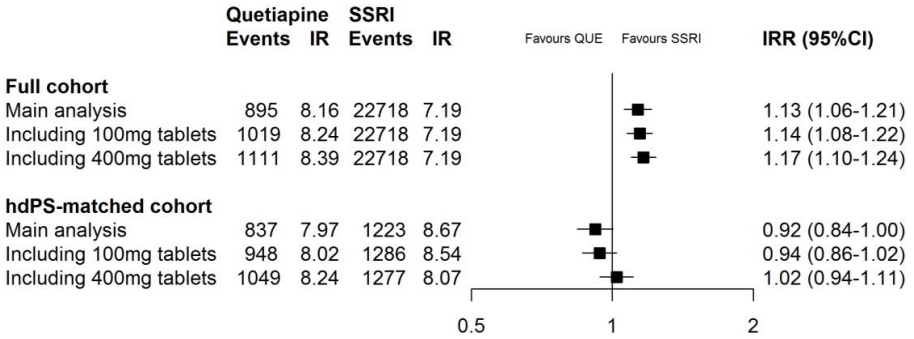
Abbreviations: DM: Diabetes mellitus, HbA1c: Glycosylated hemoglobin A1c, hdPS: High-dimensional propensity score, SSRI: Selective serotonin reuptake-inhibitor, T2DM: Type 2 diabetes mellitus.

eFigure 3: Supplementary analysis including higher tablet strengths in the exposure definition for quetiapine

eFigure 3-1: Including higher tablet strengths in as-treated analyses



eFigure 3-2: Including higher tablet strengths in the intention-to-treat analyses



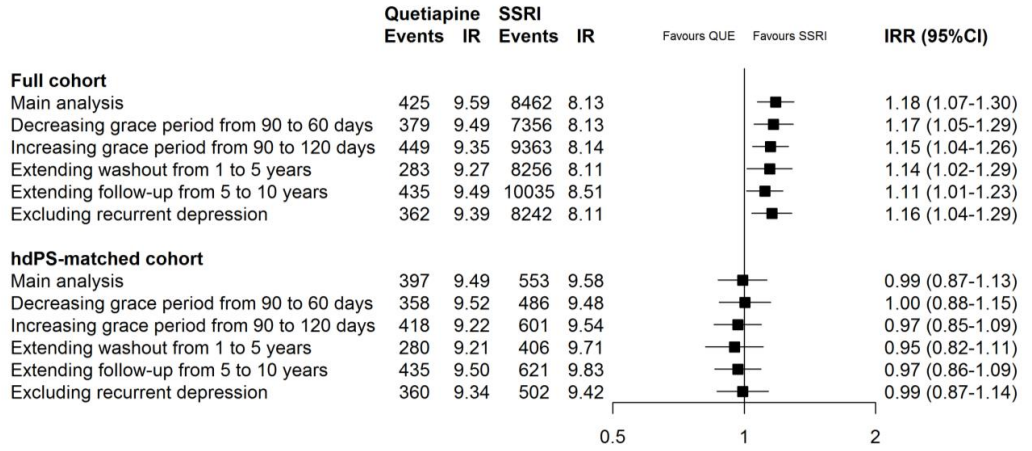
eTable 7: Case-control analysis with different exposure definitions

	Main analysis (25-50mg tablets)			Including 25-100mg tablets[a]			Including 25-400mg tablets[a]		
Exposure	**Cases, No**	**Controls, No**	**Odds ratio (95%CI)**	**Cases, No**	**Controls, No**	**Odds ratio (95%CI)**	**Cases, No**	**Controls, No**	**Odds ratio (95%CI)**
Doubling of dose	895	8831	1.02 (0.95 to 1.09)	1019	10082	1.07 (1.01 to 1.12)	1111	11009	1.08 (1.03 to 1.13)
Cumulative dose, DDD	.	.		.	.		.	.	
0-6.25	381	3796	1.00 (reference)	380	3925	1.00 (reference)	380	4009	1.00 (reference)
6.26-12.5	138	1380	0.99 (0.80 to 1.23)	146	1525	0.92 (0.74 to 1.13)	150	1527	1.00 (0.81 to 1.23)
12.51-25	114	1134	1.02 (0.81 to 1.29)	127	1325	0.99 (0.79 to 1.23)	129	1391	0.97 (0.78 to 1.22)
25.01-50	109	1063	1.02 (0.80 to 1.29)	126	1224	0.99 (0.79 to 1.23)	133	1313	1.04 (0.83 to 1.30)
50.01-100	81	798	0.95 (0.73 to 1.25)	105	981	1.00 (0.79 to 1.28)	116	1168	1.07 (0.85 to 1.36)
100.01-200	46	445	1.09 (0.77 to 1.55)	73	669	1.04 (0.78 to 1.38)	90	837	1.05 (0.80 to 1.36)
>200	26	215	1.28 (0.80 to 2.05)	62	433	1.53 (1.10 to 2.11)	113	764	1.44 (1.13 to 1.84)

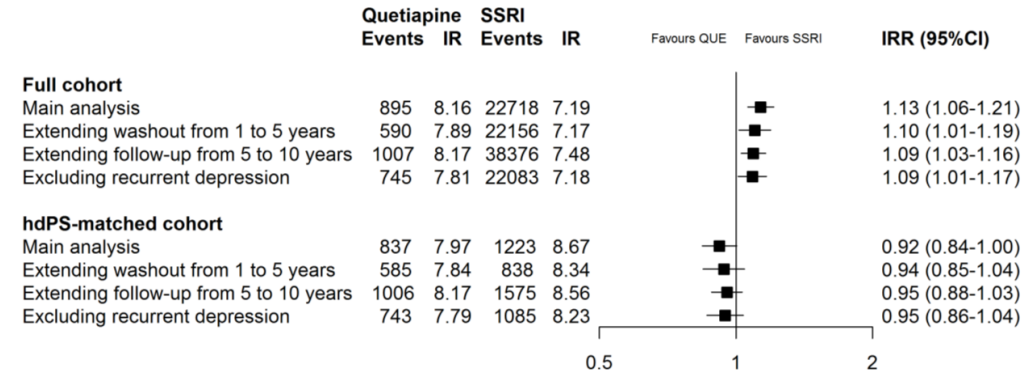
Notes: a) Including quetiapine tablets up to 100/400mg, but excluding individuals with severe mental disorders as in the main analysis, Abbreviations: CI: confidence interval, DDD: daily defined dose

eFigure 4: Sensitivity analysis varying grace period, washout period, maximum follow-up, and exclusion criteria

eFigure 4-1: Varying analytical choices in as-treated analyses



eFigure 4-2: Varying analytical choices in intention-to-treat analyses



eTable 8: Supplementary analysis using inverse probability of censoring weights

	Full cohort		hdPS-matched cohort	
	Without IPCW	**With IPCW**	**Without IPCW**	**With IPCW**
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
As-treated analysis	1.22 (1.10-1.34)	1.18 (1.07-1.31)	1.00 (0.88-1.14)	0.98 (0.85-1.12)
Intention-to-treat analysis	1.20 (1.12-1.28)	1.27 (1.17-1.36)	0.94 (0.86-1.03)	0.92 (0.84-1.01)

Abbreviations: CI: Confidence interval, hdPS: High-dimensional propensity score, HR: Hazard ratio, IPCW: Inverse probability of censoring weights.

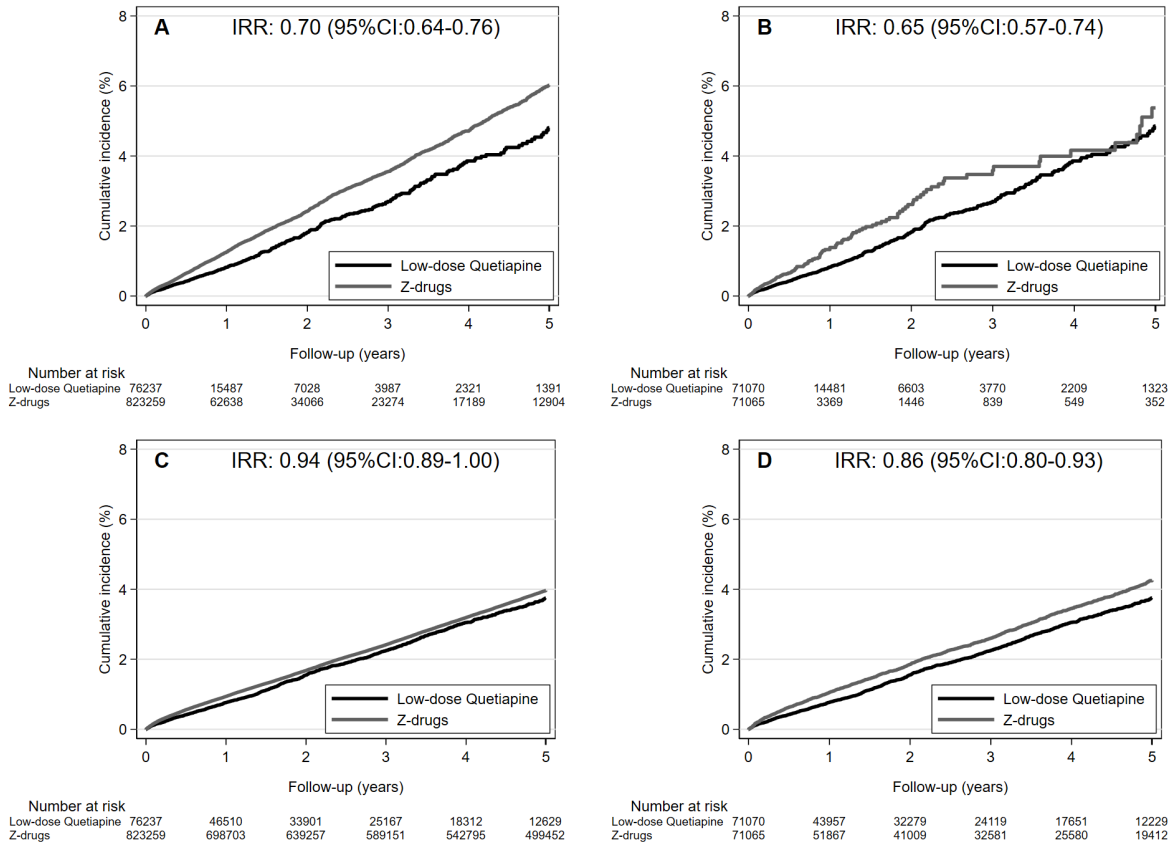
eTable 9: Supplementary analysis using standardized mortality ratio-weights

	Full cohort	
	Without SMRW	**With SMRW**
	HR (95%CI)	HR (95%CI)
As-treated analysis	1.21 (1.10-1.34)	0.98 (0.86-1.11)
Intention-to-treat analysis	1.14 (1.06-1.22)	0.94 (0.87-1.03)

Abbreviations: CI: Confidence interval, HR: Hazard ratio, SMRW: Standardized mortality ratio weights.

eFigure 5: Supplementary analysis using Z-drugs as comparator

A: On-treatment analysis on full cohort. B: On-treatment analysis on matched cohort. C: Intention-to-treat analysis on full cohort. D: Intention-to-treat analysis on matched cohort. Exposure was benzodiazepine-related drugs (Z-drugs, ATC: N05CF, any tablet strength) and SSRIs. All other inclusion, exclusion, and censoring criteria were identical to the main analysis.



eFigure 6: Control analysis using olanzapine as exposure

A: On-treatment analysis on full cohort. B: On-treatment analysis on matched cohort. C: Intention-to-treat analysis on full cohort. D: Intention-to-treat analysis on matched cohort. Exposure was olanzapine (N05AH03, any tablet strength) and SSRIs. All other inclusion, exclusion, and censoring criteria were identical to the main analysis.