STUDY PROTOCOL

Use of Low-dose Quetiapine and the Risk of Major Adverse Cardiovascular Events

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BREIF INTRODUCTION

Quetiapine is a second-generation antipsychotic labeled for the treatment of schizophrenia, bipolar disorder, and as adjunctive treatment in major depression. However, it is frequently used off-label in low-doses for its anxiolytic-hypnotic properties. Quetiapine has been associated with both metabolic disturbances and cardiac arrhythmias, when used in high doses for the treatment of severe mental illness (1,2), but it is not known whether the use of quetiapine in low doses is associated with an increased risk of major adverse cardiovascular events (MACE).

Aim

To investigate the association between the use of low-dose quetiapine and major cardiovascular adverse events.

METHODS

Study design

We will conduct a new-user, active-comparator cohort study to assess the association between use of low-dose quetiapine and the risk of MACE using Danish health registers. New users of Z-drugs are used as active comparator to control for confounding by indication as this drug class that is not thought to be associated with MACE is used for patients with insomnia where low-dose quetiapine might also be used. *A high-dimensional propensity score (hdPS) will be used to adjust for baseline confounding*. Both the full cohort and the hdPS-matched cohort will be analyzed using on-treatment (OT) and intention-to-treat (ITT)-approaches with *a maximum follow-up of 5 and 10 years, respectively*. Additionally, we will analyze the association between cumulative doses of low-dose quetiapine and MACE, using a case-control approach nested in low-dose quetiapine users.

Data sources

Danish National Prescription Register (index data source + covariates), Danish National Patient Register (outcomes + covariates), the Cause of Death Register (outcomes), and the Civil Registration System (migrations).

Study population

All new users of quetiapine or Z-drugs in Denmark from *2003* until 2017, to allow a minimum follow-up of 1 year as data availability is limited to 31dec2018. Date of first prescription of either study drugs is used as the index date.

Inclusion criteria:

- New users of quetiapine (ATC: N05AH04) or Z-drugs (ATC: N05CF).

Exclusion criteria:

- Filling of prescriptions for both study drugs on the index date.
- Filling of prescription of high dose quetiapine (>50mg tablets) on the index date (for quetiapine-users).
- Filling of prescriptions of the other study drug within 1 year before the index date.
- Filling of prescriptions for other antipsychotics within 1 year before the index date (ATC: N05A excl. N05AN01 lithium).

- History of severe mental illness (schizophrenia, schizoaffective disorder, mania, or bipolar disorder).
- History of myocardial infarction or stroke.
- *History of cancer (except of non-melanoma skin cancer [ICD-10: C44])*
- Less than 1 year of register coverage before the index date.
- Age below 18 years *or above 85 years* at the index date.

Exposure
Filling of prescriptions for 25 and 50mg quetiapine tablets. Users who filled prescriptions for quetiapine in tablet strengths >50mg will be excluded (or censored) to focus specifically on low dose use.

Outcomes
Main outcome is MACE defined as a composite of: i) Death from cardiovascular causes, ii) non-fatal myocardial infarction, or iii) non-fatal stroke. Secondary outcomes are the individual items of MACE.

Follow-up and censoring
Individuals are followed from the index date to outcome, death for non-CVD reasons, end of follow-up (*5/*10 years), end of study (31dec2018), migration, or censoring. Reasons for censoring are filling of prescriptions of the other study drug, filling of prescriptions for high dose quetiapine (for quetiapine-users), filling of more than 2 prescriptions for other antipsychotics, or new diagnosis of severe mental disorders (similar to the exclusion criteria).

For OT-analyses, the follow-up will be confined to the index treatment episode. Treatment episodes are constructed by assigning a duration to each prescription equivalent to the number of tablets dispensed (assuming use of one tablet per day), adding a *grace period of 120 days* between prescriptions to account for irregular use. Furthermore, *120 days of observation time* will be added to the last prescription in a treatment episode to capture development of MACE shortly hereafter and to avoid immortal time bias.

Statistical analysis
Main analysis:
We will analyze the full cohort *using propensity-score weighting based on a high-dimensional propensity-score (hdPS)*. The hdPS will use prescriptions filled in the year preceding the index date together with in- and outpatient diagnoses from the year preceding the index date to estimate each individual's propensity to receive treatment with low dose quetiapine. Covariate balance in the hdPS-matched cohort will be assessed using standardized mean differences (SMD), with SMD ≤0.1 indicating adequate balance.

For ITT- and OT-analyses, we will calculate *hazard ratios* for outcomes by treatment group with 95% confidence intervals (CI) *using Cow proportional hazards regression models and pooled logistic regression models (OT-analysis). For ITT-analyses, fine-stratification weights (derived from the hdPS) will be used, and in OT-analyses, we will use inverse probability of treatment weights (IPTW) and the product of IPTW and inverse probability of censoring weights (IPCW) to adjust for baseline confounding and potential selection bias.*

The IPCWs will derived from the hdPS and updated every 90 days. The proportion of cases attributable to use of low-dose quetiapine will be calculated as (HR-1)/HR.

Analysis of relationship to cumulative dose:
The case-control analysis will be nested in the treatment group of low-dose quetiapine users, and we will match each case by risk-set sampling on age and sex with up to 10 controls from this group. Odds ratios (OR) for the association between MACE and cumulative dose will be estimated using conditional logistic regression with i) cumulative dose transformed by the binary logarithm, and ii) predefined dose-strata *(2501-5000, 5001-10000, 10001-25000, 25001-50000, >50000mg*), using a cumulative dose of *≤2500mg* as reference (corresponding to ≤100 tablets of 25mg quetiapine). The observation period for the case-control study will be the same as for the main analyses (see description of follow-up above).

Subgroup analyses:
We will conduct subgroup analyses in the full and hdPS-matched cohort, stratifying on:

- Age group (below/above 65 years)
- Sex (male/female)
- History of diabetes (risk factor for CVD)
- History of ischemic heart disease.

Sensitivity analyses:
We will conduct the following sensitivity analyses to test the impact of our analytic strategy on the risk of MACE:

- Including all strengths of quetiapine tablets in the exposure definition.
- *Using selective serotonin-reuptake inhibitors as alternative comparator.*
- *Excluding individuals with a history of hospital-treated depression (in- or outpatient).*

Other

- No ethical approval is necessary for purely register-based studies as the present.
- Data access is granted from the Danish Health Data Authority.
- The study will be registered in EU PAS database (The European Union electronic Register of Post-Authorisation Studies, encepp.eu) before analyses are initiated (Registration number: EUPAS38508).
- Analyses will be conducted in *June to September* 2021 by MH and the manuscript drafted during *October* 2021 by MH.

Amendments to the initial protocol:

March 2021:
Study design and follow-up:
Maximum follow-up in on-treatment analyses is limited from 10 to 5 years as exploratory analyses found that very few individuals remained on treatment beyond that point.

June 2021:
Authors:
Dr. Lars Christian Lund has left the project group due to other work responsibilities and will be mentioned in the acknowledgement section of the manuscript for his contribution to the initial design of the study.

Study population:
The first year in the study period was changed from 1998 to 2003, as there were very few eligible quetiapine-users compared to Z-drug and SSRI-users.

Exclusion criteria:
History of cancer
Persons with history of cancer diagnoses (excluding non-melanoma skin cancer) will be excluded from the study population due to expected higher propensity to receive treatment with Z-drugs and a substantially higher risk of death, which could potentially mask relevant differences between treatment groups.

Maximum age
Maximum age at entry is limited to 85 years due to generally high incidence of cardiovascular events in persons >85 years, which could potentially mask an increased risk in either treatment group.

Follow-up:
The grace period and additional observation time after the last treatment episode is extended from 90 to 120 days based on exploratory analyses of the weighting time-distribution of quetiapine-prescriptions in the Danish National Prescription register.

Adjustment for baseline confounding:
Changed from high-dimensional propensity score (hdPS) matching to weighting. In intention-to-treat analyses, subjects are weighted using fine-stratification weights derived from the hdPS. In on-treatment analyses, subjects are weighted using inverse probability of treatment weigths (IPTW) derived from the hdPS (partial adjustment) and using the product of IPTW and inverse probability of censoring weights (IPCW) (full

adjustment). The latter to account for potential informative censoring. IPCWs are derived from the hdPS and updated every 90 days.

Statistical analysis:
To allow further adjustment for confounding in analyses of the age- and sex-matched cohort, we will change the measure of association from incidence rate ratios to hazard ratios. We will use Cox proportional hazards regression models to incorporate propensity score-weighting (fine stratification weights, inverse probability of treatment or censoring weights). For the main analysis, the number of cases attributable to use of low-dose quetiapine will be calculated as (HR-1)/HR.

Subgroup analyses:
Test for interaction included, based on the p-value for the stratification variable in a Cox proportional hazards regression model.

Sensitivity analyses:
Additional sensitivity analysis added using selective serotonin-reuptake inhibitors as alternative comparator, as Z-drug-users might have more somatic comorbidities, especially among long-term users, which could potentially mask differences in on-treatment analyses.

Case-control analysis:
Dose-strata converted from defined daily doses to milligrams (but not otherwise changed). Dose-response relationship formally tested using a non-parametric test for trend.

October 2021:
Sensitivity analyses:
Additional sensitivity analysis added excluding individuals with a history of hospital-treated major depression (in- or out-patient) to assess the potential effect of depression on cardiovascular risk.

Practical considerations:
Study dates have been updated (analyses and drafting).