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. Users of low-dose quetiapine will be matched 1:1 with users of Z-drugs using a high-dimensional propensity score (hdPS). 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 10 years. 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 when quetiapine was marketed in 1998 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.
- Less than 1 year of register coverage before the index date.
- Age below 18 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 (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 90 days between prescriptions to account for irregular use. Furthermore, 90 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 both the full cohort as well as a hdPS-matched cohort. 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 incidence rates for outcomes by treatment group and from here estimate i) incidence rate ratios, ii) incidence rate differences and iii) number-needed-to-harm (NNH) with 95% confidence intervals (CI).

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 (6.26-12.5, 12.51-25, 25.01-50, 50.01-100, 100.01-200, 200+ DDD), using a cumulative dose of 0.1-6.25DDD 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 100mg quetiapine tablets in the exposure definition.
- Including all strengths of quetiapine tablets in the exposure definition.
- Including individuals with severe mental illness in the cohort.
- Extending the washout window for prior use of study drugs/other antipsychotics from 1 to 5 years.
- Varying the grace period from 90 to 60 and to 120 days.
- Limiting the maximum follow-time in ITT-analyses from 10 to 5 years.

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 January 2021 to March 2021 by MH and the manuscript drafted during March 2021 by MH.