STUDY PROTOCOL

Version 1.0

Psychiatric adverse side-effects of montelukast in children – a Danish nationwide register study.

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Protocol September 13, 2022

Background

Montelukast is a selective leukotriene receptor antagonist (LTRA) recommended by the Global Strategy for Asthma Management and Prevention (GINA) [1]as an add-on option in children and adults with asthma not well controlled on inhaled corticosteroids (ICS) and long-acting beta2 agonists (LABA).

Although montelukast is generally well-tolerated, a number observational studies and case studies conducted especially among pediatric patients have reported of neuropsychiatric (NP) adverse effects such as depression and anxiety following its initiation [2–4].

The aim of this study is, in a large nationwide dataset, to explore the association between use of montelukast and NP conditions in children aged +5 years.

We hypothesize that use of montelukast is associated with an increase in NP conditions.

Methods

Design

We aim to conduct a nationwide register-based observational cohort study.
Data will be obtained from the following Danish registers:

1. The National Prescription Register [5]: Holds information on all prescriptions dispensed from Danish pharmacies since 2004 coded according to the Anatomical Therapeutic Chemical (ATC) classification system.
2. The Danish Central Personal Register (DCPR): Holds information on citizens of Denmark including vital status .
3. The Danish National Patient Register (DNPR) [6]: Holds information on all admissions to Danish hospitals since 1977 and hospital outpatient visits since 1995. Each hospital visit is coded by physicians with a primary diagnosis and, if relevant, one or more secondary diagnoses according to the International Classification of Diseases, 10th revision (ICD-10) from 1994 [7]. It does not include information from primary care consultations.

Cohort

The cohort is formed using data from two registers; the Danish National Prescription Register and the Danish National Patient Register. Patients can enter the cohort if they either 1) have a diagnose of asthma in the Danish National Patient Register or 2) have redeemed at least one

prescription of ICS during the inclusion period (data obtained from the National Prescription Register). Inclusion criteria are listed in figure 1 (below).

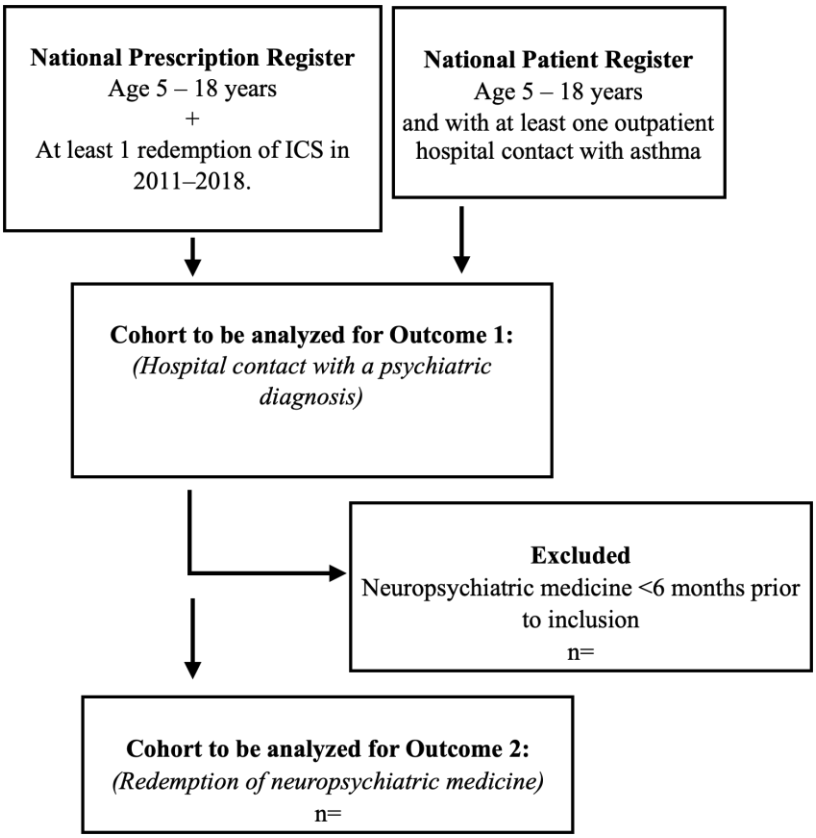


Figure 1: Study cohort

Timeline and exposure

The inclusion period will run from January 1, 2011 – December 31, 2018. Each patient will be followed for outcomes (NP-events) from the date of inclusion, as defined above, until the end of the follow-up period which runs from January 1, 2011 – December 31, 2020 (Figure 1).

We will consider patients as being exposed to montelukast from the first date of redemption of a pack of montelukast during the inclusion period with the length of the exposure period defined as the number of tablets in the pack *plus an additional 90 days* to account for delay in symptom appearance or detection. In Figure 2, three different examples of exposure-courses are illustrated.

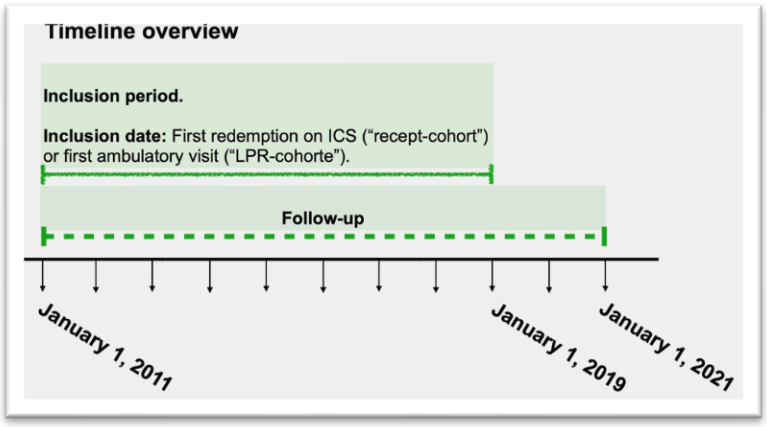
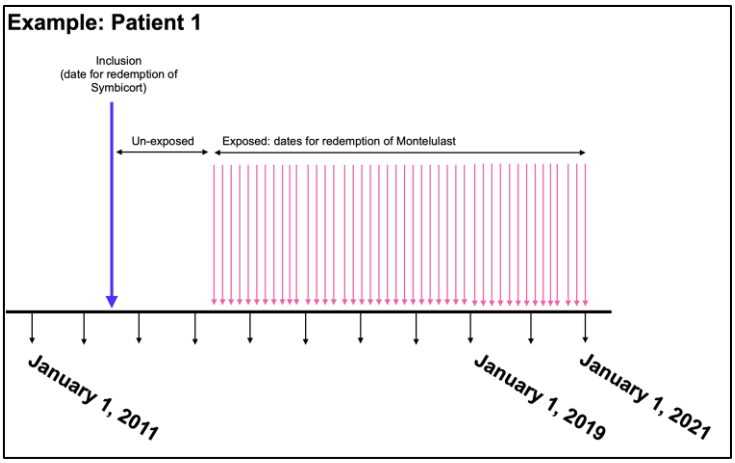
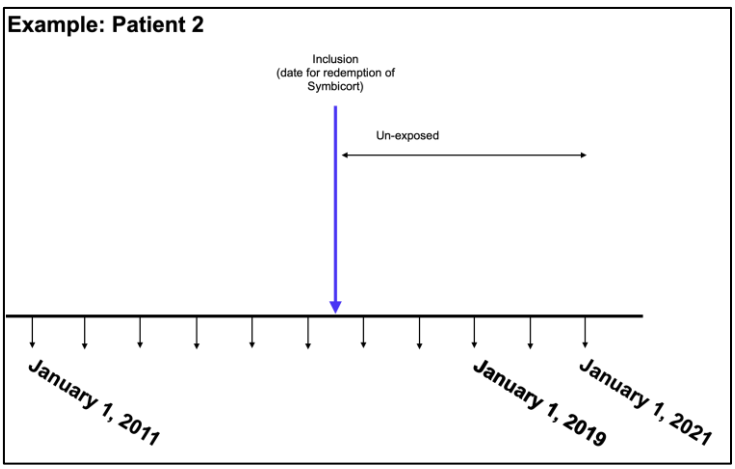


Figure 2: Timeline overview





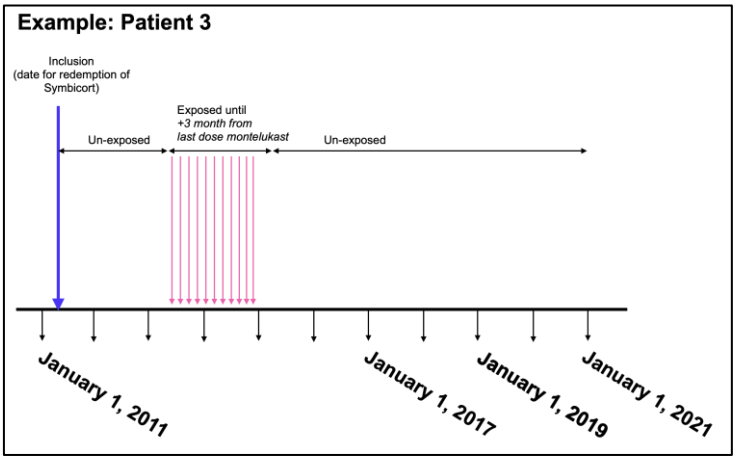


Figure 3: Three examples of inclusion, follow-up and exposure to montelukast.

Outcomes

We aim assess *two outcomes:*

Outcomes

Two outcomes will be evaluated:

- Outcome 1: Patients' redemption of neuropsychiatric medicine, defined as any of the following: Antidepressants, antipsychotics, anxiolytics, lithium and medication used for attention-deficit/hyperactivity disorder (ADHD/ADD).

In the evaluation of this outcome, patients who had redeemed any neuropsychiatric medicine during a six months period leading up to the inclusion date were excluded in order to avoid the outcome of interest to precede the exposure.

- Outcome 2: Admissions to a hospital or ambulatory contacts with a neuropsychiatric condition, including any of the following ICD-10 categories:

F10-F19: Mental and behavioral disorders due to psychoactive substance use,
F20-F29: Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders, F30-F39: Mood disorders,
F40-F48: Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders,
F50-F59. Behavioral syndromes associated with physiological disturbances and physical factors,
F60-F69: Disorders of adult personality and behavior,
F70-F79: Intellectual disabilities,
F80-F89: Pervasive and specific developmental disorders,
F90-F98: Behavioral and emotional disorders with onset usually occurring in childhood and adolescence,

F99-F99: Unspecified mental disorder

Statistics

Time-dependent Cox proportional hazard regression models will be used to estimate the risk of NP-outcomes associated with use of montelukast. Exposure to montelukast will be entered in the model as a time-dependent covariate. The model will be adjusted for age and sex and year of inclusion.

A possible interaction between age and risk of NP-side effects associated with montelukast exposure will be tested and if relevant, the analysis will be stratified in age-groups.

Interaction for sex and risk of NP-sideeffect will also be tested and a stratified analysis will be performed if interaction is present.

Results will be presented as hazard ratios (HR) with 95% confidence intervals (CI) and cause specific HRs with 95% CI.

Publication of results

The results of the study will be published whether they are positive, negative or inconclusive. Publication is planned in international peer-reviewed scientific journals. If publication in a peer-reviewed scientific journal is not possible, the results of the study will be published in report format, which will be made available via the Internet.

Ethical statement/approval

The study has been approved by the Danish Data Protection Agency. In Denmark, retrospective use of register data does not require ethical approval or patient consent.

Ref.

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