Administrative Information

**Title:**
Protocol of the systematic review on neuropsychiatric events associated with leukotriene-modifying agents

**Registration:**
This protocol is not submitted for registration.

**Authors:**
Sharon W Y Law¹, Angel Y S Wong¹, Shweta Anand¹, Ian C K Wong¹² and Esther W Chan¹

¹Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China.
²Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom.

Sharon W Y Law: swylaw@hku.hk  
Angel Y S Wong: aywong@connect.hku.hk  
Shweta Anand: shweta@hku.hk  
Ian C K Wong: i.wong@ucl.ac.uk  
Esther W Y Chan: ewchan@hku.hk

**Correspondence:**
Dr. Esther W Chan  
Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy  
Li Ka Shing Faculty of Medicine, The University of Hong Kong  
2/F Laboratory Block FMB, 21 Sassoon Road, Hong Kong SAR, China  
Tel: (852) 3917 9029  
Email: ewchan@hku.hk

**Contributions:**
SWYL, AYSW and EWC were responsible for the conception and design of the study. Each author contributed to the analysis and the drafting, revision and final approval of the manuscript. All authors were responsible for interpretation of the data.

**Amendments:** Not applicable.

**Support:**
The work described in this paper was partially supported by a grant from the Research Grants Council of the Hong Kong Special Administrative Region, China (Project No. HKU 789813).
Introduction

Rationale
Leukotriene-modifying agents (LTMAs) were first introduced to the market in the late 1990s as a new class of medication for asthma. They mainly act by blocking the effects of cysteinyl leukotrienes in the respiratory tracts to reduce inflammation. Zafirlukast (Accolate), zileuton (Zyflo) and montelukast (Singulair) are the three LTMAs approved by the U.S. Food and Drug Administration (FDA) [1-3]. They are indicated for the management of chronic asthma, prophylaxis of exercise-induced bronchoconstriction and symptom relief in allergic rhinitis [1-3]. Despite the extensive use of the medications, neuropsychiatric safety concerns were raised. There have been case reports of various neuropsychiatric events related to the use of LTMAs, including hallucinations, depression, anxiety, nightmares, hyperactivity and suicidal ideation [4-8]. Together with the post-marketing investigation, neuropsychiatric events were added to the side effects profile in the product labels of LTMAs by the FDA in 2009 [6]. However, the association between neuropsychiatric events and LTMAs was not shown to be statistically significant in previous studies [9-17]. Reviews are available to evaluate the evidence from randomised controlled trials (RCT) and case reports but not from observational studies. Therefore, it is necessary to evaluate all available evidence as rare outcomes are difficult to be detected in RCTs.

Objectives
The objective of this study is to evaluate the evidence of neuropsychiatric events in relation to LTMAs through a comprehensive literature review; and quantify the risk by conducting meta-analysis if there are more than 2 RCTs or observational studies available.

Methods
Eligibility criteria
Studies investigating the association between neuropsychiatric events and LTMAs will be included. The meta-analysis will focus on RCTs or observational studies including but not limited to cohort, case-control, self-controlled case series, case-crossover or case-time-control studies. In order to provide comprehensive information and assess publication bias, literature of different study designs and conference abstracts will also be included in the narrative review. There is no specific publication time limit for the search. The population of interest are patients (of all ages) who require the treatment of LTMAs for any indications. Animal studies will be excluded. In addition, if multiple studies with the same data source, study period and outcomes of interest are identified, only the most recently published studies will be included.

Information sources
Healthcare related electronic databases will be used as listed in the search strategy.
Search strategy

Electronic searches will be conducted on four databases including the Cochrane library, PubMed, EMBASE Classic+EMBASE 1980- via Ovid and Ovid MEDLINE® 1946. Keywords related to the drugs and neuropsychiatric effects will be searched as follows: ('leukotriene-modifying agent' OR 'LTMA' OR 'leukotriene inhibitor' OR 'leukotriene receptor blocker' OR 'leukotriene receptor antagonist' OR 'leukotriene antagonist' OR 'zafirlukast' OR 'accolate' OR 'zileuton' OR 'zyflo' OR 'montelukast' OR 'singulair') AND ('neuropsychiatric' OR 'psychiatric' OR 'hallucination' OR 'psychosis' OR 'psychotic disorder' OR 'mental disorder' OR 'mania' OR 'bipolar' OR 'personality disorder' OR 'delirium' OR 'delusion' OR 'agitation' OR 'aggression' OR 'aggressiveness' OR 'hostility' OR 'irritability' OR 'impulse control' OR 'nervousness' OR 'stress' OR 'anxiety' OR 'depression' OR 'mood disorder' OR 'suicide' OR 'suicidal' OR 'self-harm' OR 'hyperactivity' OR 'ADHD' OR 'attention deficit hyperactivity disorder' OR 'sleep disorder' OR 'insomnia' OR 'somnolence' OR 'dreams' OR 'nightmares' OR 'behavioural disorder' OR 'behaviour' OR 'restlessness' OR 'confusion' OR 'disorientation' OR 'cognitive impairment' OR 'memory loss' OR 'memory impairment' OR 'amnesia' OR 'seizure' OR 'tremor' OR 'violence'). MeSH terms will be used for PubMed and MEDLINE while Emtree will be used in EMBASE for a comprehensive search. The bibliography of the retrieved articles will be screened to further expand the search.

Study records

Data management

All the citations and abstracts of the retrieved articles will be stored in Endnote X7 for evaluation and selection.

Selection process

All literature will be screened by two independent reviewers according to the eligibility criteria to reduce selection bias. Titles and abstracts will be initially evaluated for the relevance and the potential articles will be downloaded from the databases for further assessment for inclusion. Any disagreements will be resolved through discussion and consensus [18].

Data collection process

The data of the selected studies will be extracted and examined. All data analyses will be conducted in Review Manager 5.3 (The Cochrane Collaboration, 2014). A standardised data extraction form will be used for recording the PICO items of the included studies.

Data items

PICO items including, but not limited to, the data source of study, type of study design, demographics of the participants, intervention (specific LTMA used, dose and duration of treatment), outcomes of interest (neuropsychiatric events), follow-up time, sample size and covariates for adjustment will be recorded on data extraction form.
Outcomes and prioritisation

The primary outcome of the study is the risk of suicide or suicidal ideation or self-harm associated with LTMA use. Secondary outcomes include other neuropsychiatric events such as hallucinations, psychosis, bipolar disorder, personality disorder, agitation, hostility, irritability, depression, anxiety, cognitive impairment, sleep disorder, dream abnormalities, seizure and tremor.

Risk of bias in individual studies

For observational studies, the Newcastle-Ottawa scale will be used to assess the methodological quality. The Cochrane Collaboration’s tool will be used to assess the risk of bias for RCTs.

Data synthesis

Relative risk, hazard ratio, odds ratio and the corresponding 95% confidence interval will be extracted from the studies with homogenous study design for analysis. The measures of effect for dichotomous outcomes will be pooled using generic inverse variance method with random-effects model due to heterogeneity existed between studies. The most adjusted measures of effect in the primary analysis will be included; however, if there is missing data for the measures of effect, the number of events and total number of patients will be inputted for analysis. Heterogeneity can be assessed by using the $I^2$ statistic. Forest plots will be used to display the variation of the results from the meta-analysis. Subgroup analyses will be conducted based on the specific LTMA used and different age groups of the population if there are at least two studies reporting the findings for the same age group. A narrative review will be conducted by summarising the evidence from literature of different study designs and conference abstracts.

Meta-bias(es)

Reporting and publication bias will be assessed by funnel plot if there are more than 10 studies included in the meta-analysis.

Confidence in cumulative evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be used to assess the quality of evidence if applicable [19]. The important factors (i.e. limitations of study design, imprecision and inconsistency of results, indirectness of evidence and publication bias) stated in the GRADE guideline will be evaluated to systematically grade the quality of evidence for the outcomes of interest [18].
References


