CURE: Copenhagen Unit for Respiratory Epidemiology
Alexander Jordan
Copenhagen University Hospital Gentofte

Use of inhaled corticosteroids and the risk of new onset depression in COPD patients

Project Summary

Depressive symptoms in relation to inhaled corticosteroid therapy in patients with chronic obstructive pulmonary disease.

Background

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide. These patients are in some cases treated with inhaled corticosteroids (ICS) used preventatively in stable patients to reduce the risk of future exacerbations. ICS treatment is often administered in combination with long acting β_2-agonists [1, 2]. ICS treatment generally has fewer side-effects than systemic corticosteroid (SCS) treatment with drugs like prednisolone, but treatment with ICS has been indicated to be associated with some of the side effects known from systemic treatment, including cataract [3, 4], pneumonia [5-7] and bone demineralization [8]. These effects are thought to be either due to corticosteroid entering the blood stream through the lungs or through the gastrointestinal (GI) tract. Absorption through the lungs is thought to be the primary way for ICS drugs to reach the bloodstream as they typically have a high first pass metabolism in the liver [9]. The extent of the side effects varies between ICS type, dose and delivery methods [2, 9].

Anxiety and depression are known side effects of systemic corticosteroid treatment [10, 11]. Depression is also known to appear at increased rate among COPD patients [12] and is associated with higher rates of exacerbations [13, 14], impaired quality of life [15] and increased mortality [16]. As COPD patients have an increased risk of depression and as it is a hypothetical side effect of ICS treatment, it is relevant to investigate whether ICS use increases the risk of depression in patients with COPD. A small study from 2003 found a correlation between depressive symptoms in asthma patients and ICS dose, but it is difficult to say if this was due to ICS treatment or the severity of the asthma [17]. Another small study from 2006 mentions that behavioral alterations such as increased aggression or anxiety were reported as suspected side effects to ICS treatment for asthma in children [18]. However, a randomized study found that long term treatment 200 µg budesonide lowered depressive symptoms in children with Asthma compared to placebo [19]. No studies have currently been performed on COPD patients.

Objective and hypothesis

The purpose of this study is to investigate if ICS treatment increases the risk of new onset use of antidepressants as a surrogate for new onset of depression in patients with COPD compared to COPD patients with no use of ICS. As a secondary endpoint we will examine if ICS use is associated with an increased rate of admission psychiatric hospitals as a secondary proxy for new onset depression. The study further intends to determine if there is a dose dependent relation between ICS use and antidepressant use and psychiatric admissions.

The central hypothesis is that treatment with ICS increases the occurrence of newly onset depression in a dose dependent manner (risk increases with increasing dose).

Materials and Methods

Data will be obtained from the Danish Register for Chronic Obstructive Pulmonary Disease (DrKOL) and will be linked to data from the national prescription database (Receptdatabasen), the Danish cause of death registry (Dødsårsagsregistret) and the Danish Psychiatric Central Registry (Det Psykiatriske Centralregister).

The study population is defined as all patients registered in the DrCOPD registry, spanning 2008 to 2017 with at least one outpatient contact. Patients only registered in DrCOPD with in-hospital admissions are excluded from the study, as these registrations are lacking necessary measurements of lung function. The accumulated ICS exposure for one year prior to cohort entry will be calculated in budesonide equivalents and the patients will be grouped into four groups based on the exposure. One group will contain patients without any ICS exposure while the remaining patients will be divided into three groups based on the tertiles for the accumulated ICS dose.

ICS class	**ATC codes**
Budesonide	R03AK07, R03BA02
Beclomethasone	R03BA01, R03AK08
Fluticasone	R03BA05, R03AK06, R03AK10, R03AK11
Ciclesonide	R03BA08
Mometasone	R03BA07

Antidepressant use across drug types will be quantified by calculating the number of WHO defined daily doses each patient has received of antidepressants during the study period. The following ATC codes are used to define antidepressants.

Antidepressant class	**ATC codes**
Tricarboxylic Acids (TCA)	N06AA
Serotonin Selective Reuptake Inhibitors (SSRI)	N06AB
Serotonin-Noradrenalin Reuptake Inhibitors (SNRI)	N06AX16, N06AX17, N06AX21, N06AX23
Noradrenergic and Specific Serotonergic Antidepressants (NaSSA)	N06AX03, N06AX11
Other	N06AX except those used to define SNRI and NaSSA drugs

Psychiatric admission is determined based on the following ICD10 codes:

Diagnose	**ICD10 codes**
Depression	F31
Anxiety	F32-34
Bipolar Disorder	F40-41

Statistical analysis

Differences in continuous variables among the exposure groups will be analyzed using T tests or non-parametric tests depending on the distribution of the variable. Categorical variables will be primarily analyzed using ”time-to-event” analyses such as the Kaplan Meier estimator with log-rank tests and Cox-regression to determine the hazard ratios for the incidence of depression for the different doses of accumulated ICS exposure.

The population will be propensity matched using a greedy matching algorithm to compensate for differences within the study population.

Adjustments will be made for the following covariates: FEV_1 percent of expected value grouped into four groups (0-30%, 31-50%, 51-80%, >80%), age, gender, BMI, smoking status (whether the patient is an active smoker or not), use of OCS in 24 months prior to study entry (4 groups: 0-100 mg, 101-250 mg, 251-1000 mg, >1000 mg), use of OCS during the study period and whether at least one of following comorbidities are present: prior or current myocardial infarction, atrial fibrillation, heart failure, hypertension, peripheral vascular disease, cerebrovascular disease, renal failure and asthma.

Sensitivity analysis

Further analysis will be performed to discern the individual effects of the various ICS drug types (budesonide, beclomethasone, fluticasone, ciclesonide and mometasone) as well as the effect of admission

to a psychiatric hospital or antidepressant use prior to cohort entry, on the risk of new onset antidepressant use and psychiatric admission.

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