

Author Response 1

Reviewer: 1

Comments to the Author

Evaluation Manuscript ID: TAR-20-O47

Title: The prescription of antidepressants and/or anxiolytics is higher among COPD patients compared to subjects without or with other chronic diseases

We thank the reviewer for the valuable comments and below we address them point by point

Comments

Title too long and has an acronym, which should preferably be avoided in titles

Page 1: The title has been modified:

Higher prescription of antidepressants and/or anxiolytics among COPD patients versus subjects without or with other chronic diseases.

Since COPD is a generally accepted abbreviation of a disease, and including the full name makes the title even longer, we did not change this.

Abstract

It seems messy, they mix methods with results. They should structure it better, giving it a proper order.

Page 1-2: We agree with the reviewer. We added a structure to the abstract by subdividing it by background, methods, results and conclusions. In addition, some elements have been moved to the results section.

Keywords: COPD is not a descriptor MeSH. Antidepressants is not a descriptor MeSH the correct is Antidepressive Agents, Anxiolytics is not a descriptor MeSH, the correct is Anti-Anxiety Agents. chronic use is not a descriptor MeSH.

For “COPD”, “antidepressants” and “anxiolytics” the MeSH heading is indeed different, although they fit the entry terms linked with the MeSH heading. Therefore, a search entering these keywords will lead to the correct MeSH. Since these are common keywords used in other papers, from which COPD is frequently used in TAR, we decided to keep these keywords. However, since “chronic use” does not lead to any MeSH term, we changed this to “prescriptions”.

Methods.

The authors say it is a retrospective, cross-sectional study. But they are doing an analytical cohort study, comparing the cohort of COPD patients with a control group without chronic disease. It is a retrospective cohort study.

We thank the reviewer for the comment. This study focused on examining the proportion of subject groups using chronic medication for five out of six years, between 1 January 2013 until 1 January 2019. Whereas we did not look at the proportion of starters or starting date of medication

use during this period of time within these groups. Neither did we follow medication use in time. Therefore, this study can be considered a cross-sectional study.

Why did they not include high blood pressure, which is the main chronic disease, at least by frequency?.

We thank the reviewer for this comment. The reason for including hypercholesteremia instead of hypertension is that for hypertension, a broad spectrum of drugs can be used and these drugs are often also used to treat other disorders than hypertension. Whereas for hypercholesterolemia, there are fewer drugs which are not used for other disorders. We tried to include a selection of drug classes which can represent a specific disease accurately in order to compare it to COPD. Since an accurate selection is very difficult for hypertension, we did not include this disorder in our study.

Table 1 should be a supplementary table.

We changed table 1 to a supplementary table.

The authors should explicitly say what are the 5 groups of chronic diseases.

Page 5: We thank the reviewer for this comment. These are briefly mentioned in the Methods section of the revised version:

lines 26-30

Other medication groups included statins (cardiovascular disease), oral glucose-lowering medications (type 2 diabetes mellitus), disease-modifying antirheumatic drugs (DMARDs; rheumatoid arthritis) and dermatology medication consisting of emollients and protectives, antipruritics, antipsoriatics, dermatological corticosteroids and other dermatological preparations (eczema and psoriasis).

They do not mention if the protocol received the approval of a bioethics committee or if the Dutch legislation does not require it for observational studies.

Page 5: We agree with the reviewer. We added this part to the Methods section:

Lines 10-18

Ethical approval

Data protection is a central issue for research ethics and a fundamental human right.¹⁴ Use of prescription data in the database of NControl for research purposes is legally permissible. Patient data in the database are pseudonymized. It is impossible for researchers that work with the NControl database to re-identify any natural persons. As such, it is also not possible for researchers to ask patients permission to be included in this study. NControl adheres to data protection and privacy regulations, as established in amongst others the Personal Data Protection Act in The Netherlands as well as the Netherlands Norm (NEN) 7510 standard on information protection in healthcare, which is derived from International Organisation for Standardization (ISO) norm 27001 and 27002.¹⁵

Discussion.

They should dig deeper into the reasons why COPD patients become depressed or anxious.

Page 10: We thank the reviewer for this comment. Although this is very speculative and it is not a goal of this manuscript to unravel this, we still added a sentence mentioning some factors believed to lead to depression and anxiety in COPD. This sentence can be found at the end of the third paragraph:

Lines 19-21

Several factors are thought to contribute to the development of anxiety and depression in COPD specifically, including smoking, hypoxemia, systemic inflammation and the chronic use of corticosteroids.³

In the second paragraph they talk about the GOLD initiative, but they do not include the reference.

Page 9: The reference has been added to the paragraph at the sentence starting with “The severity was reflected by...” (reference nr. 1). Line 25

In the limitations they say “Therefore, it is not known whether, and how many patients may have had anxiety or depression prior to COPD diagnosis”. This can be determined by looking at the prescriptions for these drugs before the first-time index date for COPD medications, so they would know if they were already receiving antidepressants or anxiolytics.

Page 10: We thank the reviewer for this comment. The goal of this study was to identify the relation between chronic disease, in particular COPD, and chronic antidepressant/anxiolytic use. Investigating the issue described by the reviewer would on itself be a different study. Therefore, we have rewritten this part in the Discussion section to make this more clear:

Page 10, line 34-page 11, lines 1-3

In addition, the index date of ATDs and/or ANXs in these subjects is not known. Knowledge about the index date could indicate whether there was anxiety/depression present prior to COPD diagnosis. In a follow-up cohort study, more research on incidence, causes and prognosis should be performed to, amongst others, elaborate this.

Comments: It needs major adjustments so that it can be considered for publication.

We have addressed all the comments of the reviewer and have substantially changed the manuscript.

Reviewer: 2

Comments to the Author

In general, the draft was well written

We thank the reviewer for the compliment and have addressed all comments point by point below

I have some comments

1 please address the definition of COPD more clear .

Page 3: We modified this in the first two sentences of the introduction:

Lines 3-6

Chronic obstructive pulmonary disease (COPD) is a chronic lung disorder characterized by the progression of airflow restriction associated with abnormal inflammatory responses to toxic particles or gases.¹ The obstructive bronchiolitis and parenchymal destruction are progressive and not fully reversible.

2 author may clarify the asthma with COPD? The study group excluded the asthma with COPD?

The pharmacological treatment in COPD is sometimes also applied in asthma. Although the selection of asthma cases has been limited as much as possible by including an age stratification (55 years and older) and excluding the cases using solely inhaled corticosteroids, our selection of COPD cases might still have included asthma cases as well.

3 Please discuss the life style , occupation , diet and exercise . these may be the confounding factors thank you !

Page 10: We agree with the point made by the reviewer. We have added a sentence mentioning these factors to the fourth paragraph of the discussion section.

Lines 31-34

Secondly, our findings have been based on a prescription database of pharmacies. Therefore, several confounding factors could not have been accounted for. These factors are mainly related to lifestyle such as diet and exercise. Besides, an unhealthy lifestyle is related to (the development of) depression.³⁰