Association between Antidepressants with Pneumonia and Exacerbation in Patients with COPD: A Self-Controlled Case Series (SCCS).

RA Siraj[1, 2,3], CE Bolton[1], TM McKeever[1, 2]

Authors affiliations:

[1] NIHR Nottingham Biomedical Research Centre Respiratory theme, Translational Medical Sciences, School of Medicine, University of Nottingham, City Hospital NUH Trust site, Nottingham, UK;

[2] Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, UK.

[3] Department of Therapy Care, King Faisal University, Al-Ahsa, Saudi Arabia

Correspondence to:

Professor T.M Mckeever,

Division of Epidemiology and Public Health NIHR Nottingham Biomedical Research Centre,

School of Medicine, University of Nottingham,

City Hospital Campus,

Hucknall Road, Nottingham,

NG5 1PB. UK

Email: Tricia.mckeever@nottingham.ac.uk

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Abstract

Objective: To assess whether antidepressant prescriptions are associated with an increased risk of pneumonia and COPD exacerbation.

Methods: A self-controlled case series was performed to investigate the rates of pneumonia and COPD exacerbation during periods of being exposed to antidepressants compared to non-exposed periods. Patients with COPD with pneumonia or COPD exacerbation and at least one prescription of antidepressant were ascertained from The Health Improvement Network in the UK. Incidence rate ratios (IRR) and 95% CI were calculated for both outcomes.

Results: Of 31,253 patients with COPD with at least one antidepressant prescription, 1,969 patients had pneumonia, and 18,483 had a COPD exacerbation. The 90-day risk period following antidepressant prescription was associated with a 79% increased risk of pneumonia (age-adjusted IRR 1.79, 95% CI: 1.54 to 2.07). These associations then disappeared once antidepressants were discontinued . There was a 16% (age-adjusted IRR= 1.16, 95% CI: 1.13 to 1.20) increased risk of COPD exacerbation within the 90 days following antidepressant prescription. This risk persisted and slightly increased in the remainder period ((age-adjusted IRR= 1.38, 95% CI: 1.34 to 1.41), but diminished after patients discounted the treatment.

Conclusion: Antidepressants were associated with an increased risk of both pneumonia and exacerbation in patients with COPD, with the risks diminished upon stopping the treatment. These findings suggest a close monitoring of antidepressant prescription side-effects and consideration of non-pharmacological interventions .

Key messages

- **What is already known on this topic?**

A previous study suggests that antidepressants are associated with respiratory-related morbidities in patients with COPD.

Potential confounders and bias may impair the interpretation of the association, which has been previously observed.

- **What this study adds?**

Using a self-controlled case series design, this study shows that antidepressant prescription with increased the risk of pneumonia and COPD exacerbation in patients with COPD. These risks diminished once the treatment has stopped.

- **How this study might affect research, practice, or policy?**

These findings support the monitoring of side effects associated with antidepressants and that non-pharmacological therapies should be considered.

INTRODUCTION

Poor mental health is common among patients with chronic obstructive pulmonary disease (COPD) and has a significant impact on health and prognosis. It is imperative to identify and treat with both non-pharmacological interventions including counselling as well as pharmacological therapies such as antidepressants where appropriate [1].

Antidepressants, however, are not without their side effects, some non-specific but some reports of respiratory harm in patients with COPD, even with selective serotonin reuptake inhibitors (SSRIs) or serotonin–noradrenaline reuptake inhibitors (SNRIs), which exert weak anticholinergic effects, and have better overall safety and acceptability records compared to tricyclic antidepressants (TCAs) [2, 3]. Current evidence shows that the anticholinergic property, strongest in TCAs, is associated with dry mouth [4], which may potentially lead to an increased risk of pneumonia amongst the elderly [5]. Up to 30% of antidepressant recipients (SSRs/SNRIs) experience vomiting and nausea [6, 7], which has the potential to contribute to micro-aspiration. In addition, some SSRI/SNRI agents may have immunosuppressant effects (by reducing the immune cell quantity and function), lowering the threshold of infection [8, 9]. There is also a possibility that some antidepressant agents supress the clearance of apoptotic cells in the airways, eventually leading to airway plugging.

A previous population-based study examined the association between a new antidepressant prescription (SSRI/SNRI) and adverse respiratory events in individuals with COPD [2]. In that observational analysis, new users of SSRIs and/or SNRIs with COPD had increased risks of hospitalisation, emergency visits, pneumonia and mortality compared to non-users [2]. Whether these findings reflect the causal effects of antidepressants or have been influenced by the unmeasured differences between the exposed and control groups are to be ascertained.

Therefore, this study aims to use analyses to overcome the limitation of the previous research in order to investigate whether antidepressants are associated with an increased risk of pneumonia and COPD exacerbation, using primary care electronic health records within the UK.

METHODS

Study Design

A self-controlled case series (SCCS) study design was used to examine the association between antidepressant prescription and both (but separately) incident pneumonia and incident COPD exacerbation in patients with a diagnosis of COPD. This method anchors patient observation time to the date of a given exposure (index date), and then examines the timing of events in relation to that exposure within a defined observation period. This method has the advantage of eliminating confounding between subjects as each participant acts as their own control (10, 19). The SCCS estimates the relative incidence of an outcome in the exposure risk periods (exposed periods), with incidence during other baseline times (unexposed) within a person [10].

Data source and study population

The participants' information was obtained using The Health Improvement Network (THIN), a large representative UK database, which contains longitudinal, fully anonymised patients' electronic health records (>12 million people) from over 550 general practices (GPs) and covering more than 6% of the UK population 20 [11]. The study identified all individuals aged ≥40 years with a new READ-coded COPD diagnosis between 1/01/2004 and 31/12/2015, who have at least one year of data prior to their COPD diagnosis [12] and have at least one record of anti-depressant prescription/dispensing. The index date was defined as the date patients with COPD were prescribed their first antidepressant prescription. From those with antidepressant prescription(s), we included all individuals (cases) with the outcomes of interest (pneumonia or COPD exacerbation in the SCCS analyses.

Diagnosis for COPD was solely based on READ codes, standard terminologies, maintained by the UK National Health Service Centre for Coding and Classification [12]. COPD can be identified in UK electronic primary care database using only read codes. Each healthcare professionals' diagnosis of COPD was according to their view and decision. Ethical approval for this study was provided by an independent Scientific Review Committee (SRC), reference number - 18THIN098

Exposure definition

Antidepressant prescriptions were determined and further divided into four classes: SSRIs, SNRIs, TCAs, Monoamine oxidase inhibitors (MAOIs), as well as collectively all together.

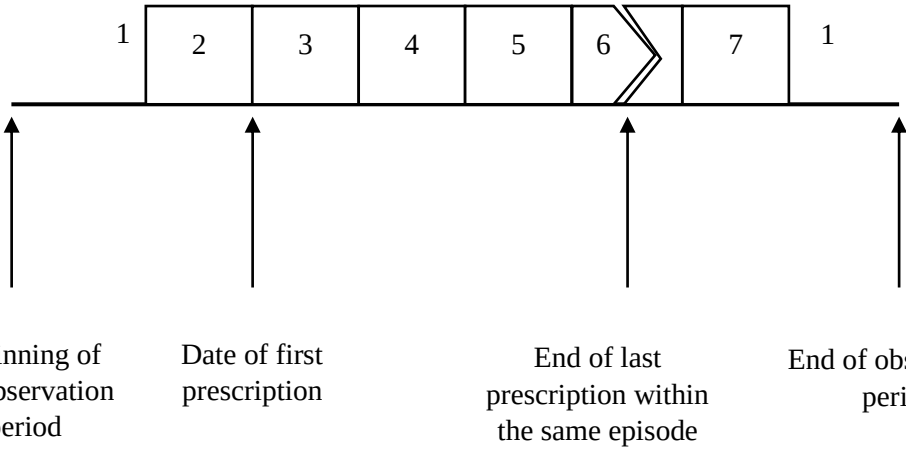
Detailed recordings of the length of prescriptions are not always found in THIN. In practice, patients are unlikely to collect the subsequent medication prescribed on exactly the day after the last day of the previous dispensing. Rather, they may collect it earlier (overlap between two prescriptions) or later (time gap between two prescriptions). To account for these irregularities, it is advised to allow for a certain number of days between prescriptions. Therefore, to constitute a new episode of antidepressants, a 90-day interval between prescriptions was used, as it has consistently been used in primary care studies, and also according to the standard practice in the UK [13, 14]. Thus, this study made a conservative assumption, in which prescriptions were part of the same episode if they were dated within 90 days of the previous prescription.

Exposed and unexposed periods definitions

The follow-up was defined as finishing when patients left the GP practice, date of death, or end of the study period. The outcomes for each case were estimated during 7 different periods (**Error! Reference source not found.**). Following a previous study [2], the decision was made to include a 90-day "hypothesised risk window" following the day of the first prescription. The selection of the 90-day risk period was made because this study intended to assess the acute effects of antidepressant related adverse events, and since it is acknowledged that antidepressant may take several weeks before it reaches its full effects.

In addition to assessing the 90-day risk window following the first prescription date, the temporal changes associated with antidepressant prescription was also investigated. This was done by dividing the 90-day window into 3 segments of 30 days each, where the risk of each period was assessed individually. A period of a variable-length was also included to cover the remainder period of that episode, followed by a 90-day washout period after the end of the antidepressant episode/course. In a situation where a new episode of antidepressant was started within these last two periods, the exposure statuses associated with that episode had taken over.

Figure 1. Diagram representing the study design



1- The period when cases are not exposed to antidepressants (baseline).
2- A 30-day pre-exposure period up to and including the first prescription date. ,
3- A 30-day period following the 1st prescription date (from day 1 to day 30 on treatment).
4- A 30-day period (from day 31 to day 60 on treatment).
5- A 30-day period (from day 61 to day 90 on treatment).
6- The remainder of that course to cover the entire exposure period (from day 91 until the end of that course).
7- A 90-day washout period following the end of that course.

Outcome definitions

The first outcome was READ-coded pneumonia and the all events of pneumonia were considered. A new event was considered as such if at least 90 days had elapsed from the previous incidence of pneumonia, based on the current literature [15, 16]. Pneumonia diagnosis using Read codes in primary care has been examined and validated [17, 18]. Secondly, we assessed the association between antidepressants and COPD exacerbation. Incidents of COPD exacerbation were defined based on algorithms constructed from multiple READ and drug codes as follows: "1) a medical diagnosis of lower respiratory tract infection (LRTI) or acute exacerbation of COPD (AECOPD), or 2) a prescription of COPD-specific antibiotic combined with oral corticosteroids (OCS) for 5–14 days, or 3) a record of two or more respiratory symptoms of AECOPD along with a prescription of COPD-specific antibiotics and/or OCS on the same day" [19]. A new COPD exacerbation episode was considered as such if at least 8 weeks (56 days) had elapsed from the previous coded exacerbation [20].

Covariates

A number of covariates were determined at the time of COPD diagnosis, including age, gender and Townsend social deprivation score (with quintile 1 being the least deprived and quintile 5 being the most deprived) [21]. Smoking status and the Medical Research Council (MRC) dyspnoea scale were recorded closest to the index date (whether prior to, or after the index date). Body mass index (BMI) was determined within 2 years (before and after) index date. Charlson Comorbidity Index (CCI) was determined before or at index date.

Statistical analysis

Baseline characteristics and demographics were summarised as relative frequencies for categorical data and mean (SD) for normally distributed continuous variables as appropriate. The incidence rate ratio (IRR) for the outcomes (pneumonia and COPD exacerbation) were calculated using fixed-effects Poisson regression by comparing the incidence ratio during each exposure period with the incidence when the same individual was unexposed (baseline), with an adjustment for age (3-year bands) [22]. The age-adjusted IRR for each antidepressant class was calculated individually, as well as when all antidepressants were collectively combined for each outcome. STATA 15.0 software was used for data management and statistical analyses.

Assumptions and sensitivity analyses

The SCCS relies on three main assumptions as follows:

1- The occurrence of pneumonia or COPD exacerbation must not alter the probability of subsequent exposure. As both pneumonia and COPD exacerbations are associated with depression and anxiety [23, 24], which, might increase the probability of antidepressants prescriptions, there is a potential short-term dependency that may lead to a change in prescription. To account for this, we created a 30-day pre-exposure period in line with previous studies [15, 25-27].
2- The second assumption is that an event should not alter the probability of a subsequent event (occurrence of outcomes is independent), especially for modelling multiple events. As a COPD exacerbation and pneumonia can increase the risk of a future event, sensitivity analyses restricting to the first event were conducted.
3- An outcome event should not increase the probability of observation censoring (does not lead to an increased risk of death). As both outcomes (pneumonia and COPD exacerbation are linked to increased risk of death, an the this study opted to carry out a secondary analysis wherein patients who died following an event were excluded (6 and 12 months following the outcome event), similar to previous studies [15, 27-30].

Since the SCCS does not control for time-varying confounders (e.g. season), and weather may be associated with increased risks of pneumonia and/or COPD exacerbations, the model was examined for the potential effect of season (adjusted for seasons) by splitting the year into two parts: 1) October to March (colder months) and 2) April to September (warmer months), in concordant to previous analyses [28, 31, 32].

RESULTS

Of the 31,253 patients with COPD with at least one record of antidepressant prescription during the study period, there were 1,969 individuals who had a coded pneumonia event and 18,483 individuals with a COPD exacerbation who were included in the SCCS analyses, Figure 2. Six-hundred and thirteen patients with COPD were presented with both codes; and thus were included in both analyses The median numbers for pneumonia and COPD exacerbation were 1 (IQR: 1-2) and 3 (IQR; 2-6), respectively, events per patient. The mean (SD) age of the 31,253 patients was 65 (11) years. The baseline characteristics of the study participants are summarised in

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Figure 2. Flow chart to the study

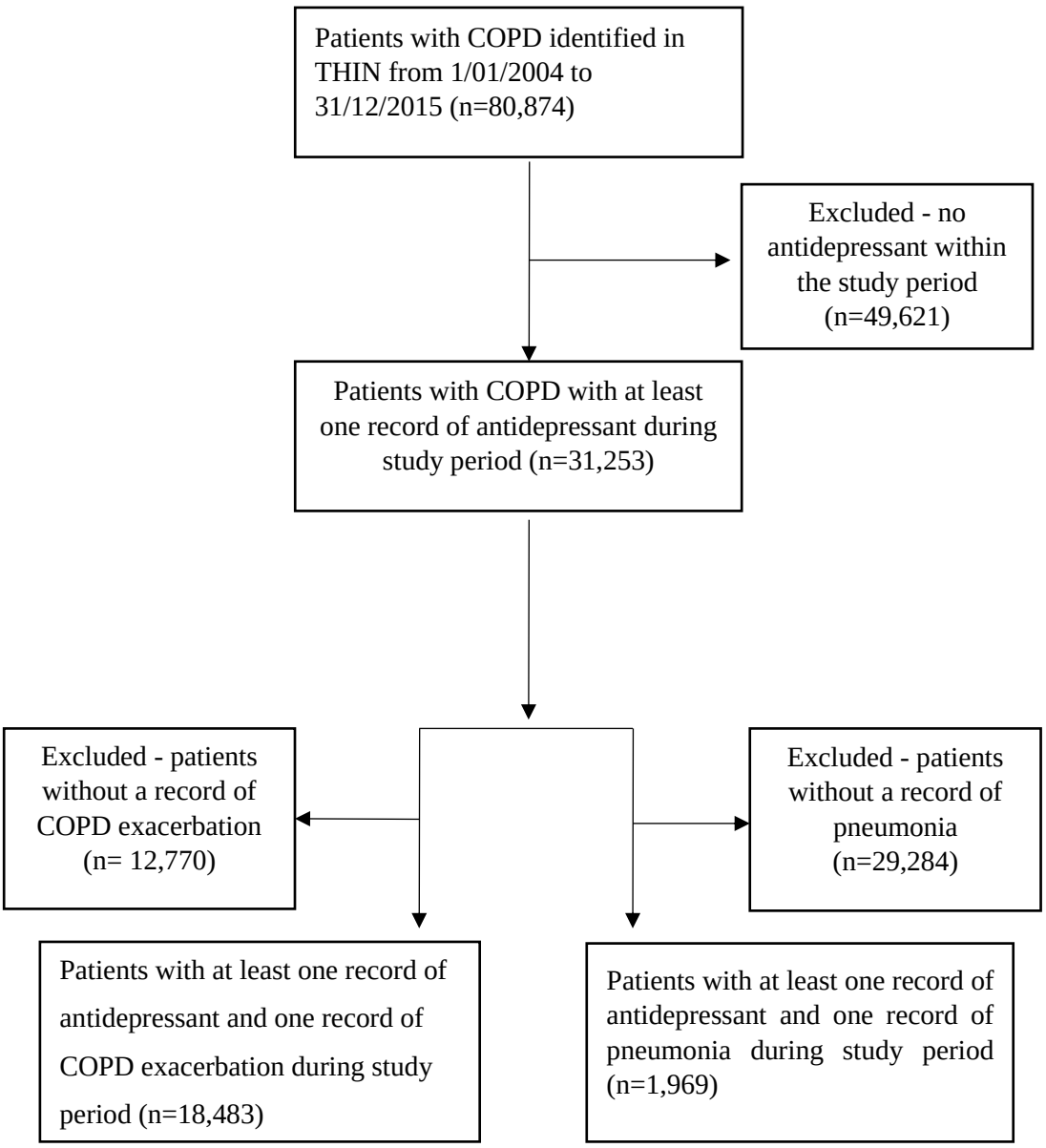

Table Error! No text of specified style in document.**1. Baseline characteristics for patients with COPD with a record of antidepressant prescription (n=31,253) with pneumonia (n=1,969) or COPD exacerbation (n=18,483) during the study period**

Characteristics	Overall (n=31,253)	Pneumonia (n=1,969)	COPD exacerbation (n=18,483)
Mean Age at COPD diagnosis (years, SD)	65.1 (11.2)	71.8 (10.8)	67.7 (10.9)
Gender			
Male	13,283 (44%)	950 (48%)	7,407 (41%)
Female	17,970 (56%)	1,019 (52%)	11,076 (59%)
Follow-up (years, median, IQR)	5.9 (3.3-8.7)	7.7 (5.5-9.8)	6.7 (4.2-9.1)
Townsend score (prior or at index date)			
1 least deprived	4,300 (14%)	252 (13%)	2,458 (14%)
2	4,927 (16.2%)	300 (15%)	2,884 (16%)
3	6,240 (20%)	386 (20%)	3,694 (20%)
4	7,541 (24%)	513 (26%)	4,494 (24%)
5 most deprived	6,902 (21.3%)	443 (22%)	4,217 (21.6%)
No records	1,343 (4.5%)	75 (4%)	736 (4.4%)
BMI (kg/m^2) (2 years either side of index date)			
underweight (<18)	13,790 (44%)	863 (43%)	13,854 (44%)
normal (18-24.99)	9,758 (31%)	623 (32%)	10,098 (32%)
Overweight (25-29.99)	4,942 (16%)	289 (15%)	4,971 (16%)
Obese (>30)	2,567 (6%)	314 (6%)	1,736 (5%)
No records	952 (3%)	75 (4%)	543 (3%)
MRC dyspnoea score (most recent record to index date)			
1	2,821 (10.3%)	94 (5%)	1,364 (7%)
2	6,856 (23.6%)	285 (14%)	3,744 (20%)
3	4,372 (14%)	231 (12%)	2,634 (14%)
4-5	2,419 (7.4%)	174 (9%)	1,463 (8%)
No records	14,785 (44.7%)	1,185 (60%)	9,278 (45.5%)
Smoking status (most recent record to COPD diagnosis)			
Never smoked	2,754 (9%)	164 (8.3%)	1,551 (8%)
EX-smoker	13,608 (44%)	959 (48.7%)	8,092 (44%)
Current smoker	14,480 (45%)	823 (42%)	8,667 (47%)
Unknown	411 (2%)	23 (1%)	173 (1%)
CCI (prior to or at index date)			
0-1	15,141 (48%)	790 (40%)	9,197 (50%)
2	5,230 (16.5%)	358 (18%)	3,004 (16%)
3	5,397 (17.5%)	368 (19%)	3,270 (18%)
≥ 4	5,485 (18%)	453 (23%)	3,012 (16%)

Results are presented as frequency and percentage unless stated otherwise

Abbreviations: BMI: Body Mass Index; CCI, Charlson comorbidity index; MRC: Medical Research Council.

Association with pneumonia

Compared to an unexposed period, collective antidepressant, SSRI/SNRI, and TCA prescriptions showed marked associations with pneumonia throughout all risk periods (Table 2). These associations were then diminished after withdrawal from the treatment. The 90-day period following any antidepressant prescription was associated with a 79% increased risk of pneumonia (age-adjusted IRR 1.79, 95% CI: 1.54 to 2.07). The risk also persisted throughout the remainder period (age-adjusted IRR 1.88, 95% CI: 1.68 to 2.11). The initiation of SSRI/SNRI and TCAs, separately, were also associated with an increased risk of pneumonia that extended to the remainder period.

Restricting the primary analysis to only the first event of pneumonia was associated with an increased risk of pneumonia in the 90-day after antidepressant prescription and the remainder period, despite slightly lower in magnitude (online supplemental appendix results E1). Following pneumonia, there were 295 and 388 patients censored within 6 and 12 months, respectively. In those who were not censored within 6 and 12 months after the incident pneumonia, there was a 48% (1.26 to 1.75) and 43% (1.21 to 1.70) increased risk of pneumonia in the 90 days following the prescription of any antidepressant (online supplemental appendices results E2 & E3).

Table 2. Age-adjusted incidence rate ratio of pneumonia (multiple events) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressants	No. of exposed cases with Pneumonia	Day 1-30 IRR (95%CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective Antidepressants	1,969	1.68 (1.33 to 2.13)	1.83 (1.48 to 2.27)	1.89 (1.43 to 2.49)	1.79 (1.54 to 2.07)	1.88 (1.68 to 2.11)	1.03 (0.76 to 1.40)
SSRI or SNRI	1,218	1.75 (1.29 to 2.38)	1.62 (1.22 to 2.15)	2.56 (1.88 to 3.50)	1.76 (1.46 to 2.12)	1.83 (1.58 to 2.12)	1.02 (0.69 to 1.50)
SSRI	1,143	1.73 (1.62 to 2.39)	1.53 (1.13 to 2.07)	2.65 (1.94 to 3.62)	1.86 (1.54 to 2.4)	1.79 (1.54 to 2.09)	0.95 (0.64 to 1.42)
SNRI	168	1.69 (0.73 to 3.91)	1.23 (0.53 to 2.86)	1.61 (0.59 to 4.36)	1.48 (0.86 to 2.55)	1.91 (1.31 to 2.79)	1.29 (0.52 to 3.2)
TCA	1,318	1.51 (1.10 to 2.03)	1.92 (1.46 to 2.52)	1.40 (0.95 to 2.07)	1.64 (1.35 to 1.98)	1.78 (1.54 to 2.07)	1.29 (0.93 to 1.79)
MAOI	50	0.82 (0.07 to 7.43)	0.93 (0.10 to 8.14)	–	0.62 (0.13 to 2.90)	2.44 (0.95 to 5.7)	1.38 (0.33 to 5.77)

The "Collective Antidepressants" does not equate to the total of all individual classes as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of the prescription (segment 1).
2- Day 31-60: A 30-day risk period starting from day 31 after the date of the prescription (segment 2).
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription (segment 3).
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of the prescription until the end of the course).
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course). Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

Association with COPD exacerbation

Compared to a period when patients were not exposed to antidepressant, there was a 16% increased risk of COPD exacerbation (age-adjusted IRR= 1.16, 95% CI: 1.13 to 1.20) in the first 90 days following any antidepressant prescription that slightly increased in the remainder period (age-adjusted IRR= 1.38, 95% CI: 1.34 to 1.41), but the association was diminished after 90 days from stopping the treatment. Similar trends were observed in SSRI/SNRI and TCAs (Table 3).

The sensitivity analyses found that antidepressant prescription were associated with a greater risk of the first event of COPD exacerbation (age-adjusted IRR= 1.41, 95% CI: 1.34 to 1.49; online supplemental appendix results E4). The risk as also extended throughout the remainder period, but then diminished in the washout period. In addition, there were 1331 and 2,078 patients censored within 6 and 12 months, respectively, following a COPD exacerbation. There was 12% increased risk of COPD exacerbation in the 90 days following any antidepressants in those whose observations were not censored within 6 and 12 months after COPD exacerbation, compared to unexposed periods (online supplemental appendices results E5 & E6).

When the season was included in the analyses, it yielded similar results; therefore, there were no obvious confounding seasonal effects on the associations of antidepressants and pneumonia or COPD exacerbation events (Table E7 and E8).

Table 3. Age-adjusted incidence rate ratio of COPD exacerbation (multiple events) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressants	No. of exposed cases with exacerbation	Day 1-30 IRR (95%CI)	Day 31-60 IRR (95%CI)	Day 61-90 IRR (95%CI)	Day 1-90 IRR (95%CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective antidepressant	18,483	1.11 (1.06 to 1.17)	1.18 (1.12 to 1.23)	1.23 (1.15 to 1.31)	1.16 (1.13 to 1.20)	1.38 (1.34 to 1.41)	0.98 (0.92 to 1.05)
SSRI or SNRI	11,770	1.10 (1.03 to 1.17)	1.16 (1.09 to 1.23)	1.22 (1.13 to 1.33)	1.15 (1.11 to 1.20)	1.39 (1.35 to 1.43)	0.99 (0.93 to 1.10)
SSRI	10,919	1.07 (1.01 to 1.45)	1.13 (1.06 to 1.21)	1.29 (1.10 to 1.30)	1.12 (1.08 to 1.17)	1.36 (1.32 to 1.41)	1.02 (0.94 to 1.11)
SNRI	1,753	1.14 (0.94 to 1.40)	1.29 (1.10 to 1.52)	1.34 (1.09 to 1.65)	1.23 (1.10 to 1.38)	1.36 (1.26 to 1.47)	1.06 (0.87 to 1.33)
TCA	11,936	1.09 (1.02 to 1.16)	1.16 (1.10 to 1.23)	1.26 (1.17 to 1.37)	1.16 (1.11 to 1.21)	1.27 (1.23 to 1.32)	1.02 (0.93 to 1.09)
MAOI	416	1.14 (0.77 to 1.68)	1.57 (1.11 to 2.23)	1.17 (0.71 to 1.92)	1.33 (1.07 to 1.66)	1.15 (0.89 to 1.50)	0.76 (0.49 to 1.18)

The "Collective Antidepressants" does not equate to the total of all individual classes as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of the prescription (segment 1).
2- Day 31-60: A 30-day risk period starting from day 31 after the date of the prescription (segment 2).
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription (segment 3).
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of the prescription until the end of the course).
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course). Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

DISCUSSION

In this self-controlled case series study utilising primary care data, there were increased risks of both pneumonia and COPD exacerbations in the 90 days following the use of antidepressants among patients with COPD. The increased risk remained even when the analyses were restricted to the first event. The risk of pneumonia and COPD exacerbation both diminished once antidepressants were discontinued.

There has been growing evidence that antidepressants may lead to respiratory-related adverse events in patients with COPD. Several mechanisms have been suggested in the literature. Such includes the anticholinergic component in TCAs, which is associated with dry mouth, leading to increased risks of pneumonia [4]. Further, the common side effects, such as vomiting and nausea, associated with some SSRIs and SNRIs, could also contribute to aspiration and eventually pneumonia [6, 7]. Other antidepressants also have immunosuppressant effects, potentially lowering the threshold of infection [8, 9], and consequently exacerbation.

The current study found that there is an increased risk of pneumonia and COPD exacerbation in the 90-day following antidepressant prescription. The risks gradually increased after initiation and peaked at extended use. Although this study further supports findings from a previous study that SSRI or SNRI users with COPD have an increased risk of pneumonia compared to non-users [2], the risk of pneumonia reported in this study was of a greater magnitude and longer period.

It is important to mention the study conducted by Vozoris et al. demonstrated that new users (patients with COPD) of antidepressants (SSRI/SNRI) were at lower risk of COPD exacerbation (in outpatient exacerbations) compared to non-users in the 90-day following antidepressant, owning this to increased and competing risk of other respiratory events and death (2). However, more severe COPD exacerbations associated with hospitalisation and emergency visits were significantly increased among the SSRI/SNRI users (2). The present study also explored these associations in other antidepressant classes and identified the precise timing and duration of the amplified risk; something that has not been investigated before.

The causal link between antidepressants and the development of pneumonia has not been established. However, there is evidence to suggest that depression and anxiety (which are both highly prevalent in COPD [33, 34], leading to antidepressant use) is independently associated with an increased risk of respiratory infection and pneumonia [35]. A previous study reported a 3-fold increased risk of pneumonia in the 90-day period after hospitalisation for depression [36], highlighting the possibility that antidepressants contribute to the increased risk. Indeed, Hennessy et al. reported an association between antidepressants and increased risk of pneumonia among elderly, although the association was nullified upon further adjustments [37]. There is also a possibility that the pharmacological side effects may contribute to an increased risk [6, 7, 38].

Each class of antidepressants contributes to increased risk of pneumonia and exacerbation by their own adverse effects. For instance, the anticholinergic property in TCAs has been associated with dry mouth [4], which may potentially lead to an increased risk of pneumonia [5]. Some antidepressants have antihistaminergic effects, which causes sedation, while others may cause sedation by the inhibition of the monoamine oxidase enzyme. Moreover, some SSRI/SNRI agents may have immunosuppressant effects lowering the threshold of infection [8, 9].

This study found an increased risk of COPD exacerbation in the 90-day period following antidepressant prescriptions, which has also extended during the time when patients were on continues antidepressant. In contrast, a previous study has shown that new users (patients with COPD) of antidepressants (SSRI/SNRI) were at lower risk of COPD exacerbation compared to non-users in the 90-day following antidepressant, owning this to increased and competing risk of other respiratory events and death [2]. Crucially, the current study compared the incidence relative risk of COPD exacerbation during antidepressant exposure periods with the patients' own stable period, not the risk of COPD exacerbation between individuals. Although having a history of COPD exacerbation is the greatest risk factor for future exacerbations [39], this study found a similar relationship ─ there is an increased risk of COPD exacerbation following antidepressant prescriptions ─ when the analysis was restricted to the first COPD exacerbation event, highlighting a potential risk associated with the side effects of antidepressant [8, 9].

Strengths and limitations of the study

This study has several strengths. First, the primary care database is large and provides a representative sample of patients with COPD within the UK [11]. Second, the use of within-individual comparison has controlled for time-independent confounders such as sex, socioeconomic status, and genetics; thus, providing a robust estimate. In addition, this study has used recommended approaches to fulfil the assumptions of the SCCS analyses, such as 1) including a pre-exposure period, 2) studying the first event, and 3) excluding those whose observations were censored because of death. Another strength is that this study used validated definitions for COPD exacerbation in electronic health records [19].

However, this study has some limitations. One limitation is that some lifestyle exposures are not regularly updated, making it difficult to exclude confounding factors that are known to accompany the issue of antidepressant prescription. For instance, smoking consumption may become more frequent during depression or anxiety episodes (and hence antidepressant prescription), which could consequently confound the observed relationship. Investigation to the dose-response association could not be considered, as a significant proportion of THIN prescription records do not contain usable dosage information. Further, indications for antidepressants (reasons for prescription) are not recorded in THIN, and we cannot exclude that some patients may have sought treatment for other illnesses for which antidepressant were eventually prescribed; and therefore, may contribute to increased risk. Further, severity of airways obstruction of COPD was lacking. Although THIN lacks maintenance COPD therapies such as supplemental oxygen and positive airway pressure, implementing the SCCS would overcome differences between exposed and unexposed periods, as each participant acts as his/her control. In addition, it was difficult to determine whether patients collected and/or adhered to their antidepressants as prescribed. Further, it was also difficult to determine whether patients were receiving palliative care or whether patients on antidepressants were at advanced stage of the disease. However, it is less likely that those patients would explain the findings of this study. Although we have split time up into 3-year age bands to account for time-varying confounders, our study is still susceptible to time varying confounders if these correlated closely in time with antidepressant prescription, such as psychotropic drugs, which are

known to have an impact on respiratory morbidities and are likely to be prescribed along with antidepressant.

Although the 30-day pre-exposure period was designed to account for any pneumonia or COPD exacerbation that might lead to prescriptions of antidepressants, there is still a possibility that this strategy might not fully circumvent this issue. This is because both subsequent outcomes (pneumonia and COPD exacerbation) during exposure period might increase the probability of antidepressant prescriptions. However, this strategy has been widely used in the literature [15, 25-27]. Moreover, the current analysis only studied pneumonia and COPD exacerbation events reported in general practice but did not necessarily comprehensively capture events diagnosed at hospital admission and needing subsequent coding in primary care. Therefore, these findings should be interpreted with cautious.

Conclusion

Antidepressants are associated with an increased risk of both pneumonia and COPD exacerbation in the 90 days following a prescription of antidepressant. Although casual relationships cannot be established from this observational study, the findings should raise awareness of if any side effects that may be particularly problematic for the individual. It is also important to consider non-pharmacological therapies that have been shown to improve mental health disorders, such as psychological support.

Figure 1. Diagram representing the study design.

Figure 2. Flow chart to the study

Contributorship statement

Conceptualisation; RS, CB and TM: data curation; RS: formal analysis; RS: investigation; RS, CB and TM: methodology; RS, CB and TM: project administration; RS, CB and TM: resources; RS, CB and TM: supervision; CB and TM: validation; RS, CB and TM: writing of the original draft; all authors contributed to the writing, review and editing.

Funding Statement

None.

Competing interests

All authors have completed the International Committee of Medical Journal Editors (ICMJE) Form for Disclosure of Potential Conflicts of Interest (available upon request from the corresponding author) and declare that the following: C.E.B reports grants from BLF Early COPD Study - various pharma, grants from Pfizer, grants from GSK, other from Chiesi, outside the submitted work; and no financial relationship with any organisation that might have an interest in the submitted work in the previous three years, no other relationship or activity that could appear to have influenced the submitted work.

Ethical approval statement

Ethical approval for this study was provided by an independent Scientific Review Committee (SRC), reference number - 18THIN098

Data Sharing

All data relevant to the study are included in the article or uploaded as supplementary information.

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Table E1. Age-adjusted incidence rate ratio of pneumonia (first event) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressants	No. of exposed cases with Pneumonia	Day 1-30 IRR (95%CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective Antidepressants	1,969	1.54 (1.13 to 2.10)	1.57 (1.18 to 2.08)	1.59 (1.08 to 2.34)	1.51 (1.45 to 2.17)	2.15 (1.86 to 2.48)	0.92 (0.62 to 1.38)
SSRI or NRI	1,218	1.69 (1.21 to 2.35)	1.55 (1.15 to 2.10)	2.51 (1.80 to 3.15)	1.79 (1.46 to 2.18)	1.91 (1.64 to 2.23)	1.02 (0.68 to 1.54)
SSRI	1,143	1.71 (1.21 to 2.41)	1.45 (1.05 to 2.01)	2.60 (1.85 to 3.66)	1.70 (1.38 to 2.08)	1.89 (1.61 to 2.22)	0.95 (0.61 to 1.47)
SNRI	168	1.99 (0.85 to 4.69)	1.42 (0.60 to 2.38)	1.47 (0.46 to 4.66)	1.59 (0.90 to 2.80)	2.20 (1.35 to 3.02)	2.23 (01.03 to 4.84)
TCA	1,318	1.61 (1.17 to 2.21)	1.75 (1.29 to 2.38)	1.28 (0.83 to 1.98)	1.55 (1.26 to 1.90)	1.77 (1.51 to 2.08)	1.28 (0.90 to 1.81)
MAOI	50	1.02 (0.09 to 11.2)	1.22 (0.10 to 12.3)	–	0.95 (0.18 to 4.81)	2.03 (0.66 to 6.21)	1.06 (0.14 to 8.18)

The "Collective Antidepressants" does not equate to the total of all individual class as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of prescription.
2- Day 31-60: A 30-day risk period starting from day 31 after the date of prescription.
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription.
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of prescription until the end of the course).
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course). Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

Table E2. Age-adjusted incidence rate ratio of pneumonia (excluding cases who died within 6 months following the date of pneumonia diagnosis) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressants	No. of exposed cases with Pneumonia	Day 1-30 IRR (95%CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective Antidepressants	1,674	1.33 (1.12 to 1.66)	1.64 (1.30 to 2.07)	1.44 (1.04 to 2.02)	1.48 (1.26 to 1.75)	1.56 (1.37 to 1.77)	0.85 (0.59 to 1.23)
SSRI or SNRI	1,048	1.32 (0.92 to 1.89)	1.44 (1.05 to 1.97)	2.03 (1.41 to 2.91)	1.50 (1.22 to 1.84)	1.51 (1.28 to 1.78)	0.86 (0.55 to 1.34)
SSRI	978	1.26 (0.86 to 1.85)	1.41 (1.02 to 1.95)	2.15 (1.49 to 3.1)	1.55 (1.26 to 1.91)	1.48 (1.26 to 1.75)	0.83 (0.52 to 1.33)
SNRI	157	0.89 (0.30 to 2.70)	1.15 (0.46 to 2.84)	1.72 (0.63 to 4.67)	1.17 (0.64 to 2.15)	1.81 (1.22 to 2.70)	2.03 (0.93 to 4.39)
TCA	1,121	1.24 (0.88 to 1.74)	1.71 (1.27 to 2.30)	1.21 (0.77 to 1.88)	1.42 (1.15 to 1.74)	1.56 (1.32 to 1.83)	1.04 (0.71 to 1.54)
MAOI	45	0.83 (0.08 to 7.86)	0.91 (0.10 to 8.46)	–	0.62 (0.13 to 3.02)	1.70 (0.58 to 4.94)	1.47 (0.36 to 6.14)

The "Collective Antidepressants" does not equate to the total of all individual class as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of prescription.
2- Day 31-60: A 30-day risk period starting from day 31 after the date of prescription.
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription.
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of prescription until the end of the course)
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course).

Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

Table E3. Age-adjusted incidence rate ratio of pneumonia (excluding cases who died within 12 months following the date of pneumonia diagnosis) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressants	No. of exposed cases with Pneumonia	Day 1-30 IRR (95%CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective Antidepressants	1,581	1.32 (1.02 to 1.75)	1.51 (1.18 to 1.92)	1.46 (1.04 to 2.05)	1.43 (1.21 to 1.70)	1.48 (1.30 to 1.68)	0.79 (0.53 to 1.17)
SSRI or SNRI	989	1.33 (0,92 to 1.91)	1.38 (1.01 to 1.89)	1.97 (1.36 to 2.87)	1.48 (1.19 to 1.83)	1.42 (1.20 to 1.68)	0.87 (0.57 to 1.39)
SSRI	922	1.24 (0.85 to 1.84)	1.23 (0.87 to 1.74)	2.02 (1.38 to 2.69)	1.51 (1.22 to 1.86)	1.34 (1.12 to 1.60)	0.86 (0.54 to 1.38)
SNRI	153	0.91 (0.30 to 2.76)	1.16 (0.47 to 2.90)	1.77 (0.65 to 4.82)	1.19 (0.65 to 2.19)	1.75 (1.61 to 2.63)	2.09 (0.97 to 4.54)
TCA	1,065	1.25 (0.88 to 1.76)	1.58 (1.16 to 2.15)	1.19 (0.75 to 1.88)	1.40 (1.13 to 1.72)	1.50 (1.27 to 1.78)	0.95 (0.62 to 1.44)
MAOI	44	0.85 (0.09 to 8.05)	0.93 (0.10 to 8.64)	–	0.64 (0.13 to 3.10)	1.76 (0.60 to 5.16)	1.50 (0.36 to 6.32)

The "Collective Antidepressants" does not equate to the total of all individual class as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of prescription.
2- Day 31-60: A 30-day risk period starting from day 31 after the date of prescription.
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription.
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of prescription until the end of the course)
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course).

Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

Table E4. Age-adjusted incidence rate ratio of COPD exacerbation (first event) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressant	No. of exposed cases with exacerbation	Day 1-30 IRR (95% CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective Antidepressants	18483	1.41 (1.30 to 1.52)	1.21 (1.12 to 1.31)	1.73 (1.59 to 1.89)	1.41 (1.34 to 1.49)	1.34 (1.28 to 1.39)	0.97 (0.85 to 1.10)
SSRI or SNRI	11,770	1.48 (1.34 to 1.64)	1.19 (1.08 to 1.32)	1.73 (1.54 to 1.93)	1.43 (1.34 to 1.53)	1.39 (1.32 to 1.45)	1.12 (0.98 to 1.27)
SSRI	20,885	1.45 (1.30 to 1.61)	1.18 (1.06 to 1.31)	1.62 (1.44 to 1.83)	1.39 (1.30 to 1.49)	1.37 (1.30 to 1.44)	0.97 (0.85 to 1.10)
SNRI	4,128	1.29 (0.97 to 1.72)	1.56 (1.17 to 2.07)	2.24 (1.71 to 2.92)	1.64 (1.38 to 1.95)	1.32 (1.16 to 1.50)	1.26 (0.88 to 1.78)
TCA	23,786	1.36 (1.22 to 1.51)	1.22 (1.10 to 1.35)	1.70 (1.52 to 1.91)	1.23 (1.16 to 1.30)	1.23 (1.17 to 1.31)	0.98 (0.86 to 1.07)
MAOI	416	0.98 (0.48 to 2.00)	1.18 (0.67 to 2.09)	1.62 (0.83 to 13.1)	1.23 (0.83 to 1.81)	1.15 (0.78 to 1.70)	1.07 (0.54 to 2.10)

The "Collective Antidepressants" does not equate to the total of all individual class as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of prescription.
2- Day 31-60: A 30-day risk period starting from day 31 after the date of prescription.
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription.
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90)
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of prescription until the end of the course)
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course).

Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

Table E5. Age-adjusted incidence rate ratio of COPD exacerbation (excluding cases who died within 6 months following the date of COPD exacerbation) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressant	No. of exposed cases with exacerbation	Day 1-30 IRR (95% CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective Antidepressants	17,152	1.07 (1.02 to 1.13)	1.12 (1.07 to 1.18)	1.18 (1.11 to 1.26)	1.12 (1.08 to 1.15)	1.30 (1.27 to 1.33)	0.99 (0.93 to 1.07)
SSRI or SNRI	10,938	1.07 (1.01 to 1.15)	1.13 (1.06 to 1.20)	1.18 (1.08 to 1.28)	1.12 (1.07 to 1.17)	1.32 (1.28 to 1.36)	1.01 (0.92 to 1.08)
SSRI	10,133	1.05 (0.97 to 1.12)	1.10 (1.03 to 1.18)	1.16 (1.06 to 1.27)	1.09 (1.05 to 1.14)	1.30 (1.25 to 1.34)	1.02 (0.94 to 1.11)
SNRI	1,666	1.11 (0.90 to 1.36)	1.24 (1.05 to 1.47)	1.27 (1.02 to 1.58)	1.19 (1.06 to 1.33)	1.32 (1.23 to 1.43)	1.08 (0.87 to 1.34)
TCA	11,114	1.05 (0.98 to 1.12)	1.12 (1.05 to 1.19)	1.22 (1.12 to 1.32)	1.11 (1.07 to 1.16)	1.21 (1.17 to 1.25)	1.02 (0.95 to 1.11)
MAOI	394	1.10 (0.74 to 1.65)	1.61 (1.16 to 2.23)	1.22 (0.74 to 1.95)	1.37 (1.10 to 1.71)	1.19 (0.93 to 1.52)	0.95 (0.62 to 1.45)

The "Collective Antidepressants" does not equate to the total of all individual class as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of prescription.
2- Day 31-60: A 30-day risk period starting from day 31 after the date of prescription.
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription.
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of prescription until the end of the course)
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course).

Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

Table E6. Age-adjusted incidence rate ratio of COPD exacerbation (excluding cases who died within 12 months following the date of COPD exacerbation) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressant	No. of exposed cases with exacerbation	Day 1-30 IRR (95% CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective Antidepressants	16,405	1.07 (1.02 to 1.13)	1.11 (1.05 to 1.16)	1.17 (1.10 to 1.26)	1.12 (1.07 to 1.15)	1.27 (1.24 to 1.30)	0.99 (0.93 to 1.07)
SSRI or SNRI	10,472	1.06 (0.99 to 1.14)	1.11 (1.04 to 1.18)	1.19 (1.09 to 1.30)	1.11 (1.06 to 1.16)	1.29 (1.25 to 1.33)	1.01 (0.92 to 1.09)
SSRI	9,696	1.04 (0.96 to 1.11)	1.09 (1.02 to 1.16)	1.17 (1.07 to 1.28)	1.09 (1.04 to 1.14)	1.26 (1.22 to 1.31)	1.06 (0.94 to 1.12)
SNRI	1,609	1.10 (0.89 to 1.36)	1.22 (1.03 to 1.44)	1.24 (0.99 to 1.55)	1.17 (1.04 to 1.31)	1.29 (1.20 to 1.40)	1.08 (0.87 to 1.35)
TCA	10,638	1.05 (0.97 to 1.12)	1.10 (1.03 to 1.17)	1.21 (1.11 to 1.31)	1.10 (1.06 to 1.15)	1.18 (1.13 to 1.22)	1.02 (0.96 to 1.11)
MAOI	381	1.11 (0.75 to 1.63)	1.61 (1.16 to 2.24)	1.27 (0.79 to 1.02)	1.39 (1.11 to 1.74)	1.24 (0.97 to 1.59)	0.96 (0.62 to 1.49)

The "Collective Antidepressants" does not equate to the total of all individual class as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of prescription.
2- Day 31-60: A 30-day risk period starting from day 31 after the date of prescription.
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription.
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of prescription until the end of the course)
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course).

Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

Table E7. The incidence rate ratio of pneumonia (multiple events) after antidepressant prescription relative to unexposed periods in patients with COPD adjusted for age and seasons, calculated by case series analytical technique, UK, 2004-2015

Antidepressants	No. of exposed cases with Pneumonia	Day 1-30 IRR (95%CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective Antidepressants	1,969	1.79 (1.31 to 2.25)	1.91 (1.43 to 2.55)	2.53 (1.82 to 2.86)	2.10 (1.66 to 2.44)	2.21 (1.90 to 2.57)	1.18 (0.84 to 1.65)
SSRI or SNRI	1,218	1.87 (1.31 to 2.66)	2.21 (1.58 to 3.20)	3.22 (2.26 to 3.81)	2.43 (1.95 to 2.99)	2.06 (1.72 to 2.43)	1.05 (0.70 to 1.59)
SSRI	1,143	1.87 (1.30 to 2.69)	2.32 (1.63 to 3.31)	3.44 (2.43 to 4.86)	1.86 (1.54 to 2.4)	1.97 (1.64 to 2.36)	1.30 (0.89 to 1.88)
SNRI	168	1.30 (0.43 to 3.98)	1.32 (0.43 to 4.01)	1.75 (0.55 to 5.53)	1.20 (0.51 to 2.22)	2.1 (1.35 to 3.18)	1.55 (0.68 to 3.55)
TCA	1,318	1.53 (1.04 to 2.24)	1.99 (1.41 to 2.80)	1.99 (1.66 to 2.38)	1.75 (1.39 to 2.21)	1.97 (1.64 to 2.37)	1.32 (0.96 to 1.83)
MAOI	50	0.99 (0.11 to 9.07)	1.10 (0.12 to 10.07)	–	0.79 (0.17 to 3.66)	2.30 (0.82 to 6.40)	2.35 (0.72 to 7.66)

The "Collective Antidepressants" does not equate to the total of all individual classes as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of the prescription (segment 1).
2- Day 31-60: A 30-day risk period starting from day 31 after the date of the prescription (segment 2).
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription (segment 3).
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of the prescription until the end of the course).
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course).

Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

Table E8. The incidence rate ratio of COPD exacerbation (multiple events) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD adjusted for age and seasons, calculated by case series analytical technique, UK, 2004-2015

Antidepressants	No. of exposed cases with exacerbation	Day 1-30 IRR (95%CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective antidepressant	18,483	1.19 (1.06 to 1.32)	1.21 (1.04 to 1.40)	1.29 (1.16 to 1.43)	1.24 (1.17 to 1.34)	1.47 (1.39 to 1.55)	0.99 (0.87 to 1.11)
SSRI or SNRI	11,770	1.03 (0.94 to 1.13)	1.18 (1.10 to 1.28)	1.25 (1.15 to 1.35)	1.15 (1.11 to 1.20)	1.17 (1.09 to 1.22)	1.04 (0.95 to 1.13)
SSRI	10,919	1.01 (0.91 to 1.31)	1.14 (1.01 to 1.27)	1.21 (1.11 to 1.31)	1.13 (1.07 to 1.20)	1.40 (1.35 to 1.46)	1.04 (0.96 to 1.13)
SNRI	1,753	1.13 (0.85 to 1.48)	1.17 (0.95 to 1.49)	1.45 (1.19 to 1.76)	1.28 (1.11 to 1.46)	1.42 (1.30 to 1.56)	1.05 (0.84 to 1.30)
TCA	11,936	1.14 (1.05 to 1.24)	1.18 (1.09 to 1.27)	1.30 (1.24 to 1.36)	1.16 (1.11 to 1.21)	1.19 (1.12 to 1.24)	1.01 (0.93 to 1.10)
MAOI	416	1.17 (0.79 to 1.72)	1.55 (1.10 to 2.20)	1.20 (0.73 to 1.96)	1.32 (1.04 to 1.67)	1.22 (0.94 to 1.58)	0.78 (0.48 to 1.19)

The "Collective Antidepressants" does not equate to the total of all individual classes as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of the prescription (segment 1).
2- Day 31-60: A 30-day risk period starting from day 31 after the date of the prescription (segment 2).
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription (segment 3).
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of the prescription until the end of the course90 days washout:
6- A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course). Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.