PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	What proportion of initially prescribed antidepressants is still being prescribed chronically after 5 years in general practice? A longitudinal cohort analysis.
AUTHORS	Verhaak, Peter FM; de Beurs, Derek; Spreeuwenberg, Peter

VERSION 1 – REVIEW

REVIEWER	Bruno Stricker Erasmus Medical Center, Rotterdam, the Netherlands
REVIEW RETURNED	22-Jul-2018

GENERAL COMMENTS	This observational study with general practice data concerns the prevalence of chronic use of antidepressants in a Dutch population, and determinants for long-term use. The study found an overall prevalence of use of 7% but much higher prevalences in subgroups from the study population. The message is that chronic antidepressant use is very high, especially in higher age categories. Although reviewer shares the worries about overprescribing these drugs in Western countries, especially for sometimes vague discomfort, I have a number of points to consider. 1. It is a well-known pitfall of cross-sectional studies that prevalences of chronic disease [and chronic drug use] are overestimated. For instance, 45% in group 45-65 yr seems very high. This holds here because combining years led to a substantial loss of study participants [189 out of more than 367 practices]. 2. Multilevel logistic regression analysis was apparently used because of potential differences between practices. However, this does not solve potential confounding within practices or the difference in population disease mix. 3. In my experience [CPRD, IPCI, Mediplus etc], many records miss an indication. How were these figures here. Can the authors say anything about dosage [low dosage of TCA is often gicen for neuropathic pain in elderly]. 4. How many patients started via a psychiatrist/specialist [as notified as a a referral in the medical history ?] 5. In the methods, only diagnosis codes for depression and anxiety are given. What about the other indications in the results section ? Are these among the somatic disorders ? 6. p.10, the outcome was not the number of patients but the

	proportion of cases [?]. Rephrase into a more clear outcome 7. Table 1 is unclear. Does it show that women have a 15% higher chance of having 4 prescriptions each year for 5 years ? Where are those with 4-3-4-3-4-4 etc. ? Are they in the reference group ? 8. The table with Strobe criteria can be n a supplement, rather than main text.

REVIEWER	Michael Moore University of Southampton, UK I have received grants and published in this field. I am currently involved in a study to develop and test an intervention to aid antidepressant discontinuation (NIHR Reduce study)
REVIEW RETURNED	25-Jul-2018

GENERAL COMMENTS	The authors present an analysis of antidepressant prescribing not limited by indication using a large dutch database. It is widely recognised that antidepressant prescribing is rising and one explanation is an increase in longer term prescribing in depression. This study adds to the literature in that it examined all antidepressant prescribing regardless of indication. There are limitations with this kind of analysis since assumptions are made regarding what constitutes prescribing (4 or more prescriptions per year) and also limitations in the coding of prescription indication. Nevertheless the analysis is able to add useful information to the debate on longer term use of antidepressants. Longer term use is more likely with depression and in women. 7% of adults received a prescription in the index year of which 42% received a prescription for the subsequent 4 years. The authors need to be more clear about the population being studied, as I understood it they only examined data on those age 18 and over. So the population of participants in the abstract should include this. The first line of the results should include this as should the first line of the discussion (e.g. 7% of the adult general practice population). The introduction appeared balanced and made the case for the study. The methods and data analysis were clearly described. The authors provided an appropriate summary of the main findings and comparison with previous literature. There is much more extensive literature on the potential risks of longer term exposure to antidepressants (self harm, suicide, falls, fractures, fits, cv outcomes, GI outcomes and global mortality-search on Coupland antidepressants) and I think some reference to this would be helpful. The observation regarding practice effect on antidepressant use is striking and the authors do consider this in the discussion and offer prescription review as one explanation. An alternative is simply the propensity to prescribe with some practices having higher initiation rates, this behaviour is linked to other prescribing (antibiotics) and the authors could touch on alternative explanations. The authors do consider discontinuation but stopping these drugs is not easy and may require more than just a prescription review. There are few studies yet published in this area but one of them using a simple intervention failed to increase discontinuation so maybe a little more circumspection is needed in this section.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Bruno Stricker
Institution and Country: Erasmus Medical Center, Rotterdam, the Netherlands
Please state any competing interests or state 'None declared': None

This observational study with general practice data concerns the prevalence of chronic use of antidepressants in a Dutch population, and determinants for long-term use. The study found an overall prevalence of use of 7% but much higher prevalences in subgroups from the study population. The message is that chronic antidepressant use is very high, especially in higher age categories. Although reviewer shares the worries about overprescribing these drugs in Western countries, especially for sometimes vague discomfort, I have a number of points to consider.

page 10:

1. It is a well-known pitfall of cross-sectional studies that prevalences of chronic disease [and chronic drug use] are overestimated. For instance, 45% in group 45-65 yr seems very high. This holds here because combining years led to a substantial loss of study participants [189 out of more than 367 practices].

We have expressed ourselves not carefully enough in the first paragraph of the results. We reported 71/1000 registered patients with antidepressants (AD) in 2011. We then intended to present the age-sex distribution of the patients, using AD in 2011 and reported a sex distribution between women and men of 2:1 and an age distribution between 18-44, 45-64 and 65+ of 30:45:25. Hence, not 45% of 45-64 year old patients were using AD, but of the AD users, 45% was 45-64 years old.

We adjusted the paragraph as follows:

The results about long-term antidepressants use are based on data for 326,025 patients from 189 practices with valid prescription data for all five years of the study. In 2011, antidepressants were prescribed to ±71/1000 registered patients aged ≥18 years. About two-thirds of the prescriptions were for women and about one-third were for men. 30% of antidepressants were prescribed to, those aged 18–44 years, 45% to 45–64 years old and 25% to those above65 years. The distribution of the population at risk in 2011 was 43: 37: 20

Page 9:

2. Multilevel logistic regression analysis was apparently used because of potential differences between practices. However, this does not solve potential confounding within practices or the difference in population disease mix.

Multilevel logistic regression was used to solve potential confounding at practice level accounting for differences in case-mix and inter-doctor variation. Additionally, at the patient level, we controlled for patients' sex, age and indication for AD

3. In my experience [CPRD, IPCI, Mediplus etc], many records miss an indication. How were these figures here. Can the authors say anything about dosage [low dosage of TCA is often gicen for neuropathic pain in elderly].

In 71% of the cases, prescription records could be merged with morbidity records, containing the indication.
As we report in our discussion, our analyses have been done on a final dataset with complete data (after loss by missing indications and loss by not complete 5-years registration) that is only a fraction of the numbers at risk in the separate datasets on prescription per year: from more than a million each year to 326,025 patients in the final dataset. We have added the specific loss of data because of missing indications in the limitations section:

Page 14 :
Limitations

Although prescription data were available of 1–2 million patients, substantial numbers were lost by merging prescription and morbidity data (providing us with the indication) and by merging the data over several years (e.g., some practices were not part of the NPCD for the full period and some patients were not registered for the full period). Therefore, the final analyses were conducted on 326,025 cases from 189 practices.

In our data, no information about dosage is available. In another study I conducted recently with NPCD prescription data used in this study merged with a pharmaceutical database (concerning depressed elderly > 60 years), we found that 1.2% of TCAs was prescribed below the usual one day dose, compared with 4.7% of SSRIs and 2.4% of other AD.

4. How many patients started via a psychiatrist/specialist [as notified as a a referral in the medical history ?]

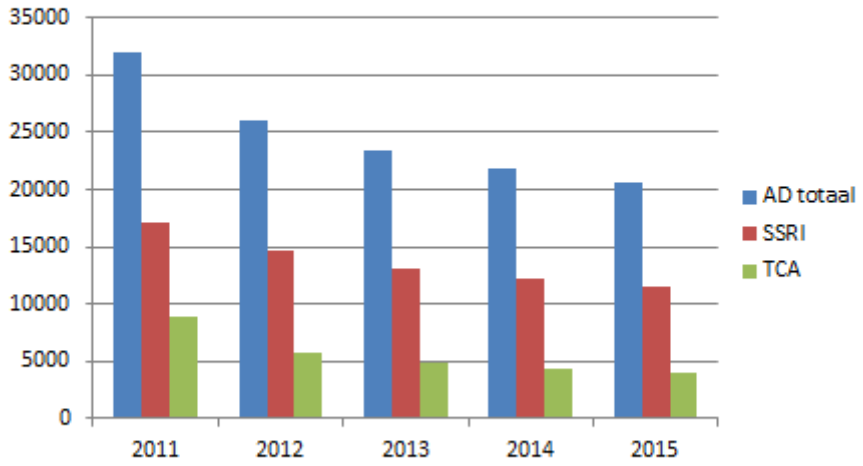
Again this information is not available in our dataset. In the above mentioned study on depressed elderly, 86% of TCA, 94% of SSRI and 80% of other AD were prescribed by the general practitioner

Page 8:
5. In the methods, only diagnosis codes for depression and anxiety are given. What about the other indications in the results section ? Are these among the somatic disorders ?

No, about 20% of all AD were prescribed for psychological indications, other than depression or anxiety. As we were focussed on anxiety and depression we did not include this category in the analysis.

Page 10:
6. p.10, the outcome was not the number of patients but the proportion of cases [?]. Rephrase into a more clear outcome

Figure 1: number of AD-users in 2011, who used AD chronically (≥ 4 prescription/year) in the subsequent years



The number of patients was the outcome. We thought it would be easier to compare the number of patients still using ≥4 prescriptions for AD, SSRI and TCA when we present the proportion. The figure above gives the number of patients who kept getting ≥ 4 prescriptions each year (having received ≥ 4 prescriptions all the previous years).

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7. Table 1 is unclear. Does it show that women have a 15% higher chance of having 4 prescriptions each year for 5 years ? Where are those with 4-3-4-3-4-4 etc. ? Are they in the reference group ?

The dependent variable, chronic prescription, is a dichotomous variable. Regarding this dependent variable in the logistic regression (4 of more prescriptions each year), only 4-4-4-4-4 are considered chronic (=1). All others are considered not-chronic (=0).

Table 1 shows the odds for females (compared with men) to receive such a chronic dosage. The same is for age: the odds for 19-44 compared to 65+ and the odds for 45-64 compared to 65+ are presented.

There is a mistake in table 1 regarding the variable “disorder”. This should be : anxiety (as compared to no anxiety), depression (as compared to no depression) and somatic disorder (as compared to no somatic disorder).

The improved table:

Table 1. Odds for Receiving an Antidepressant for Each Year between 2011 and 2015 after Receiving the First Prescription in 2011

Variable	*Coefficient*	*SE*	*p-value*	*OR*	*95% CI*	
Sex (ref = male)						
Female	***0.1400***	***0.0409***	***0.0006***	***1.15***	***1.06***	***1.25***
Age (ref = 65+ years)						
19–44	***-0.1161***	***0.0541***	***0.0320***	***0.89***	***0.80***	***0.99***
45–64	***0.2320***	***0.0476***	***0.0000***	***1.26***	***1.15***	***1.38***
Disorder						
Anxiety (ref = no anxiety)	***0.3196***	***0.0558***	***0.0000***	***1.38***	***1.23***	***1.54***
Depression (ref = no depression)	***0.3224***	***0.0488***	***0.0000***	***1.38***	***1.25***	***1.52***
Somatic disorder (ref = no somatic disorder)	***0.0153***	***0.0565***	***0.7864***	***1.02***	***0.91***	***1.13***
Practice variance	***6.763***	***0.8653***				
ICC	***0.67***					
Constant	***-4.2012***	***0.2276***				

Abbreviations: CI, confidence interval; ICC, intraclass correlation coefficient; OR, odds ratio; SE, standard error

8. The table with Strobe criteria can be n a supplement, rather than main text.

We will remove the table

Reviewer: 2
Reviewer Name: Michael Moore
Institution and Country: University of Southampton, UK
Please state any competing interests or state 'None declared': I have received grants and published in this field. I am currently involved in a study to develop and test an intervention to aid antidepressant discontinuation (NIHR Reduce study)

The authors present an analysis of antidepressant prescribing not limited by indication using a large Dutch database. It is widely recognised that antidepressant prescribing is rising and one explanation is an increase in longer term prescribing in depression. This study adds to the literature in that it examined all antidepressant prescribing regardless of indication. There are limitations with this kind of analysis since assumptions are made regarding what constitutes prescribing (4 or more prescriptions per year) and also limitations in the coding of prescription indication.

We agree with the reviewer that our definition of "chronic prescribing" as having received at least 4 AD-prescriptions each year and that for 2011 and four consecutive years is somehow arbitrary. We have added this as a limitation in the discussion section. The limitation of GP coding has already been mentioned there

Page 14:
Limitations

Although prescription data were available of 1–2 million patients, substantial numbers were lost by merging prescription and morbidity (providing us with the indication) data and by merging the data over several years (e.g., some practices were not part of the NPCD for the full period and some patients were not registered for the full period). Therefore, the final analyses were conducted on 326,025 cases from 189 practices. This final sample included more patients aged >45 years and fewer men compared with the original database, so may have not been truly representative of the Dutch population. Our definition of chronic prescribing (at least four prescriptions in all years) is arbitrary. However, when we increase the threshold to e.g. five prescriptions a year, chronic users having a repeat prescripton each three months would not be included. When we decrease the threshold to one prescription in each of five years, the number of "chronic users" increases to 65%. Morbidity data were also highly dependent on the coding registered by the GP. It is well known that GP variations in diagnosis are large and that sensitivity can be suboptimal (24). However, the antidepressant prescribing data were not dependent on the morbidity coding, which is a major strength.

Because we add with the changing threshold a new result in our discussion, we have added this additional finding of 65% chronic users when a lower threshold is used to the result section as well:

Page 10-11:
Of those who received at least four prescriptions in 2011, we found that 65% were still receiving at least four prescriptions per year at two years and that 58% were still receiving them at three years. However, only 42% of patients received at least four prescriptions of antidepressants through each year from 2011 to 2015; by SSRI and TCA use, this was 38% and 35%, respectively (Figure 1).
When we lower the threshold for chronic prescribing to at least one prescription a year, 65% of patients receiving an AD prescription in 2011 kept receiving yearly at least one

Nevertheless the analysis is able to add useful information to the debate on longer term use of antidepressants. Longer term use is more likely with depression and in women. 7% of adults received a prescription in the index year of which 42% received a prescription for the subsequent 4 years.

The authors need to be more clear about the population being studied, as I understood it they only examined data on those age 18 and over. So the population of participants in the abstract should include this. The first line of the results should include this as should the first line of the discussion (e.g. 7% of the adult general practice population).

We have added the age restriction to the abstract, the result section and the discussion section

Page 3:
Objectives. Antidepressant prescribing almost doubled in the Netherlands between 1996 and 2012, which could be accounted for by longer continuation after the first prescription. This might be problematic given a growing concern of large-scale antidepressant dependence. We aimed to assess the extent and determinants of chronic antidepressant prescribing among patient aged 18 years and older. We hypothesize a relatively large prevalence of chronic (> 2 years) prescription.

Page 10:
RESULTS

The results about long-term antidepressants use are based on data for 326,025 patients (older than 18 years) from 189 practices with valid prescription data for all five years of the study. In 2011, antidepressants were prescribed to ±71/1000 registered patients aged ≥18 years.

Page 12:
DISCUSSION

Antidepressants were prescribed to almost 7% of the general practice population, aged 18 years and older, in this study.

The introduction appeared balanced and made the case for the study.
The methods and data analysis were clearly described.
The authors provided an appropriate summary of the main findings and comparison with previous literature.

Thank you for this positive evaluation

Page 12:
There is much more extensive literature on the potential risks of longer term exposure to antidepressants (self harm, suicide, falls, fractures, fits, cv outcomes, GI outcomes and global mortality- search on Coupland antidepressants) and I think some reference to this would be helpful.

Thank you for this recommendation. We have studied the several studies of Carol Coupland, Trevor Hill and others and we have incorporated their findings regarding negative side effects and potential risks of AD use in our conclusion

Page 12-13:
Antidepressant medication use is a prominent topic of discussion in society. Opponents of their widespread use, such as Gøtzsche(24) and Greenberg(25), point to the lack of efficacy and the possible harms of long-term use. Risk of falls and fractures, upper gastro-intestinal bleed and epilepsy/seizures is increased among adult (20-64 year)AD users(26, 27). A higher

risk for falls, attempted suicides, stroke, fracture and epilepsy is reported for older people, using AD(28).

26. Coupland C, Hill T, Morriss R, Moore M, Arthur A, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in people aged 20-64 years: cohort study using a primary care database. BMC Med. 2018;16(1):36.

27. Hill T, Coupland C, Morriss R, Arthur A, Moore M, Hippisley-Cox J. Antidepressant use and risk of epilepsy and seizures in people aged 20 to 64 years: cohort study using a primary care database. BMC Psychiatry. 2015;15:315.

28. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ. 2011;343:d4551.

The observation regarding practice effect on antidepressant use is striking and the authors do consider this in the discussion and offer prescription review as one explanation. An alternative is simply the propensity to prescribe with some practices having higher initiation rates, this behaviour is linked to other prescribing (antibiotics) and the authors could touch on alternative explanations.

Thank you for the suggestion to look to other, practice bound prescribing routines. We have incorporated that point in our discussion

Page 14:
The large practice variation that we found suggests long term AD prescribing to be a practice policy, as has been reported in the case of antibiotics prescribing(37), where patient characteristics could not explain the variation at practice level as well(38). Medication reviews may reflect such a policy, possibly by routine consultations between GP and pharmacist. As proven in other studies, medication reviews may be routine in some practices, leading to reduced long-term antidepressant use, but may non-existent in other practices, with opposing results (39).

37. Kim JK, Chua ME, Ming JM, Braga LH, Smith GHH, Driver C, et al. Practice variation on use of antibiotics: An international survey among pediatric urologists. J Pediatr Urol. 2018.

38. Manne M, Deshpande A, Hu B, Patel A, Taksler GB, Misra-Hebert AD, et al. Provider Variation in Antibiotic Prescribing and Outcomes of Respiratory Tract Infections. South Med J. 2018;111(4):235-42.

*The authors do consider discontinuation but stopping these drugs is not easy and may require more than just a prescription review. There are few studies yet published in this area but one of them using a simple intervention failed to increase discontinuation so maybe a little more circumspection is needed in this sectio*n.

We agree with the difficulties associated with stopping AD. We have failed to find examples of successful discontinuation on the long term, so we stick to the few suggestions (tapering strips, prescription review) by the lack of more promising suggestions

VERSION 2 – REVIEW

REVIEWER	Michael Moore University of Southampton UK
REVIEW RETURNED	20-Sep-2018

GENERAL COMMENTS	Thank you the authors have addressed the concerns in my original review.