

# BMJ Open What proportion of initially prescribed antidepressants is still being prescribed chronically after 5 years in general practice? A longitudinal cohort analysis

Peter F M Verhaak,<sup>1,2</sup> Derek de Beurs,<sup>1</sup> Peter Spreeuwenberg<sup>1</sup>

**To cite:** Verhaak PFM, de Beurs D, Spreeuwenberg P. What proportion of initially prescribed antidepressants is still being prescribed chronically after 5 years in general practice? A longitudinal cohort analysis. *BMJ Open* 2019;**9**:e024051. doi:10.1136/bmjopen-2018-024051

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2018-024051>).

Received 19 May 2018

Revised 5 November 2018

Accepted 15 November 2018



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<sup>1</sup>Netherlands Institute of Health Services Research (NIVEL), Utrecht, The Netherlands

<sup>2</sup>Department of General Practice, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

## Correspondence to

Dr Peter F M Verhaak;  
[p.verhaak@nivel.nl](mailto:p.verhaak@nivel.nl)

## ABSTRACT

**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 hypothesise a relatively large prevalence of chronic (>2 years) prescription.

**Design** A longitudinal observational study based on routinely registered prescription data from general practice.

**Setting** 189 general practices in the Netherlands.

**Participants** 326 025 patients with valid prescription data for all 5 years of the study.

**Outcome measures** Primary outcome measure: the number of patients (N) receiving at least four antidepressant prescriptions in 2011, as well as during each of the four subsequent years. Secondary outcome measure: the above, but specified for selective serotonin reuptake inhibitors and for tricyclic antidepressants.

**Results** Antidepressants were prescribed to almost 7% of our 326 025 participants each year. They were prescribed for depression (38%), anxiety (17%), other psychological disorders (20%) and non-psychological indications (25%). Antidepressants were prescribed in all 5 years to the 42% of the population who had at least four prescriptions dispensed in 2011. Chronic prescribing was higher among women than men, for those aged 45–64 years than for those aged >65 years and for those treated for depression or anxiety than for non-psychological indications (eg, neuropathic pain). Chronic prescribing also varied markedly among general practices.

**Conclusion** Chronic antidepressant use is common for depression and for anxiety and non-psychological diagnoses. Once antidepressants have been prescribed, general practitioners and other prescribers should be aware of the risks associated with long-term use and should provide annual monitoring of the continued need for therapy.

## INTRODUCTION

Antidepressants are recommended for the treatment of both major depression and anxiety disorders in most clinical guidelines.

## Strengths and limitations of this study

- Large database, largely representative for Dutch population.
- Routinely collected prescription data, reliable because needed for delivery by pharmacist.
- Morbidity data, needed for prescription *indication*, are dependent on coding by general practitioners.

Based on evidence that they are more efficacious than placebo in adults with major depressive disorder,<sup>1</sup> antidepressants were used by more than 12% of the adult US population in 2013, with the prevalence in women being approximately double than in men, and increasing with age.<sup>2</sup> However, antidepressants are also prescribed off-label for disorders other than depression, most often in nursing homes and for older populations, with evidence supporting off-label use available in Dutch, UK, Swedish, Canadian and US populations.<sup>3–7</sup> In the Netherlands, selective serotonin reuptake inhibitors (SSRIs) have typically been prescribed off-label for other psychological problems, while tricyclic antidepressants (TCAs) have tended to be preferred for pain disorders.<sup>3</sup>

Dutch guidelines for the treatment of depression in general practice initially recommend watchful waiting and non-medical therapy, except for comparably rare presentations with suicidal ideation or psychosis. If symptoms persist, antidepressant medication can be considered if a depressive disorder is present, but not merely for the presence of depressive symptoms.<sup>8</sup> According to the Dutch College of General Practitioners, psychopharmacological agents should not be used to treat anxiety symptoms, but they are considered to have efficacy for anxiety disorders.<sup>9</sup> Despite this cautious approach, the prevalence of antidepressant

prescribing almost doubled between 1996 and 2012 in the Netherlands.<sup>10</sup>

In the 1990s, there was an increase in the prevalence and incidence of SSRI use, with more patients starting SSRIs and receiving antidepressant therapy for longer durations.<sup>11–16</sup> An explanation for this increase in antidepressant prescribing might, therefore, be longer continuation after initial treatment. For example, Mars *et al*<sup>14</sup> reported that the incidence of antidepressant prescriptions was stable between 1995 and 2011, but that the prevalence more than doubled in the same period. In the Netherlands, Noordam *et al*<sup>10</sup> showed the same trends between 1996 and 2012. Given that equal numbers start therapy each year, but the total number of users increases, the increase in prevalence might reflect longer continuation of therapy.

Long-term antidepressant use has been reported in several studies that have used primary care databases. In a recent Dutch study, antidepressants were used for long term (>15 months) by 30% and 44% in the periods 1995–2005 and 2005–2015, respectively.<sup>17</sup> In a study of a primary care database from Scotland, 40% of patients received SSRIs for longer than 180 days, and it was shown that practice variation accounted for most of the differences in prescribing durations.<sup>18</sup> In UK general practice, it has been reported that the mean durations of antidepressant treatment were 4.8 years for depression, 7.4 years for anxiety and 5 years for pain.<sup>19</sup> Read *et al* also reported that 52% of a New Zealand sample continued antidepressant treatment for 3 or more years, with this proportion increasing with age,<sup>20</sup> while Ambresin *et al* reported that therapy was continued for more than 2 years in 47% of antidepressant users. However, Sihvo *et al*<sup>12</sup> reported that only 14% of antidepressant users in Finland continued therapy for more than 2 years. The results of an Australian study were consistent with this latter finding, showing that 50% and 61% of new antidepressant users had discontinued therapy within 6 and 12 months, respectively, and that only 20% had continued therapy at 3 years. Receiving psychological or psychiatric care was associated with longer antidepressant use, while the presence of either cancer or multiple morbidities was associated with an increased likelihood of shorter treatment duration.<sup>21</sup>

Little is known about the factors associated with long-term antidepressant use. Moreover, although current Dutch guidelines recommend stopping treatment 6 months after remission,<sup>9</sup> they are not explicit about how to stop or about when long-term continuation is appropriate. Regular monitoring and medication reviews are also recommended when prescribing continues in the long term. Overall, the current real-world situation raises many questions about the appropriateness of the current guidelines for clinical practice. Therefore, we aimed to assess the extent of chronic antidepressant prescribing and to evaluate the determinants of that chronic prescribing. Our main research questions were what proportion of patients were prescribed antidepressants continuously during a 5 year period and what

predicted long-term prescribing? We also wanted to answer four specific sub-questions<sup>1</sup>: What proportions of patients continue therapy for more than 2, 3 and 4 years?<sup>2</sup> Are there differences in long-term prescribing by sex and age?<sup>3</sup> Are there differences in long-term prescribing by the indication for antidepressant prescribing? and<sup>4</sup> Are there differences in long-term prescribing between SSRIs and TCAs?

## METHOD

### Study design and participants

This was a cross-sectional observational study based on the data obtained in the NIVEL Primary Care Database (NPCD). Participants were all patients aged 18 years and older, registered in Dutch general practices participating in the NPCD.

### NIVEL database

Data were obtained from the NPCD. This database contains routinely collected data on symptoms, diagnoses, medications and laboratory results related to the consultations for patients from 367 to 519 general practices (the number of participating practices each year varied) in the Netherlands. All non-institutionalised inhabitants of the Netherlands are registered at a general practice, and the general practices and patient populations in the NPCD have proven representativeness for wider Dutch society, although group practices are somewhat over-represented. For this study, we used data for adult patients aged 18 years and older, covering the period 2011–2015.

### Patient and public involvement

Patients and public were not involved in design or conduct of the study.

## Data

### Prescriptions

Each medication prescription, including repeat prescriptions, were recorded by date and code based on the Anatomical Therapeutic Chemical Classification System (ie, ATC codes). The following codes for antidepressants were included: N06AA (TCA), N06AB (SSRI), N06AF (non-selective monoamine oxidase inhibitors (MAOI)), N06AG (type A MAOI) and N06AX (other antidepressants).

### Diagnosis

Symptoms and diagnoses related to a given prescription were classified according to the International Classification of Primary Care,<sup>22</sup> using the P.xxxx codes for psychological symptoms and disorders. Codes P03 (depressive symptom) and P76 (depressive disorder) were taken to mean 'depression', while codes P01 (feeling nervous) and P74 (anxiety disorder) were taken to mean 'anxiety'. Codes not in Chapter P were recorded as somatic symptoms and diagnoses.

### Prevalence of antidepressant prescription

For each year, we calculated the number of patients (N) prescribed an antidepressant, SSRI or TCA and whether the prescription was linked to a record of depression, anxiety or other disorder (non-psychological/somatic). We recorded the number of patients with a prescription per 1000 patient-years, linked to age and gender, within a certain year. These data allow for extrapolation to the Dutch population based on a yearly weighted population at risk in the NPCD, which varied annually from 1 087 395 to 1 641 806 patient-years.

### Long-term use

To calculate the numbers of patients using prescriptions for several years, the data for different years were merged to give the number of patients with a recorded antidepressant prescription and diagnosis of depression in each of the study years (ie, 2011, 2012, 2013, 2014 and 2015). Merging data for the 5 subsequent years resulted in a loss of cases, because the NIVEL database did not include all practices or patients in some years.

### Statistical analysis

We use multilevel logistic regression with patients clustered by general practice. The models were then analysed in MLwiN V.2.30,<sup>23</sup> using the options 'PQL' and 'second order' ('first order' was used if the model failed to converge), and 'constrained level one variance'.

### Outcome measures

The main outcome measure was the number of patients (N) receiving at least four antidepressant prescriptions in 2011, as well as during each of the 4 subsequent years. We assumed that receiving four or more prescriptions in 1 year was consistent with chronic use, based on the common Dutch practice to prescribe antidepressants on repeat prescriptions for 3-month periods.

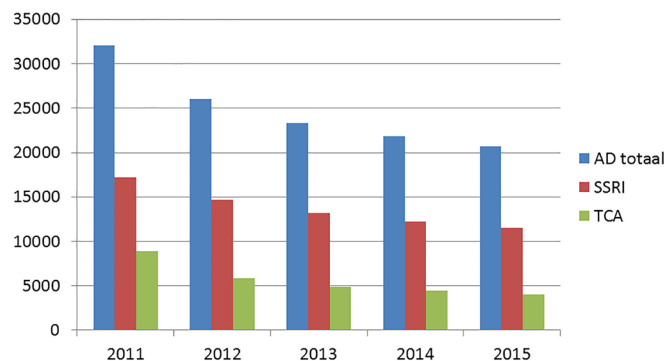
### Independent variables

At level 1, we controlled for variation at the practice level. At level 2, the patient level, we considered age in 2011, sex and diagnosis associated with the prescription (ie, depression, anxiety or somatic problem).

## 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 5 years of the study. In 2011, antidepressants were prescribed to  $\pm 71/1000$  registered patients aged  $\geq 18$  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 above 65 years. The distribution of the population at risk in 2011 was 43:37:20.

Of the antidepressants prescribed, SSRIs and TCAs accounted for 52% and 28%, respectively. Overall, 38% were prescribed for depression, 17% for anxiety, 20%



**Figure 1** Number of AD-users in 2011, who used AD chronically ( $\geq 4$  prescription/year) in the subsequent years. SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants. ■ Total antidepressants. ■ SSRI. ■ TCA.

for other psychological diagnoses and 25% for somatic indications. SSRIs were more frequently prescribed for depression (47%) and anxiety (23%), while TCAs tended to be prescribed frequently for somatic disorders (44%) or other psychological disorders (21%). The main somatic indications for TCAs were generalised pain (1.7%), lumbago (2.5%), low back pain with radiation (2.5%), headache (2.7%), tension headache (2%), neuropathy (4.8%), sleeping problems (4.1%) and type 2 diabetes mellitus (1.5%).

The data for the proportions of patients who continued to be prescribed antidepressants in each year after 2011 are summarised in figure 1 and table 1.

Of those who received at least four prescriptions in 2011, we found that 65% were still receiving at least four prescriptions per year at 2 years and that 58% were still receiving them at 3 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 prescription each year to 2015.

The odds for receiving antidepressants over 5 consecutive years based on patients' characteristics are shown in table 1.

Specifically, the odds were higher for women than for men, for patients aged 45–65 years and for a diagnosis of anxiety or depression. However, there was substantial practice variation, meaning that the proportions were even larger in some practices but much smaller in others. Online supplementary tables 1 and 2 in the appendix show similar patterns for SSRIs and TCAs analysed separately, though with some exceptions. A diagnosis of anxiety, for example, did not affect long-term SSRI prescribing. Also, sex and older age affected long-term TCA prescribing, but indication did not.

**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	P<0.001	1.15	1.06 to 1.25
Age (ref=65+ years)					
19–44	–0.1161	0.0541	0.0320	0.89	0.80 to 0.99
45–64	0.2320	0.0476	P<0.001	1.26	1.15 to 1.38
Disorder					
Anxiety (ref=no anxiety)	0.3196	0.0558	P<0.001	1.38	1.23 to 1.54
Depression (ref=no depression)	0.3224	0.0488	P<0.001	1.38	1.25 to 1.52
Somatic disorder (ref=no somatic disorder)	0.0153	0.0565	0.7864	1.02	0.91 to 1.13
Practice variance	6.763	0.8653			
ICC	0.67				
Constant	–4.2012	0.2276			

ICC, intraclass correlation coefficient.

## DISCUSSION

Antidepressants were prescribed to almost 7% of the general practice population, aged 18 years and older, in this study. The main indication was for depression (38%), but anxiety (17%), other psychological disorders (20%) and non-psychological indications, mostly pain related (25%), were frequent. Interestingly, nearly half of the population (42%) received antidepressants throughout all 5 years of the study. The odds of long-term use were higher for women than for men, for those aged 45–64 years than for those aged ≥65 years and for those with psychological indications than for those with non-psychological indications. However, long-term prescribing habits varied markedly among practices.

Consistent with our results, Huijbregts *et al*<sup>17</sup> reported that about 44% of antidepressant use was long term (defined as >15 months) based on one region in the Netherlands. In our larger nationwide population, with a much stricter definition of long-term use as 5 years of continuous receipt of four antidepressant prescriptions a year, 42% used antidepressants chronically. We also found the same risk factors for long-term use, with female sex, older age and having a diagnosis of anxiety or depression being most important. However, in contrast with their data, we found that the group aged 45–64 years was at higher risk than the group aged ≥65 years.

Antidepressant medication use is a prominent topic of discussion in society. Opponents of their widespread use, such as Gøtzsche<sup>24</sup> and Greenberg,<sup>25</sup> point to the lack of efficacy and the possible harms of long-term use. Risk of falls and fractures, upper gastrointestinal bleed and epilepsy/seizures is increased among adult (20–64 years) AD users.<sup>26–27</sup> A higher risk for falls, attempted suicides, stroke, fracture and epilepsy is reported for older people, using AD.<sup>28</sup> By contrast,

proponents, such as Allan H Young and John Crace, cited in Gøtzsche *et al*,<sup>29</sup> consider psychiatric drugs to be as beneficial as other medical treatments and argue that concerns about long-term use are overinflated. So, just how harmful is antidepressant use in the long term? We know that antidepressant use is now on a large scale, partly for depression and anxiety, but also for other psychological and non-psychological indications. This is important to understand because antidepressants have only demonstrated slight effectiveness for the treatment of depression and anxiety,<sup>30</sup> and have unknown efficacy for those other disorders. Although some patients will benefit from long-term use,<sup>31</sup> at best, such use may be unhelpful to many patients. Indeed, there is no conclusive evidence about the safety of antidepressants over years, and Andrews *et al* even claim that such use will generally do more harm than good by disrupting key adaptive processes regulated by serotonin.<sup>32</sup> Harm may also be expected among older antidepressant users who are at risk of polypharmacy; antidepressant use, for example, has an important negative impact on the Drug Burden Index, an indicator of the cholinergic and sedative stress imposed by medication.<sup>33</sup>

At first glance, general practitioners (GPs) might view antidepressant treatment as a good initial therapy that is in the patient's interest. Despite the potential risks, and perhaps because of the lack of clear evidence of harm, or reports of continuation problems, the option of long-term use also remains acceptable.<sup>34</sup> This is compounded by the fact that, when patients have benefited from relief of depressive symptoms, they often become reluctant to stop therapy for fear of becoming depressed again.<sup>35</sup> Therefore, large groups of patients with single episodes of low severity depression, who probably received effective antidepressant therapy in the beginning, progress to long-term use with less clearly defined benefits.

A way to prevent unnecessary long-term antidepressant use might be to institute annual medication reviews. This issue is especially pertinent given that proactive medication reviews have been reported to become increasingly sparse the longer antidepressants have been prescribed, especially when not for an overt mental health reason.<sup>36</sup>

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,<sup>37</sup> where patient characteristics could not explain the variation at practice level as well.<sup>38</sup> 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 be non-existent in other practices, with opposing results.<sup>39</sup> New initiatives, such as the introduction of tapering strips<sup>40</sup> or the continuous monitoring of patients who discontinue antidepressants, could offer new insights and help develop recommendations for GPs to help patients stop treatment when it is no longer needed. Developing a consensus on how to discontinue antidepressants in general practice could reduce practice variation and decrease the proportions of patients who continue to take antidepressants beyond the required period for acute treatment and stabilisation.

### 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 (eg, 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, for example, five prescriptions a year, chronic users having a repeat prescription each 3 months would not be included. When we decrease the threshold to one prescription in each of 5 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.<sup>41</sup> However, the antidepressant prescribing data were not dependent on the morbidity coding, which is a major strength.

### Conclusions

Chronic antidepressant use was common in this cohort, with 42% of patients prescribed antidepressants in 2011 continuing to use them at 5 years. Although the initial prescribing of antidepressants might have become stable, patients continue to take their prescriptions for many

years, though with considerable variation in this trend between practices. It was noteworthy that depression was not the main indication for antidepressant prescription, with a quarter of prescriptions being for non-psychological indications and a fifth being for anxiety. Therefore, we conclude that the high levels of antidepressant use can only partly be attributed to depression, with the main issue appearing to be an increase in chronic usage after initial prescribing. GPs and other prescribers should be aware of the risks of long-term antidepressant use and ensure annual monitoring to reduce unnecessary prescribing.

**Acknowledgements** We thank Robert Sykes ([www.doctored.org.uk](http://www.doctored.org.uk)) for providing editorial services.

**Contributors** PFMV conceived the concept, analysed the data and wrote the paper. DdB discussed the concept and commented on all drafts. PS performed the multilevel analysis and commented on all drafts.

**Funding** All authors are appointed by the Netherlands Institute of Health Services Research and had access to NIVEL Primary Care Database.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** This study has been approved according to the governance code of Nivel Primary Care Database, under number NZR-00318.012. European law allows the use of electronic health records for research purposes under certain conditions. According to this legislation, neither obtaining informed consent from patients nor approval by a medical ethics committee is obligatory for this type of observational studies containing no directly identifiable data. This study was conducted in accordance with the requirements of the Helsinki Declaration. Patients in participating practices are informed about participation of the practice in NPCD with an opportunity for opting out.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** We have got access to the anonymous database under condition that data will be used only for the answering of the current research questions. Researcher interested in our analyses can contact the first author or Dr Derek de Beurs (second author) at NIVEL for possible secondary analysis of our data set.

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