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Long-term Antidepressant Prescribing in General Practice

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Complete List of Authors:	Verhaak, Peter; Netherlands Institute of Health Services Research; Universitair Medisch Centrum Groningen, general practice de Beurs, Derek; Netherlands Institute of Health Services Research Spreeuwenberg, Peter; Netherlands Institute of Health Services Research
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Long-term Antidepressant Prescribing in General Practice

Article category: Epidemiology

Verhaak PFM[1], Beurs DP[2] de, Spreeuwenberg P[2]

[1] Netherlands institute of health services research (NIVEL), Utrecht, the Netherlands

University of Groningen, University Medical Center Groningen, Department of General Practice, Groningen, the Netherlands

[2] Netherlands institute of health services research, Utrecht, the Netherlands

Corresponding author:

Prof. dr P. F. M. Verhaak

Netherlands institute of health services research (NIVEL)

P.O. Box 1568

3500 BN Utrecht

The Netherlands

p.verhaak@nivel.nl

What is already known

- Antidepressant use increased considerably the past twenty years
- This increase was among others attributed to longer continuation of antidepressant treatment

What this study adds

- Of the patients prescribed an antidepressant in 2011, treatment was chronic in 42% during at least four following years
- Patients aged 45–64 years had the highest odds of being prescribed antidepressants in the long term.
- There is substantial practice variation in chronic antidepressant prescribing.

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. We hypothesize a relatively large prevalence of chronic (> 2 years) prescription.

Setting. 189 General practices in the Netherlands

Participants. 326,025 patients with valid prescription data for all five 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 Inhibators and for Tricyclic Antidepressants

Results. Antidepressants were prescribed to almost 7% of our 326,025 participants each year. They were prescribed for depression (38%), for anxiety (17%), other psychological disorders (20%) and non-psychological indications (25%). Antidepressants were prescribed in all five 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 (e.g., neuropathic pain). Chronic prescribing also varied markedly among general practices.

Conclusion. Chronic antidepressant use is common not only for depression but also 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.

Strengths and limitations of the study

- Strength: Large database, largely representative for Dutch population
- Strength: Routinely collected prescription data, reliable because needed for delivery by pharmacist
- Limitation: Morbidity data, needed for prescription *indication*, are dependent on coding by GP

INTRODUCTION

Antidepressants are recommended for the treatment of both major depression and anxiety disorders in most clinical guidelines. Based on evidence that they are more efficacious than placebo in adults with major depressive disorder (1), antidepressants were used by more than 12% of the adult US population in 2013, with the prevalence in women being approximately double that in men, and increasing with age (2). 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 (3–7). 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 (3).

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 (8). 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 (9). Despite this cautious approach, the prevalence of antidepressant prescribing almost doubled between 1996 and 2012 in the Netherlands (10).

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 (11–16). An explanation for this increase in antidepressant prescribing might, therefore, be longer continuation after initial treatment. For example, Mars et al. (14) 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. (10) 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 long-term (>15 months) by 30% and 44% in the periods 1995–2005 and 2005–2015, respectively (17). 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 (18). 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 (19). Read et al. also reported that 52% of a New Zealand sample continued antidepressant treatment for three or more years, with this proportion increasing with age (20), while Ambresin et al. reported that therapy was continued for more than 2 years in 47% of antidepressant users. However, Sihvo (12) reported that only 14% of antidepressant users in Finland continued therapy for more than two 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 three 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 (21).

Little is known about the factors associated with long-term antidepressant use. Moreover, although current Dutch guidelines recommend stopping treatment six months after remission (9), 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 five-year period and what predicted long-term prescribing? We also wanted to answer four specific sub-questions: (1) What proportions of patients continue therapy for more than two, three and four years? (2) Are there differences in long-term prescribing by sex and age? (3) Are there differences in long-term prescribing by the indication for antidepressant prescribing? and (4) 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 367–519 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 overrepresented. For this study, we used data for adult patients aged 18 years and

older, coving the period 2011–2015.

Patient and Public involvement

The data collection was approved by our institutional review board, who waived the need to obtain specific consent. The 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.

Data

Prescriptions

Each medication prescription, including repeat prescriptions, were recorded by date and code based on the Anatomical Therapeutic Chemical Classification System (i.e., 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 (22), 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 (i.e., 2011, 2012, 2013, 2014 and 2015). Merging data for the five 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 2.30 (23), using with 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 four subsequent years. We assumed that receiving four or more prescriptions in one year was consistent with chronic use, based on the common Dutch practice to prescribe antidepressants on repeat prescriptions for three-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 (i.e., depression, anxiety or somatic problem)

RESULTS

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. By age, antidepressants were prescribed to 30%, 45% and 25% of those aged 18–44 years, 45–64 years and >65 years, respectively.

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

Here figure 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 two years and that 58% were still receiving them at three years. However, only 42% of patients received antidepressants through each year from 2011 to 2015; by SSRI and TCA use, this was 38% and 35%, respectively (Figure 1). The odds for receiving antidepressants over five consecutive years based on patients' characteristics are shown in Table 1.

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 (ref = no anxiety)						
Anxiety	0.3196	0.0558	0.0000	1.38	1.23	1.54
Depression	0.3224	0.0488	0.0000	1.38	1.25	1.52
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

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. 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.

DISCUSSION

Antidepressants were prescribed to almost 7% of the general practice population 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 five 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. (17) 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 five 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 (25) and Greenberg (26), point to the lack of efficacy and the possible harms of long-term use. By contrast, proponents, such as Young and Crace (27), 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 (28), and have unknown efficacy for those other disorders. Although some patients will benefit from long-term use (29), 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 (30). 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 (31).

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 (32). This is compounded by the fact that, when patients have benefitted from relief of depressive symptoms, they often become reluctant to stop therapy for fear of becoming depressed again (33). 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 (34). Medication reviews may be a practice characteristic that explains the substantial variation among practices in our analyses. 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 (35). The lack of evidence on how best to discontinue medication makes this between-practice variation unsurprising. New initiatives, such as the introduction of tapering strips (36) 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 stabilization.

Limitations

Although prescription data were available of 1–2 million patients, substantial numbers were lost 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. 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.

Conclusions

Chronic antidepressant use was common in this cohort, with 42% of patients prescribed antidepressants in 2011 continuing to use them at five 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.

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Author contributions

Peter Verhaak conceived the concept, analysed the data and wrote the paper. Derek de Beurs discussed the concept and commented on all drafts. Peter Spreeuwenberg performed the multilevel analysis and commented on all drafts.

Conflicts of interest

None

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Transparency declaration

The lead author (PV) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical issues

The data collection was approved by our institutional review board, who waived the need to obtain specific consent. The study was conducted in accordance with the requirements of the Helsinki Declaration. Patients in participating practices were informed about the practice's participation in NPCD and were free to opt out.

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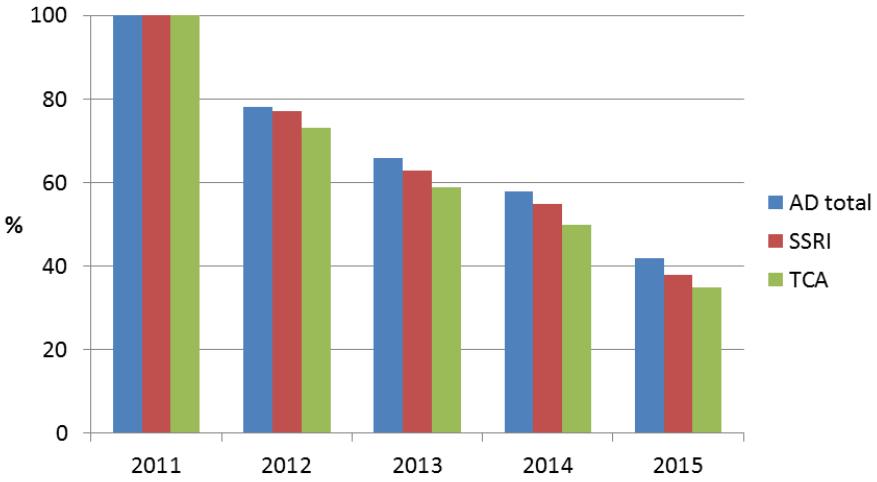
Figure 1: proportion of AD-users in 2011, who used AD chronically in the subsequent years



Each column shows the proportions using antidepressants, SSRIs or TCAs based on those who received at least four prescriptions of that drug in 2011 (the start year; 100%). By 2015, only 42% of antidepressant users continued to use them through each year to 2015; for SSRI and TCA use, this rate was 38% and 35%, respectively.

254x190mm (96 x 96 DPI)

Table 1. Odds for receiving an SSRI prescription each year between 2011 and 2015

Variable	Coefficient	Standard Error	p-value	Odds ratio	95% Confidence Interval	
Sex (male = ref)						
Female	0.1699	0.0576	0.0032	1.19	1.06	1.33
Age (65+ = ref)						
19–44	-0.1077	0.0767	0.1600	0.90	0.77	1.04
45–64	0.2582	0.0700	0.0002	1.29	1.13	1.49
Disorder						
Anxiety (no anxiety = ref)	0.0333	0.0771	0.6656	1.03	0.89	1.20
Depression (ibidem)	-0.1207	0.0698	0.0838	0.89	0.77	1.02
Somatic disorder (ibidem)	0.1537	0.0849	0.0703	1.17	0.99	1.38
Practice variance	4.711	0.626				
ICC	0.59					
Constant	-3.6397	0.2066				

Table 2. Odds for receiving a TCA prescription during each year between 2011 and 2015

Variable	Coefficient	Standard Error	p-value	Odds ratio	95% Confidence Interval	
Sex (male = ref)						
Female	0.2030	0.0917	0.0268	1.23	1.02	1.47
Age (65+ = ref)						
19–44	-0.6821	0.1300	0.0000	0.51	0.39	0.65
45–64	0.0393	0.0915	0.6673	1.04	0.87	1.24
Disorder						
Anxiety (no anxiety = ref)	0.2098	0.1387	0.1303	1.23	0.94	1.62
Depression (ibidem)	0.3797	0.1137	0.0008	1.46	1.17	1.83
Somatic disorder (ibidem)	-0.0631	0.1098	0.5654	0.94	0.76	1.16
Practice variance	2.763	0.4156				
ICC	0.46					
Constant	-3.6022	0.1936				

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Action
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	In abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	done
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	done
Objectives	3	State specific objectives, including any prespecified hypotheses	"we aimed to assess the extent of chronic antidepressant prescribing and to evaluate the determinants of that chronic prescribing."
Methods			
Study design	4	Present key elements of study design early in the paper	Design is presented in first paragraph of Method section
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Not applicable
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Done: we defined outcome measures and independent variables
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	done
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Done
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	done
		(*b*) Describe any methods used to examine subgroups and interactions	done
		(*c*) Explain how missing data were addressed	Not applicable

		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Not applicable
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Done
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	Done
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Done
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Done
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Done
Generalisability	21	Discuss the generalisability (external validity) of the study results	Done
Other information			

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Not applicable

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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What proportion of initially prescribed antidepressants is still being prescribed chronically after 5 year in general practice? A longitudinal cohort analysis.

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What proportion of initially prescribed antidepressants is still being prescribed chronically after 5 year in general practice? A longitudinal cohort analysis.

Article category: Epidemiology

Verhaak PFM[1], Beurs DP[2] de, Spreeuwenberg P[2]

[1] Netherlands institute of health services research (NIVEL), Utrecht, the Netherlands

University of Groningen, University Medical Center Groningen, Department of General Practice, Groningen, the Netherlands

[2] Netherlands institute of health services research, Utrecht, the Netherlands

Corresponding author:

Prof. dr P. F. M. Verhaak

Netherlands institute of health services research (NIVEL)

P.O. Box 1568

3500 BN Utrecht

The Netherlands

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 hypothesize 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 five 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 Inhibators and for Tricyclic Antidepressants

Results. Antidepressants were prescribed to almost 7% of our 326,025 participants each year. They were prescribed for depression (38%), for anxiety (17%), other psychological disorders (20%) and non-psychological indications (25%). Antidepressants were prescribed in all five 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 (e.g., neuropathic pain). Chronic prescribing also varied markedly among general practices.

Conclusion. Chronic antidepressant use is common not only for depression but also 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.

Strengths and limitations of the study

- Strength: Large database, largely representative for Dutch population
- Strength: Routinely collected prescription data, reliable because needed for delivery by pharmacist
- Limitation: Morbidity data, needed for prescription *indication*, are dependent on coding by GP

INTRODUCTION

Antidepressants are recommended for the treatment of both major depression and anxiety disorders in most clinical guidelines. Based on evidence that they are more efficacious than placebo in adults with major depressive disorder(1), antidepressants were used by more than 12% of the adult US population in 2013, with the prevalence in women being approximately double that in men, and increasing with age(2). 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 (3-7). 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 (3).

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 (8). 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 (9). Despite this cautious approach, the prevalence of antidepressant prescribing almost doubled between 1996 and 2012 in the Netherlands (10).

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 (11-16). An explanation for this increase in antidepressant prescribing might, therefore, be longer continuation after initial treatment. For example, Mars et al.(14) 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. (10) 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 long-term (>15 months) by 30% and 44% in the periods 1995–2005 and 2005–2015, respectively(17). 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 (18). 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 (19). Read et al. also reported that 52% of a New Zealand sample continued antidepressant treatment for three or more years, with this proportion increasing with age(20), while Ambresin et al. reported that therapy was continued for more than 2 years in 47% of antidepressant users. However, Sihvo (12) reported that only 14% of antidepressant users in Finland continued therapy for more than two 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 three 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 (21).

Little is known about the factors associated with long-term antidepressant use. Moreover, although current Dutch guidelines recommend stopping treatment six months after remission (9), 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 five-year period and what predicted long-term prescribing? We also wanted to answer four specific sub-questions: (1) What proportions of patients continue therapy for more than two, three and four years? (2) Are there differences in long-term prescribing by sex and age? (3) Are there differences in long-term prescribing by the indication for antidepressant prescribing? and (4) 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 367–519 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 overrepresented. For this study, we used data for adult patients aged 18 years and

older, coving the period 2011–2015.

Patient and Public involvement

The data collection was approved by our institutional review board, who waived the need to obtain specific consent. The 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.

Data

Prescriptions

Each medication prescription, including repeat prescriptions, were recorded by date and code based on the Anatomical Therapeutic Chemical Classification System (i.e., 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 (22), 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 (i.e., 2011, 2012, 2013, 2014 and 2015). Merging data for the five 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 2.30 (23), using with 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 four subsequent years. We assumed that receiving four or more prescriptions in one year was consistent with chronic use, based on the common Dutch practice to prescribe antidepressants on repeat prescriptions for three-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 (i.e., 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 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

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

Here figure 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 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 prescription each year to 2015.

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

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

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. 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.

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 five 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. (17) 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 five 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(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). By contrast, proponents, such as Young and Crace(29), 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 (30), and have unknown efficacy for those other disorders. Although some patients will benefit from long-term use (31), 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(32). 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(33).

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 (34). This is compounded by the fact that, when patients have benefitted from relief of depressive symptoms, they often become reluctant to stop therapy for fear of becoming depressed again(35). 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(36).

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). New initiatives, such as the introduction of tapering strips(40) 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 stabilization.

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. 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(41). 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 five 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.

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

Legend: : Total Antidepressants

: SSRI

: TCA

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Author contributions

Peter Verhaak conceived the concept, analysed the data and wrote the paper. Derek de Beurs discussed the concept and commented on all drafts. Peter Spreeuwenberg performed the multilevel analysis and commented on all drafts.

Conflicts of interest

None

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Transparency declaration

The lead author (PV) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical issues

The data collection was approved by our institutional review board, who waived the need to obtain specific consent. The study was conducted in accordance with the requirements of the Helsinki Declaration. Patients in participating practices were informed about the practice's participation in NPCD and were free to opt out.

Data sharing statement

We've got access to the anonymous database under condition that data will be used only for the answering of the currend research questions.

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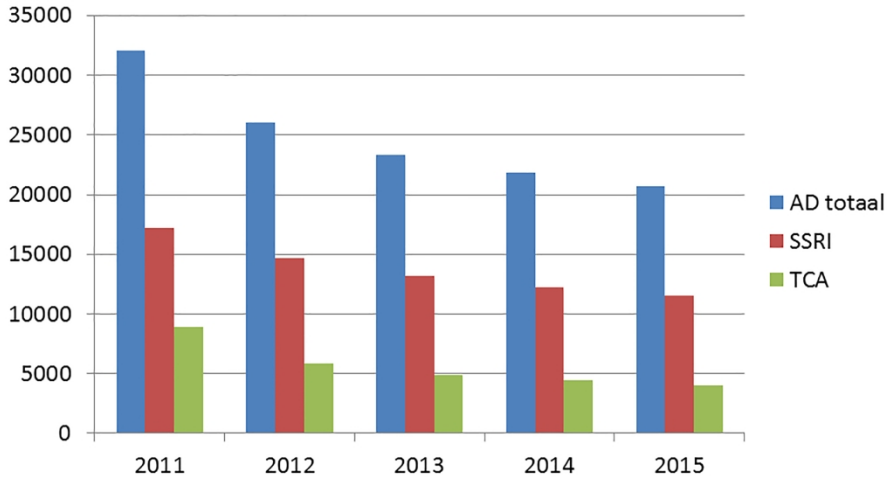
Figure 1: number of AD-users in 2011, who used AD chronically (≥ 4 prescription/year) in the subsequent years



254x190mm (300 x 300 DPI)

Table 1. Odds for receiving an SSRI prescription each year between 2011 and 2015

Variable	Coefficient	Standard Error	p-value	Odds ratio	95% Confidence Interval	
Sex (male = ref)						
Female	0.1699	0.0576	0.0032	1.19	1.06	1.33
Age (65+ = ref)						
19–44	-0.1077	0.0767	0.1600	0.90	0.77	1.04
45–64	0.2582	0.0700	0.0002	1.29	1.13	1.49
Disorder						
Anxiety (no anxiety = ref)	0.0333	0.0771	0.6656	1.03	0.89	1.20
Depression (no depression = ref))	-0.1207	0.0698	0.0838	0.89	0.77	1.02
Somatic disorder (no somatic disorder = ref)	0.1537	0.0849	0.0703	1.17	0.99	1.38
Practice variance	4.711	0.626				
ICC	0.59					
Constant	-3.6397	0.2066				

Table 2. Odds for receiving a TCA prescription during each year between 2011 and 2015

Variable	Coefficient	Standard Error	p-value	Odds ratio	95% Confidence Interval	
Sex (male = ref)						
Female	0.2030	0.0917	0.0268	1.23	1.02	1.47
Age (65+ = ref)						
19–44	-0.6821	0.1300	0.0000	0.51	0.39	0.65
45–64	0.0393	0.0915	0.6673	1.04	0.87	1.24
Disorder						
Anxiety (no anxiety = ref)	0.2098	0.1387	0.1303	1.23	0.94	1.62
Depression (no depression = ref)	0.3797	0.1137	0.0008	1.46	1.17	1.83
Somatic disorder (no somatic disorder = ref)	-0.0631	0.1098	0.5654	0.94	0.76	1.16
Practice variance	2.763	0.4156				
ICC	0.46					
Constant	-3.6022	0.1936				

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Action
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	In abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	done
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	done
Objectives	3	State specific objectives, including any prespecified hypotheses	"we aimed to assess the extent of chronic antidepressant prescribing and to evaluate the determinants of that chronic prescribing."
Methods			
Study design	4	Present key elements of study design early in the paper	Design is presented in first paragraph of Method section
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Not applicable
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Done: we defined outcome measures and independent variables
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	done
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Done
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	done
		(*b*) Describe any methods used to examine subgroups and interactions	done
		(*c*) Explain how missing data were addressed	Not applicable

		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Not applicable
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Done
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	Done
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Done
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Done
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Done
Generalisability	21	Discuss the generalisability (external validity) of the study results	Done
Other information			

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Not applicable

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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

Article category: Epidemiology

Verhaak PFM[1], Beurs D[2] de, Spreeuwenberg P[2]

[1] Netherlands institute of health services research (NIVEL), Utrecht, the Netherlands

University of Groningen, University Medical Center Groningen, Department of General Practice, Groningen, the Netherlands

[2] Netherlands institute of health services research, Utrecht, the Netherlands

Corresponding author:

Prof. dr P. F. M. Verhaak

Netherlands institute of health services research (NIVEL)

P.O. Box 1568

3500 BN Utrecht

The Netherlands

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 hypothesize 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 five 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%), for anxiety (17%), other psychological disorders (20%) and non-psychological indications (25%). Antidepressants were prescribed in all five 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 (e.g., neuropathic pain). Chronic prescribing also varied markedly among general practices.

Conclusion. Chronic antidepressant use is common not only for depression but also 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.

Strengths and limitations of the study

- Strength: Large database, largely representative for Dutch population
- Strength: Routinely collected prescription data, reliable because needed for delivery by pharmacist
- Limitation: Morbidity data, needed for prescription *indication*, are dependent on coding by GP

INTRODUCTION

Antidepressants are recommended for the treatment of both major depression and anxiety disorders in most clinical guidelines. Based on evidence that they are more efficacious than placebo in adults with major depressive disorder(1), antidepressants were used by more than 12% of the adult US population in 2013, with the prevalence in women being approximately double that in men, and increasing with age(2). 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 (3-7). 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 (3).

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 (8). 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 (9). Despite this cautious approach, the prevalence of antidepressant prescribing almost doubled between 1996 and 2012 in the Netherlands (10).

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 (11-16). An explanation for this increase in antidepressant prescribing might, therefore, be longer continuation after initial treatment. For example, Mars et al.(14) 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. (10) 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 long-term (>15 months) by 30% and 44% in the periods 1995–2005 and 2005–2015, respectively(17). 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 (18). 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 (19). Read et al. also reported that 52% of a New Zealand sample continued antidepressant treatment for three or more years, with this proportion increasing with age(20), while Ambresin et al. reported that therapy was continued for more than 2 years in 47% of antidepressant users. However, Sihvo (12) reported that only 14% of antidepressant users in Finland continued therapy for more than two 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 three 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 (21).

Little is known about the factors associated with long-term antidepressant use. Moreover, although current Dutch guidelines recommend stopping treatment six months after remission (9), 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 five-year period and what predicted long-term prescribing? We also wanted to answer four specific sub-questions: (1) What proportions of patients continue therapy for more than two, three and four years? (2) Are there differences in long-term prescribing by sex and age? (3) Are there differences in long-term prescribing by the indication for antidepressant prescribing? and (4) 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 367–519 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 overrepresented. 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 (i.e., 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 (22), 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 (i.e., 2011, 2012, 2013, 2014 and 2015). Merging data for the five 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 2.30 (23), using with 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 four subsequent years. We assumed that receiving four or more prescriptions in one year was consistent with chronic use, based on the common Dutch practice to prescribe antidepressants on repeat prescriptions for three-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 (i.e., 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 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

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

Here figure 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 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

prescription each year to 2015.

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

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 < .001	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	p < .001	1.26	1.15	1.38
Disorder						
Anxiety (ref = no anxiety)	0.3196	0.0558	p < .001	1.38	1.23	1.54
Depression (ref = no depression)	0.3224	0.0488	p < .001	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, intra-class correlation coefficient; OR, odds ratio; SE, standard error

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. 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.

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 five 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. (17) 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 five 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(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). By contrast, proponents, such as Young and Crace(29), 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 (30), and have unknown efficacy for those other disorders. Although some patients will benefit from long-term use (31), 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(32). 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(33).

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 (34). This is compounded by the fact that, when patients have benefitted from relief of depressive symptoms, they often become reluctant to stop therapy for fear of becoming depressed again(35). 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(36).

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). New initiatives, such as the introduction of tapering strips(40) 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 stabilization.

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. 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 prescription 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(41). 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 five 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.

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

Legend: : Total Antidepressants

: SSRI

: TCA

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Author contributions

Peter Verhaak conceived the concept, analysed the data and wrote the paper. Derek de Beurs discussed the concept and commented on all drafts. Peter Spreeuwenberg performed the multilevel analysis and commented on all drafts.

Conflicts of interest

None

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Transparency declaration

The lead author (PV) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical issues

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. The 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

Data sharing statement

We've got access to the anonymous database under condition that data will be used only for the answering of the current research questions.

Researchers interested in our analyses can contact the first author or Dr Derek de Beurs (second author; d.debeurs@nivel.nl) at NIVEL for possible secondary analysis of our dataset.

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

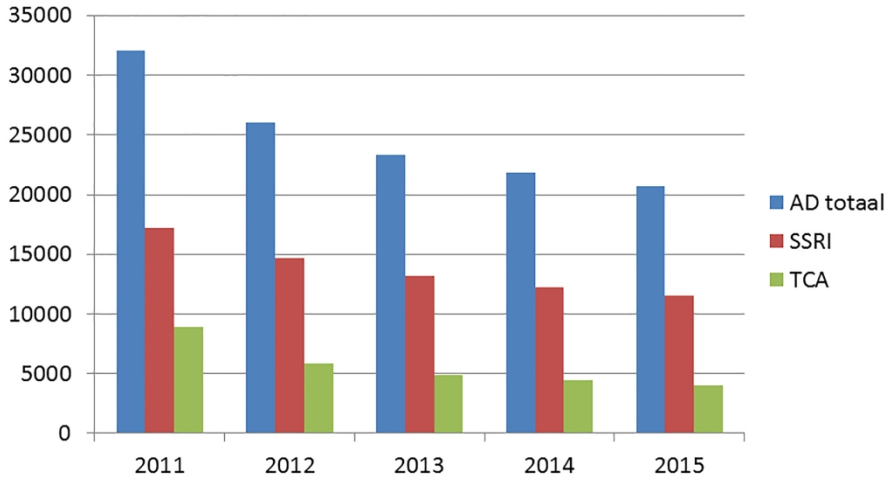

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Table 1. Odds for receiving an SSRI prescription each year between 2011 and 2015

Variable	Coefficient	Standard Error	p-value	Odds ratio	95% Confidence Interval	
Sex (male = ref)						
Female	0.1699	0.0576	0.0032	1.19	1.06	1.33
Age (65+ = ref)						
19–44	-0.1077	0.0767	0.1600	0.90	0.77	1.04
45–64	0.2582	0.0700	p < .001	1.29	1.13	1.49
Disorder						
Anxiety (no anxiety = ref)	0.0333	0.0771	0.6656	1.03	0.89	1.20
Depression (no depression = ref))	-0.1207	0.0698	0.0838	0.89	0.77	1.02
Somatic disorder (no somatic disorder = ref)	0.1537	0.0849	0.0703	1.17	0.99	1.38
Practice variance	4.711	0.626				
ICC	0.59					
Constant	-3.6397	0.2066				

Table 2. Odds for receiving a TCA prescription during each year between 2011 and 2015

Variable	Coefficient	Standard Error	p-value	Odds ratio	95% Confidence Interval	
Sex (male = ref)						
Female	0.2030	0.0917	0.0268	1.23	1.02	1.47
Age (65+ = ref)						
19–44	-0.6821	0.1300	p < .001	0.51	0.39	0.65
45–64	0.0393	0.0915	0.6673	1.04	0.87	1.24
Disorder						
Anxiety (no anxiety = ref)	0.2098	0.1387	0.1303	1.23	0.94	1.62
Depression (no depression = ref)	0.3797	0.1137	p < .001	1.46	1.17	1.83
Somatic disorder (no somatic disorder = ref)	-0.0631	0.1098	0.5654	0.94	0.76	1.16
Practice variance	2.763	0.4156				
ICC	0.46					
Constant	-3.6022	0.1936				

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Action
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	In title (p.1) and abstract (p.3)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Done (p.3)
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Done (p. 5-7)
Objectives	3	State specific objectives, including any prespecified hypotheses	"we aimed to assess the extent of chronic antidepressant prescribing and to evaluate the determinants of that chronic prescribing."(abstract, p.3)
Methods			
Study design	4	Present key elements of study design early in the paper	Design is presented in first paragraph of Method section (p.7)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Not applicable
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Done: we defined outcome measures and independent variables (p.9)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Done (p.8-9)
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Done (p.8-9)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Done (p.9)
		(*b*) Describe any methods used to examine subgroups and interactions	Done (p.9)

		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Not applicable (p.7; 9; 14-15)
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Done (p.10)
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	Done (p.10)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Done (p.10-12)
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Done (p.12)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Done (p.14-15)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Done (p.15)
Generalisability	21	Discuss the generalisability (external validity) of the study results	Done (p.12, p.14|)

Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Not applicable

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.