

Utilization and Unintended Effects of Antidepressants in an Ageing Population

Nikkie Aarts

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Utilization and Unintended Effects of Antidepressants in an Ageing Population

Gebruik en bijwerkingen van antidepressiva
in een ouder wordende populatie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

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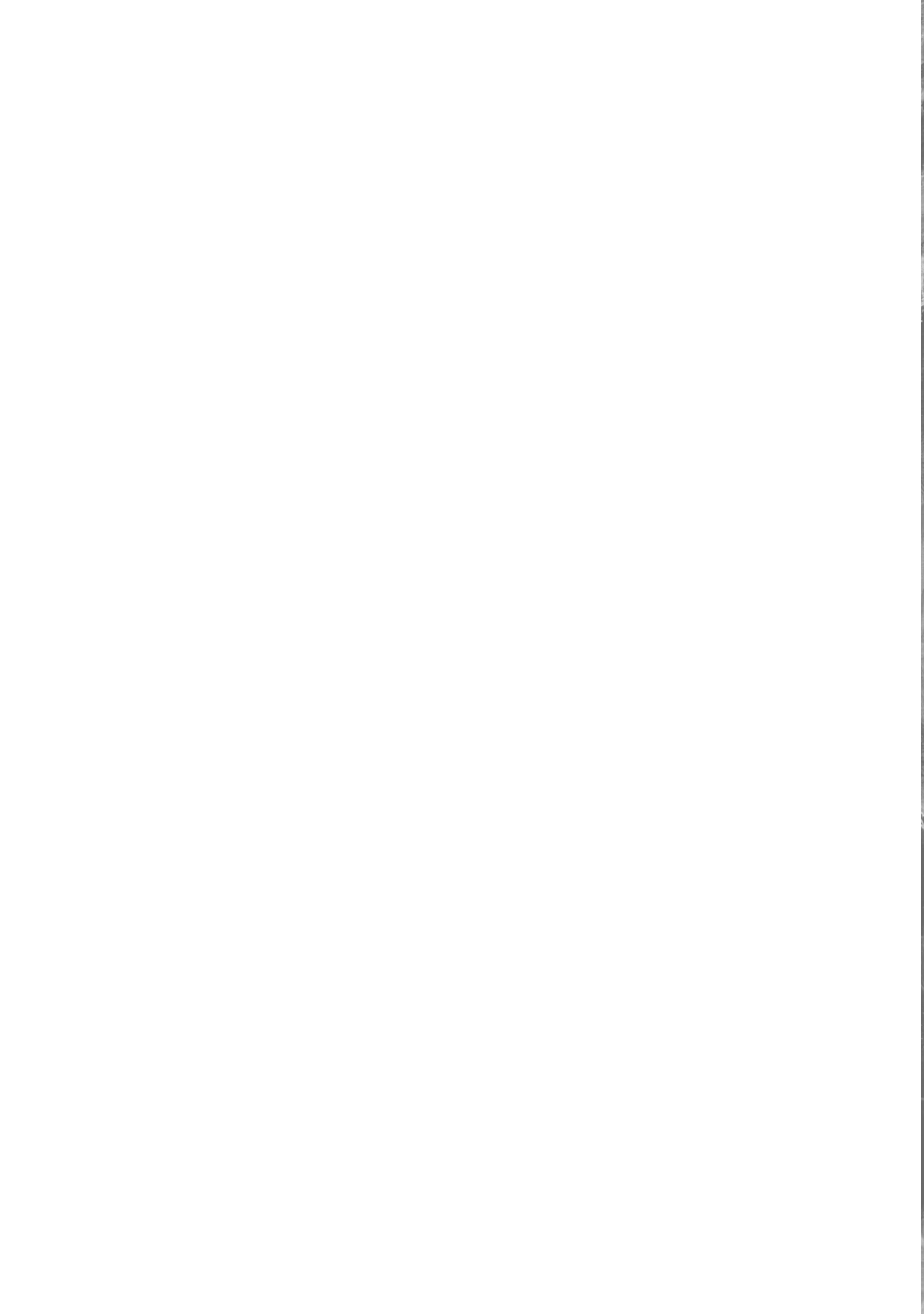
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Contents

Chapter 1. General introduction	7
Chapter 2. Utilization of antidepressants	15
2.1 Utilization patterns of antidepressants between 1991 and 2011 in a population-based cohort of middle-aged and elderly	17
2.2 Prescription and indication trends of antidepressant drugs in the Netherlands between 1996 and 2012: a dynamic population-based study	31
2.3 Self-reported indications for antidepressant use in a population-based cohort of middle-aged and elderly	45
2.4 Adherence and persistence to antidepressant drug treatment in a population-based study of older adults and elderly	55
Chapter 3. Unintended effects of antidepressants	71
3.1 Inhibition of serotonin reuptake by antidepressants and cerebral microbleeds in the general population	73
3.2 Antidepressant use is associated with an increased risk of developing microbleeds	89
3.3 Use of selective serotonin reuptake inhibitors and sleep quality: a population-based study	97
3.4 Antidepressants and the risk of hyponatremia: a population-based study	113
3.5 Use of selective serotonin reuptake inhibitors and bone mineral density change: a population-based longitudinal study in middle-aged and elderly individuals	129
Chapter 4. General discussion	145
Chapter 5. Appendices	165
Summary	167
Samenvatting	171
List of publications	175
PhD portfolio	177
Dankwoord	181
Curriculum Vitae	185



The background of the page is a complex, abstract composition of various shades of gray, black, and white. It features numerous brushstrokes, splatters, and smudges, creating a textured and layered appearance. The overall effect is that of a heavily used and perhaps discarded piece of paper or canvas, with some areas appearing more saturated and others more faded or worn. The composition is dense and chaotic, with no discernible geometric shapes or patterns.

1

General introduction

Antidepressants

Antidepressants for the treatment of depression have been on the market since the 1950s. Two specific classes were introduced: the monoamine-oxidase inhibitor iproniazide which is chemically related to isoniazide and which was first developed as a tuberculostatic drug but proved also to have antidepressant properties, and tricyclic antidepressants (TCAs) [1]. The pills were considered 'miracle cures' and revolutionized the treatment of depressive symptoms [1, 2]. However, it was not until the introduction of selective serotonin reuptake inhibitors (SSRIs) in the late 80's that antidepressants became so immensely popular [1, 3]. Older antidepressants caused serious adverse drug reactions and posed a potential risk for overdose, whereas SSRIs selectively target the neurotransmitter serotonin which is associated with fewer types of adverse drug reactions [4]. From then on, antidepressant drug use increased exponentially over the years [3, 5]. Recently, it was estimated that almost 1 million persons in the Netherlands were prescribed an antidepressant in 2013 [6]. This is approximately 5.8% of the total Dutch population. Although some antidepressants may have been prescribed for other indications [e.g. pain], concerns have been raised regarding the high prevalence of antidepressant drug prescribing and its off-label use [7, 8]. It was proposed that antidepressants might be prescribed too easily for off-label indications or mild depressive symptoms, while effectiveness is not always proven and antidepressants are not free of risks [7-11].

Elderly population

Especially in a specific population such as the elderly, antidepressants should potentially be prescribed with more care. Elderly are underrepresented in clinical trials, therefore it is difficult to predict the effectiveness and prevalence or severity of adverse drug reactions in the older population in daily practice [12, 13]. The trial population is younger, healthier and psychologically different [14]. Ageing conforms to physiological changes which alter pharmacokinetic mechanisms. This may increase the risk of drug toxicity and adverse drug reactions [13]. Besides, the context of treatment is different in the elderly population. They often have multiple comorbidities which require drug treatment [15], while on the other hand subsequent polypharmacy increases the risk of drug-drug interactions and adverse drug reactions [16]. Moreover, off-label indications, non-adherence or early discontinuation of treatment are common in daily practice and should also be taken into account [9, 17, 18]. Thus, studies in real-life settings are needed to investigate the safety of antidepressants in the specific population of elderly.

Rotterdam Study and Integrated Primary Care Information project

Studies in this thesis were embedded in the prospective population-based Rotterdam Study cohort, or data were retrieved from the Integrated Primary Care Information (IPCI) project, respectively. First, the Rotterdam Study is situated in Ommoord, a suburb of Rotterdam, and consists of 14,926 participants all aged 45 years or older [19, 20]. Follow-up examinations are conducted every 4-5 years. Medication dispensing data is available on a daily basis, and major morbidity and mortality are continuously monitored since 1990 onwards. Second, the IPCI project is an observational dynamic database which contains electronic medical records from general practitioners [21, 22], comprising approximately 1.5 million individuals in the Netherlands. These records are de-identified and contain data on diagnoses, laboratory findings, hospitalizations, discharge letters, and drug prescriptions.

Aim and outline of the thesis

In this thesis, we had two main aims: 1) to study the characteristics of antidepressant use in clinical practice 2) to study the unintended effects of antidepressant treatment in clinical practice in an ageing population.

In **chapter 2**, we aimed to characterize antidepressant use in the general older Dutch population in clinical practice. In **chapter 2.1** and **2.2**, we reported the prevalence and incidence of antidepressant use over a 15- and 20-year period in the Netherlands and in the Rotterdam area, respectively. Besides, indications for treatment and persistence to treatment are also briefly discussed, but are covered in more detail in consecutive chapters. In **chapter 2.3**, we assessed all possible indications for antidepressant treatment based on self-report, while we studied persistence and adherence to antidepressant treatment in **chapter 2.4**.

In **chapter 3**, we aimed to assess potential unintended effects related to antidepressant treatment. In previous studies, antidepressants with a high potential to inhibit serotonin reuptake (mostly SSRIs) were associated with an increased risk of clinical bleedings [23, 24]. Antidepressants have never been studied in association with subclinical microbleeds, which are highly prevalent in the general population and have been linked to larger intracerebral hemorrhages [25, 26]. In **chapter 3.1** and **3.2**, we studied the association between use of antidepressants, categorized by their affinity for the serotonin transporter, and the presence of, or incident occurrence of, cerebral microbleeds defined on MRI. Moreover, in **chapter 3.3**, we studied the association between use of SSRIs and sleep quality assessed with a questionnaire. SSRIs have a positive effect on subjective sleep in clinically-depressed populations; however, the possible relief in depressive symptoms is an important and time-varying confounding factor. Studies in healthy individuals are inconsistent and evidence for an association between SSRIs and better sleep in daily practice is lacking [27-30]. Furthermore, a well-known adverse drug reaction is SSRI-induced hyponatremia, with an

occurrence ranging between 0.06 and 40% [31]. However, the underlying mechanism of antidepressant-induced hyponatremia is still under debate, and the less extensively studied TCAs or other antidepressants also seem to be associated with hyponatremia but to a lesser extent [31, 32]. Therefore, in **chapter 3.4**, we assessed the association between use of all antidepressants and the occurrence of hyponatremia based on electronic medical records from general practitioners. Finally, in **chapter 3.5**, we focused on the association between use of SSRIs and change in bone mineral density. SSRIs are assumed to play a role in bone metabolism via the modulation of serotonin levels [33]. However, so far, longitudinal studies showed conflicting results and had limited longitudinal exposure information [34-36].

The contributions of all authors to the chapters within this thesis are specified in Table 1. To conclude, we discuss the most important results of the studies presented in this thesis in **chapter 4**. Furthermore, we will discuss methodological considerations and future perspectives for upcoming research. A summary of the main results can be found in **chapter 5**.

Table 1. Contributions of the authors to the chapters within this thesis.

Authors	Chapter									
	2.1	2.2	2.3	2.4	3.1	3.2	3.3	3.4	3.5	
N. Aarts	1, 2, 3, 4, 5	1, 3, 5	1, 2, 3, 4, 5	1, 2, 3, 4, 5	1, 2, 3, 4, 5	1, 2, 3, 4, 5	1, 2, 3, 4, 5	1, 2, 3, 4, 5	1, 2, 3, 4, 5	
R. Noordam	1, 2, 3, 5	1, 2, 3, 4, 5	2, 3, 5	2, 3, 5	2, 3, 5	2, 3, 5	2, 3, 5	2, 3, 5	2, 3, 5	
A. Hofman	1, 5		1, 5	1, 5	1, 5	1, 5	1, 5		1, 5	
H. Tiemeier	1, 3, 5		1, 3, 5	1, 3, 5	1, 3, 5	1, 3, 5	1, 3, 5		1, 3, 5	
B.H. Stricker	1, 2, 3, 5	1, 3, 5	1, 3, 5	1, 2, 3, 5	1, 3, 5	1, 3, 5	1, 3, 5	1, 3, 5	1, 3, 5	
L.E. Visser	1, 3, 5	1, 3, 5	1, 2, 3, 5	1, 3, 5	1, 3, 5	1, 3, 5	1, 3, 5	1, 3, 5	1, 3, 5	
K.M. Verhamme		1, 3, 5								
M.C.J.M. Sturkenboom		1, 5						1, 3, 5		
S. Akoudad					1, 2, 3, 4, 5	1, 2, 3, 4, 5				
M.A. Ikram					1, 3, 5	1, 3, 5				
M.W. Vernooij					1, 3, 5	1, 3, 5				
L.A. Zuurbier							1, 2, 3, 5			
J.C. Blijderveen								1, 2, 3, 5		
E.M. Rodenburg								1, 2, 3, 5		
A.C. Ham									1, 2, 3, 4, 5	
F. Rivadeneira									1, 3, 5	
G. Ziere									1, 3, 5	
C.M. Zillikens									1, 3, 5	
N. van der Velde									1, 3, 5	
A.G. Uitterlinden									1, 5	

Contributions are divided into:

- 1) Conception and design of the study
- 2) Data analysis
- 3) Interpretation of the results
- 4) Drafting of manuscript
- 5) Critical revising and approval of final manuscript

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2

Utilization of antidepressants





2.1

Utilization patterns of antidepressants between 1991 and 2011 in a population-based cohort of middle-aged and elderly

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Eur Psychiatry. 2014 Aug;29(6):365-70

Abstract

Background: In middle-aged and older patients in whom antidepressant use increased in last decades, patterns of use might be of concern. The objective of this study was to investigate the patterns of prevalence, incidence and duration of antidepressant use in an ageing population.

Methods: All participants (aged ≥ 45 years) from the population-based Rotterdam Study were followed from January 1st 1991 until death, loss to follow-up, or end of the study period (December 31st 2011). Antidepressant drug dispensing, based on pharmacy records, were subdivided into tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and other antidepressants. One-year prevalence, 5-year incidence and duration of antidepressant use were calculated.

Results: Yearly prevalence of antidepressant use increased from 3.9% in 1991 to 8.3% of the population in 2011. The increase in SSRI use was 5.8-fold, whereas use of other antidepressants doubled and TCA use remained stable over time. Incidence of all antidepressants decreased from 19.2 to 15.1 per 1,000 person-years between 1992 and 2011. The duration of a first treatment episode increased over time.

Conclusion: Despite the increase in prevalence of antidepressant use over time, incidence did not, which is most likely explained by a longer treatment duration and recurrent episodes.

Introduction

During the last decades, the number of antidepressant drug prescriptions has increased in the Western countries [1-6], especially in elderly populations [4-7]. Given these rising trends, concerns are raised on the justification of antidepressant drug use [8-11]. Antidepressant drugs are not risk free, especially the elderly have an increased risk of drug-drug interactions and adverse drug reactions [12, 13]. Regularly, it is suggested that the rise of antidepressant drug use may indicate that the threshold to prescribe antidepressants has been lowered. Also, antidepressant drug prescriptions are prescribed to a broader range of patients without psychiatric diagnosis [3, 5, 14, 15]. Especially, an excessive rise in the total number of selective serotonin reuptake inhibitor (SSRI) prescriptions was observed [4-6]. Compared to tricyclic antidepressants (TCAs), SSRIs might be prescribed more easily and are taken for longer periods, since they have a milder adverse effect profile, a lower risk of toxicity and do not require monitoring of plasma levels [4, 6]. In contrast to the increasing number of prescriptions, recent studies of adult populations in Western countries showed a declining or constant rate of incident antidepressant users over the years after 2000. These trends were observed for all age categories [4, 5, 16]. However, before the year 2000, incident use of SSRIs still increased in the Netherlands [2]. Similar to other Western countries, dispensing trends and the number of antidepressant users also showed a steep increase during the last decades in the Netherlands [6, 17, 18]. Immediately after the introduction of SSRIs on the market in the 1980s, SSRIs were increasingly prescribed. Especially in the elderly, SSRIs are more desirable as first choice of treatment, considering the anticholinergic characteristics of TCAs [12, 19].

Recent utilization studies, which combine multiple utilization characteristics, are missing in the middle-aged and elderly. To understand the rising trends of antidepressant drug use, more utilization characteristics are needed besides dispensing trends. Therefore, the objective of our study was to investigate antidepressant drug utilization (incidence, prevalence and duration of antidepressant drug use) within a population-based cohort of middle-aged and elderly over a 21-year period from 1991 through 2011.

Methods

Setting

The Rotterdam Study is a prospective population-based cohort in which incidence and risk factors of diseases in an ageing population are investigated. From 1990 to 1993, all inhabitants aged 55 years or over in the Ommoord district in the city of Rotterdam in the Netherlands, were invited to participate in the Rotterdam Study I. The response rate

was 78%, including a total of 7,983 participants. Moreover, in 2000 and 2006 extended cohorts were enrolled. All inhabitants of Ommoord, aged 45 years of age and older and not already previously enrolled were invited to participate. A total of 6,943 participants were additionally included (response rate 66%). Informed consent was signed by all participants; including permission for retrieval of medical records and use of pharmacy data. The medical ethics committee of the Erasmus Medical Center, Rotterdam, the Netherlands, approved the study. After baseline measurements, follow-up examinations were conducted every 4–5 years including interviews and an extensive set of examinations. Furthermore, fully computerized pharmacy records from the pharmacies in the Ommoord district continuously monitored pharmacy records from January 1st 1991 onwards. All information is available in a computerized format on a day-to-day basis. This includes the date of dispensing, the total number of drug units per dispensing, the dispensed daily number of units, the product name of the drugs and the Anatomical Therapeutic Chemical code (ATC). Detailed information on design, objectives and methods of the Rotterdam Study has been described elsewhere [20, 21].

Study population

For our study population, we included participants who were in the Rotterdam study after January 1st 1991, as fully automated pharmacy data was available since that date. All participants were followed until death, loss to follow-up or end of the study period (December 31st, 2011). Participants who were followed in a calendar year contributed to the denominator of the prevalence analyses. For the incidence analysis, follow-up started 1 year after entering our study to ensure that participants were incident users. Follow-up was until death, loss to follow-up, end of study period, or incident antidepressant use. Antidepressant drug users in the first year and prevalent users were censored and did not contribute to the person-years for the incidence analysis. Participants could only become an incident user once. After their first dispensing, they were censored for incidence analysis. Denominators of the incidence calculations were person-years of participants who were included in the follow-up, and were not excluded based on the previous requirements. However, in additional analyses, participants could also become recurrent incident antidepressant drug users and were then still at risk after incident antidepressant drug use.

Outcome definitions

Dispensings with ATC-codes N06AA (TCA), N06AB (SSRI) or N06AF/N06AG/N06AX (other) were defined as antidepressant drug dispensing. The dispensing lengths were calculated in days by dividing the number of units issued per prescription by the dispensed daily number of units. Corresponding daily doses were expressed as the daily numbers of standardized defined daily doses (DDD). To describe the dispensing patterns of antidepressant drugs we calculated the prevalence, incidence rate and duration of use over the calendar years.

Prevalence of antidepressant drug use was defined as the number of antidepressant users with at least one dispensing in one year per total number of participants present in that year. In case of switching between antidepressant drug classes within one calendar year, a participant was counted only once for the overall prevalence, whereas the antidepressant drug user could contribute to other antidepressants drug classes within a year. Moreover, we also defined the prevalence of more adequate antidepressant drug use, to exclude single-filling antidepressant drug users. We took as cut-off at least four antidepressant drug prescriptions within a year interval.

The incidence rate indicates the number of incident users within a 5-year interval divided by the total person-years at risk during those 5 years. Moreover, the duration of use of the first episode was calculated for the incident users who had a follow-up of at least two years at start of treatment. Duration was defined as the number of days from the date of the first antidepressant drug prescription until end of the drug episode. A gap of 90 days was allowed between the dispensings. When this gap of 90 days was exceeded, discontinuation of treatment was assumed. Moreover, we determined whether participants started antidepressant drug treatment again after at least 90 days after discontinuation of antidepressant therapy. If they initiated treatment again after 90 days, these participants were considered recurrent users and this would represent re-initiation of treatment [22]. Incidence rates for these recurrent users were the number of (recurrent) incident users within a 5-year interval divided by the total person-years at risk during those 5 years.

Co-factors

Age and sex were studied as potential determinants of prevalent and incident use of the different antidepressant drug classes. Age was used as categorical variable. Age categories were based on the ranking of age for the different calendar years, with similar group sizes. They were categorized into four age groups: 45–64, 65–71, 72–77, and > 78 years of age.

Data analysis

Incident rates over the calendar years (1992–2011) were studied for specific trends when split by age categories, sex, and type of antidepressant (TCA/SSRI/other). Incidence rates were shown in categories of 5 years. Similar trends were studied for the prevalence of (adequate) antidepressant drug use from 1991 until 2011. Moreover, incidence rates with recurrent users were calculated and incidence proportions were calculated for the different antidepressant drug classes. Proportions were calculated as percentage of the total number of incident users per 5 years. Finally, cox proportional hazard regression models were used to study calendar year (1992–2011) and type of antidepressant as potential determinants of discontinuation of treatment. Discontinuation of treatment was the outcome of interest and indicated (preliminary) discontinuation of treatment.

Results

Study population characteristics

The total study population of the Rotterdam Study comprised 14,926 participants with an average age of 65.5 years (SD 10.5) at baseline of whom 59.1% were female (Table 1). In total, 89,622 antidepressant drug prescriptions were dispensed by the pharmacies during follow-up. A total of 1,905 incident users were observed during the 113,308 years of follow-up. The average starting dose was 0.79 DDDs (SD 0.31) for SSRIs, 0.31 DDDs (SD 0.22) for TCAs and 0.64 DDDs (SD 0.66) for other antidepressants.

Table 1. Characteristics of the study population.

	Study population (N= 14,926)
Age (years)	
Mean (SD)	65.5 (10.5)
Sex (% female)	8,823 (59.1)
Total number of antidepressant drug prescriptions ^a	89,622
Total follow-up (years)	113,308
Follow-up (years) ^b	
Mean (SD)	9.6 (6.0)
Number of incident users ^b	1,905
Start dose incident users (PDD/DDD ratio)	
Mean (SD)	
TCA	0.31 (0.22)
SSRI	0.79 (0.31)
Other	0.64 (0.66)

^aTotal of number of antidepressant drug prescriptions after 01-01-1991. ^bAfter 01-01-1992, after the exclusion criteria. Abbreviations: SD= standard deviation, PDD = prescribed daily dose, DDD = defined daily dose, TCA = tricyclic antidepressant, SSRI = selective serotonin reuptake inhibitor.

Prevalence

There was a 2.1-fold increase in the annual prevalence of overall antidepressant use from 3.9% in 1991 to 8.3% in 2011. This increase was also observed if analyses were performed stratified by sex (women 2.1-fold, men 2.3-fold). Women had on average a higher 1-year prevalence of antidepressant drug use over the calendar years than men, 7.9% (SD 2.0) versus 4.3% (SD 1.0), respectively. The prevalence of 'adequate antidepressant drug treatment' showed a steeper increase (2.4-fold), from 2.1% in 1991 to 5.1% in 2011. Figure 1 illustrates the 1-year prevalence over the calendar years stratified by the type of antidepressant. The largest increase was seen for SSRI use, with a 5.8-fold increase between 1991 and 2011. The same, but less pronounced, increase was observed for the other antidepressants (2.1-fold); while prevalent use of TCAs remained relatively stable. Amitriptyline (24.6%) and paroxetine (25.9%) are the most commonly dispensed antidepressants. The other antidepressants with

mirtazapine (6.2%) and venlafaxine (5%) of all dispensings were also commonly prescribed. The higher age categories showed on average a higher prevalence of antidepressant use. This was shown in the age categories of 72–77 years of age (6.5%, SD 0.8) and in elderly > 78 years of age (7.4% , SD 1.7) when compared with the two lower age categories 45–64 year (6.3%, SD 2.3) and 65– 71 years (6.0%, SD 1.3). All age categories showed an increase in the annual prevalence.

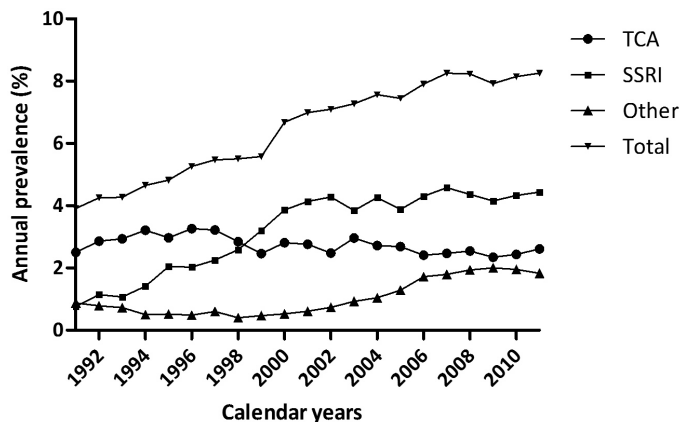


Figure 1. Annual prevalence of the different antidepressant drug classes over the calendar years. Abbreviations: TCA= tricyclic antidepressant, SSRI= selective serotonin reuptake inhibitor.

Incidence

A total of 1,905 individuals received a first dispensing of an antidepressant drug between 1992 and 2011. Overall, total incidence of antidepressant drug use decreased from 19.2 to 15.1 per 1,000 person-years (PY) between 1992 and 2011. Incidence rates were on average higher in women (19.4 incident users per 1,000 PY, SD 2.7) than in men (13.8 incident users per 1,000 PY, SD 3.0). The higher age categories (72–78 years, > 78 years) had on average a higher annual incidence rate over the 20-year period, respectively 17.5 (SD 4.3) and 22.1 (SD 6.2) incident users per 1,000 PY versus 14.6 (SD 2.5) and 13.7 (SD 4.2) incident users per 1,000 PY in the lower age categories. Of the 1,905 incident users and their recurrent episodes, we showed an increased incidence rate over the calendar years, from 30.7 to 33.8 per 1,000 PY between 1992 and 2011. Per 1,000 PY, incident use of SSRIs increased from 5.9 in 1992–1996 to 9.5 individuals in 1997–2001 (Figure 2). After 2001, the incident rates decreased again, to an annual incidence rate of 5.3 antidepressant users in 2007–2011. Incident use of TCAs decreased over the 20-year time-interval (11.9 incident users per 1,000 PY in 1992–1996 to 6.2 incident users per 1,000 PY in 2007–2011). Incident use of other antidepressants showed an increase from 1997–2001 onwards, from 0.6 incident users per 1,000 PY to 3.6 incident users per 1,000 PY in 2007–2011.

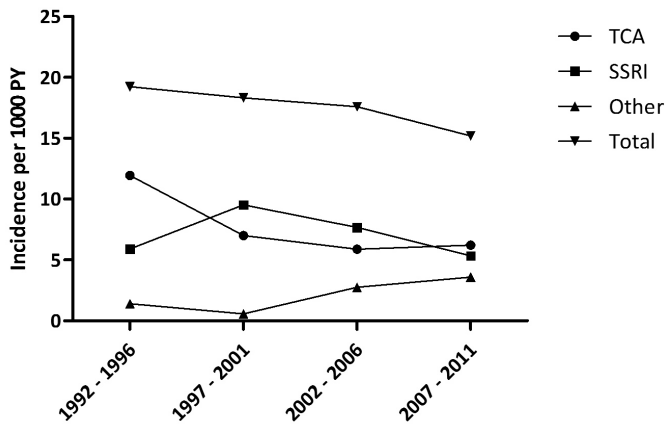


Figure 2. Incidence rates of antidepressant drug classes over the calendar years (5-year range). Abbreviations: TCA= tricyclic antidepressant, SSRI= selective serotonin reuptake inhibitor, PY= person-years.

These trends were also reflected in the incidence proportions for the different antidepressant drug groups (Figure 3). The first choice treatment for SSRIs increased from 30.7% until 55.7% of all incident antidepressant dispensings (1992–1996 until 1997–2001). After 2001, other antidepressants gained in popularity as initial dispensed antidepressant (3.3% until 23.7%). Overall, TCA use as a percentage of total incident antidepressant use decreased over the 20-year interval (62.0% until 41.0%). The percentages of incident antidepressant use show that amitriptyline (36.6%), paroxetine (19.7%) and mirtazapine (7.2%) are most often chosen at start of therapy.

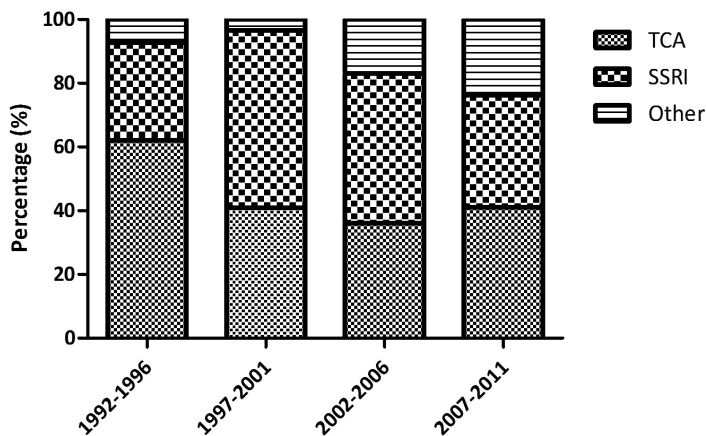


Figure 3. Proportions of antidepressant drug classes in incident users over the calendar years. Abbreviations: TCA= tricyclic antidepressant, SSRI= selective serotonin reuptake inhibitor.

After adjustment for age and sex, the risk of discontinuation decreased over the calendar years in SSRI and other antidepressant drug users, showing longer treatment duration in later years than in the first calendar years of follow-up (Table 2). When considering the different antidepressant drugs as determinants for discontinuation, SSRI use (hazard ratio [HR] 0.68, 95%CI 0.61; 0.77) and other use (HR 0.70, 95%CI 0.59; 0.83) were associated with a longer treatment duration compared to TCA use. Modifying the minimal follow-up time for the duration analyses from two years to three or four years did not materially change the results.

Table 2. The association between calendar years and risk of discontinuation.

Calendar years	TCA Hazard ratio (95%CI)	SSRI Hazard ratio (95%CI)	Other Hazard ratio (95%CI)
1992 - 1996	Reference	Reference	Reference
1997 – 2001	1.06 (0.86; 1.31)	0.82 (0.66; 1.01)	1.23 (0.58; 2.60)
2002 – 2006	1.03 (0.83; 1.27)	0.73 (0.58; 0.91)	0.69 (0.43; 1.11)
2007 – 2011	1.09 (0.86; 1.39)	0.72 (0.55; 0.95)	0.65 (0.40; 1.06)

Calendar years were adjusted for age and sex. N= 1,432 incident users in the analyses, exclusion of incident users with a shorter follow-up than 2 years after start of treatment episode.

Abbreviations: CI= confidence interval, TCA= tricyclic antidepressant, SSRI= selective serotonin reuptake inhibitor.

Discussion

In this population-based cohort study of middle-aged and elderly in the Netherlands, we showed that the prevalence of antidepressant drugs increased from 1991 until 2011, while the number of incident users did not increase over the years. The increasing numbers of prevalent use are mostly related to the recurrent episodes of use. The duration of treatment also increased over the years, and was mainly caused by SSRI and other use, which were used more persistently. From 2000 onwards, SSRI incident use decreased, while incident use increased for other antidepressants.

The 1994 guidelines from the Dutch College of General Practitioners suggested pharmacological treatment only for a severe depression, with TCAs being the first choice of pharmacological treatment [23]. The revision of these guidelines in 2003 did not make a distinction between mild and severe depression anymore, but the guidelines were more reserved regarding pharmacological treatment as first choice of treatment for depression [24]. SSRIs were considered equally beneficial to TCAs, and the choice of treatment should be based on the contraindications, possible adverse effects and previous treatment success. The original guidelines and the revision recommend 6 months of treatment continuation after disappearance of depressive symptoms [24, 25]. Since the changes in these guidelines are

minor, they cannot explain the decreasing numbers of incident users, the rising prevalence trends over the years and the excessive rise in use of SSRI and other antidepressants. We have no clear explanation for the decrease in incidence over the years. However, the observed decline in incident users might represent a saturation effect. Subjects who would start using antidepressants had already initiated an antidepressant drug, which will create a declining incidence.

The opposing patterns observed between prevalent and incident use are in line with previous Western literature and were previously explained by the long-term treatment of antidepressant drugs [3-5]. An increase in treatment duration over the years has been reported [2], indicating that there is a better compliance with the (international) treatment guidelines to treat a depressive episode for at least 6 months after disappearance of the symptoms [23, 24, 26]. We also observed an increase in the duration of antidepressant drug treatment over the calendar years, and a steeper increase in prevalence of “more adequate antidepressant drug treatment”. The increase in duration was mainly caused by SSRI and other use, which were used more persistently. Moreover, for the incidence analyses we only included the first episode of use, while after inclusion of recurrent antidepressant drug episodes we even observed a small increase in the incidence rates. The increase in duration of treatment and recurrent episodes might explain the opposing patterns between prevalence and incidence trends observed in our study.

This study confirms the increase in SSRI dispensings in the middle-aged and elderly population [4, 6, 7]. A mild adverse drug reaction profile, low toxicity and no need for plasma monitoring for SSRIs might explain this [4, 6, 27]. Despite the excessive increase in SSRI dispensings, incident use of SSRIs decreased after 2000, which was already shown by a previous study and might be explained by the substitution with other antidepressants [5]. We showed an increased prevalence and incidence of other/newer antidepressants from 2000 until 2011, of which mirtazapine and venlafaxine were the most popular ones. Recent utilization figures of antidepressant use in the Western population also observed an increase in use of other antidepressants [4, 5, 18, 27]. The multidisciplinary guideline for the treatment of depression for medical specialists (and general practitioners) also mentioned mirtazapine as first choice of treatment because of beneficial characteristics [25]. The stable prevalence and small decrease in incident TCA use is consistent with previous literature [5, 19]. We expected a larger decrease in TCA use, as they are not the first choice in the elderly population and other, more tolerable, antidepressants became available [4, 27, 28]. Specific guidelines were developed in later years for antidepressant drug use for the treatment of depression in the elderly, with SSRIs or nortriptyline as first choice treatment [29]. The relatively high use of TCAs in our study might also be explained by the multiple indications for which antidepressant drugs are prescribed. For example, amitriptyline is often the choice of treatment for neuropathic pain, which is more common in the older adults and elderly

[28, 30]. The increase of antidepressant drug use with age was consistent with previous literature [4-7, 31]. This age-related effect may be related to worsening of chronic diseases, physical health problems and related disabilities or increasing loneliness [4, 5, 7, 32].

We should consider a number of issues when we evaluate the results. Indications of antidepressant drug use may vary over the years and are related to multiple person specific characteristics (e.g. age, sex and comorbidities). As the information regarding the indication of antidepressant drug use and the clinical condition of the subjects is missing, we could not draw conclusions regarding treatment appropriateness for different indications. Moreover, the study might be influenced by its finite population, as participants who are prone to start taking antidepressants become incident users, finally leaving the participants who are not susceptible to antidepressant drug use in the cohort. Moreover, participants in our study had to have a 1-year antidepressant drug free period at start of the study to become incident user which may have caused some misclassification [33]. However, because the findings in our study are in line with previous research about the prevalence and incidence of antidepressant use, we do not think the effect we observed is completely explained by these limitations. Participants of the Rotterdam Study lived in a district of the city of Rotterdam in the Netherlands, which might influence the generalizability of our study. Preferences for antidepressant drugs can differ per region [34], although antidepressant use in our study was not extraordinary compared to national trends [34, 35].

Our study has some strong points which we would like to emphasize. Firstly, since local pharmacies provided us with an electronically standardized list of all dispensed medications from nearly all participants of the Rotterdam Study and because these data were prospectively gathered without knowledge of our research hypothesis, information bias and recall bias were unlikely. Pharmacy data was only missing for hospitalized participants and participants who moved into a nursing home. This might have decreased our number of total antidepressant users, but we do not expect that specific trends are influenced by these missing data. Secondly, we presented an antidepressant drug utilization study with data up to 2012 and a total follow-up of 21 years (1991–2011). We did not only look at dispensing trends, but used incidence and duration of treatment as well to characterize antidepressant drug use. Thirdly, we focused our analysis only on the middle-aged and elderly population. Antidepressant drug use increases most in the elderly population, but they are also at a higher risk of drug-drug interactions and adverse events [4-7, 12].

Conclusion

In our population of middle-aged and elderly, we can confirm the rise in antidepressant drug use. However, the total number of incident users did not increase. The rise might be explained by an increased duration of treatment and recurrent episodes of antidepressant drug treatment. Moreover, use of TCAs remained high in our middle-aged and elderly

population and we showed a shift from SSRIs to the other/newer antidepressants. With our results we gained more insight into antidepressant drug utilization patterns, which can be used to tackle the problems with high psychotropic drug use rates in the elderly.

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2.2

**Prescription and indication trends of antidepressant
drugs in the Netherlands between 1996 and 2012:
a dynamic population-based study**

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Abstract

Purpose: Antidepressant drug use increases worldwide. It is pivotal to closely monitor the use of antidepressants and to determine in what subpopulations the rise is most substantial. In a Dutch primary care database, we aimed to investigate the (sex- and age-specific) prevalence and incidence of antidepressant prescribing and to monitor the indication of incident prescriptions over a 17-year period (1996 – 2012).

Methods: This study, embedded in the Integrated Primary Care Information database, included all patients aged 10 years or older. Per calendar year, prevalence and incidence of antidepressant drug prescribing were calculated by drug class (tricyclic antidepressants, selective serotonin reuptake inhibitors [SSRIs] and others), sex and age. The indication of incident prescriptions (e.g. depression, anxiety, sleep disorders and neuropathic pain) was determined based on the International Classification of Primary Care codes.

Results: In total, 1.49 million patients were included. For all antidepressants together, the prevalence increased over time. However, incident prescribing of specifically SSRIs decreased from 2000 onwards. During the study period, incidence and prevalence were higher in older and female patients. The increase in prevalence and the decrease in incidence were more pronounced in females than in males. Furthermore, antidepressants were increasingly prescribed for indications as neuropathic pain and sleep disorders instead of depression.

Conclusions: In Dutch primary care, prevalent prescribing of antidepressants continued to increase, but incident prescribing of particularly SSRIs decreased from 2000 onwards. In later years, antidepressants were less frequently prescribed for depression-related indications in incident users.

Introduction

Antidepressant drug use increased substantially during the last decades [1-5]. The rise in antidepressants can be explained by an increasing number of indications (e.g. neuropathic pain and sleep disorders) and by a lower threshold to prescribe antidepressants [3, 4, 6, 7]. The rise in use was shown to be most pronounced for the selective serotonin reuptake inhibitors (SSRIs) [4, 5, 8]. Compared with the older tricyclic antidepressant (TCAs), SSRIs have a milder adverse drug reaction profile, have a lower risk of severe consequences in case of overdosing, and do not require continuous monitoring of blood levels in a number of indications [5, 8-10]. Although increasingly prescribed, it was shown in some studies that incident antidepressant drug use only increased until the year 2000. Thereafter, the number of new users of antidepressants stabilized or even decreased [4, 11]. The discrepancy between patterns of prevalence and incidence of antidepressant use was most likely caused by an increased recurrent antidepressant use and increased treatment duration over time [2, 12].

Although antidepressant use was higher in the older aged, an excessive rise in antidepressant use by the older aged was not demonstrated consistently [4, 8, 11, 13]. Nevertheless, there are concerns whether the indication to prescribe antidepressants is always justified in elderly [14-17]. This patient population is at higher risk for drug-drug interactions and adverse drug reactions, as they have a lower drug metabolism, a lower renal clearance, have more co-morbidities and use more medications concomitantly [10, 18, 19]. To minimize the risk of adverse drug reactions in the elderly, an addendum of the multidisciplinary guidelines for general practitioners and medical specialists was published in 2008. In this guideline, it was recommended to use SSRIs or nortriptyline, instead of the other TCAs [20]. However, it is unclear to what extent general practitioners adhere to these guidelines.

The increase in antidepressant use in the last decades was also observed in the Netherlands [2, 5, 12, 21]. However, most studies did not yet investigate whether some subpopulations were specifically prescribed an increasing number of antidepressants (e.g., females or elderly), which is pivotal to estimate what subpopulations are specifically at risk to develop particular antidepressant-related adverse effects. For example, it is unknown whether the preference of the TCA nortriptyline for the treatment of depression in elderly is also reflected by a faster increase in prescribing in this subpopulation [20]. In addition, although antidepressants are prescribed for an increasing number of indications, the indications for antidepressant use over time are poorly studied.

We aimed to investigate the (sex- and age-specific) prevalence and incidence of antidepressant drug prescribing in a population-based study of specifically middle-aged and elderly in the Netherlands. Besides, we aimed to investigate indications for incident antidepressant drug prescribing over time.

Methods

Setting of the Integrated Primary Care Information database

This study was conducted within the Integrated Primary Care Information (IPCI) database. A more detailed description about this database has been published elsewhere [22]. In summary, this database is a research database containing the electronic medical records of general practitioners (GPs) and currently comprises more than 1.5 million patients in the Netherlands. The IPCI database was initiated in 1992 and expanded greatly since then. With regard to demographic factors such as age and sex, the distribution of the IPCI population is representative of the overall Dutch population [23]. Research in the IPCI database is optimal in several ways. First, all Dutch inhabitants are registered with a GP practice, limiting selection bias. Second, in the Dutch healthcare system, the GP acts as a gatekeeper between primary and secondary care. Medical records of GPs therefore also contain information from secondary care. And finally, participating GP practices are not allowed to use additional paper-based medical records which makes the electronic database more complete.

The IPCI database contains information on demographics, symptoms, diagnoses, referrals, clinical and laboratory findings, hospitalizations and drug prescriptions. Information on drug prescriptions comprises the brand name, generic name, number of pills/capsules/solution, prescribed daily dose, and the Anatomical Therapeutic Chemical (ATC) classification code [24]. The IPCI database follows the European Union guidelines on the use of medical data for medical research and has been validated for the use of pharmacoepidemiological research [22]. The current study was approved by The Scientific and Ethical Advisory Board of the IPCI project (project number: 12/12).

Study population

For the current study we included all patients aged 10 years and older with at least one year of medical history from the IPCI database. Patients, who had a follow-up of at least one year, were followed from start of study (January 1, 1996) until death, loss to follow-up or end of the study period (December 31, 2012), whichever came first. For the calculation of the incidence rate, patients were censored at the date of their first antidepressant drug prescription.

Study outcome

An antidepressant drug prescription was defined based on the (4-digit) ATC-code "N06A". Antidepressants were classified into antidepressant drug classes (ATC-code: TCA, "N06AA"; SSRI, "N06AB"; other, "N06AX"). Amitriptyline (ATC-code: "N06AA09") and nortriptyline (ATC-code: "N06AA10") were identified based on the individual complete (7-digit) ATC-codes. Changes in ATC coding were taken into account. For all these categories both prevalence and incidence rates were calculated.

The yearly prevalence of antidepressant prescriptions was calculated by dividing the total number of patients with at least one antidepressant drug prescription by the total number of person years in a calendar year. Because of data conversion in different health care software systems in 2006, prevalence rates could not be calculated correctly in this year. For this reason prevalence rates in this year were interpolated based on the average of the surrounding years.

To calculate the incidence of antidepressant prescribing, we divided the total number of patients who were prescribed an antidepressant for the first time during follow-up by the total number of person years (PY) within a calendar year. We defined a prescription as incident when no antidepressant drug prescription was identified in the one year medical history prior to study inclusion. For this analysis, no interpolation was necessary, as interpolated results and actual calculated results were similar in 2006.

The indication of incident antidepressant prescriptions was based on International Classification of Primary Care (ICPC) codes [25]. We selected only those indications from whom we expected to have sufficient numbers in middle-aged and elderly patients. The following indications were considered when identified within 90 days before or after the first antidepressant prescription: depression (ICPC code: P03, P76), anxiety (P01, P74), sleep disorders (P06), neuropathic pain (N94) and psychosis and schizophrenia (P71, P72, P98). When more than one indication was recorded within 90 days around initiation of incident antidepressant therapy, the incident antidepressant prescription was considered to be prescribed for “multiple indications”.

Co-factors

Prevalent and incident antidepressant prescribing were studied over time, and stratified by sex and different age strata. Strata were defined as such that a sufficient number of patients were available in all strata. The following age strata were defined: 10 – 19, 20 – 39, 40 – 59, 60 – 79 and ≥ 80 years. For the analysis on amitriptyline and nortriptyline, we applied a different stratification, as the number of patients treated with amitriptyline or nortriptyline ≥ 80 years was too low. This age stratum was combined with the patients between the age of 70 and 79 years (denoted hereafter as elderly). This group was compared with patients between the age of 50 and 69 (denoted hereafter as middle-aged), to compare the patterns in middle-aged and elderly patients.

Data analysis

The characteristics of the study population were studied by calculating the number of patients in an age group stratified by sex. During follow-up patients were allowed to switch age-groups, therefore these numbers exceeded the total number of patients included in the study.

The prevalence and incidence rates were calculated per calendar year. Results were presented by calculating the average of the rates per pair of calendar years as in some of the subanalyses an insufficient number of prescriptions was available. Rates were calculated for all antidepressants together, separately per drug class and separately for amitriptyline and nortriptyline.

We stratified the analyses additionally by sex and age strata. The comparison of prevalence and incidence rates over time between different age categories and between males and females was conducted using linear regression analysis. As the number of patients increased over time, we weighted the analyses for the total number of person years in two consecutive years. The comparisons were statistically tested by including a multiplicative interaction term between the calendar year and the studied factor (for example, is a rise or decrease in prevalent or incident prescribing specific for a particular subpopulation). Analyses were conducted with SPSS statistical software (version 21.0, IBM Corporation, Armonk, NY). A two-sided p-value below 0.05 was considered statistically significant.

To study the indications of incident antidepressant prescriptions over time, the total number of known indications within a pair of calendar years, as extracted from the study population, was considered as 100 percent. The contribution of an individual indication was calculated as a percentage relative to the total number of identified indications.

Results

Population characteristics

In total, approximately 1.49 million patients had an age above 10 years during follow-up and were included in the study (Table 1). The study population comprised slightly more females than males. Females were also more frequently older than 70 years.

Table 1. Characteristics of the study population.

	Females N = 767,492	Males N = 724,870
Age, years, N (%)		
10 – 19	122,914 (16.0)	127,358 (17.6)
20 – 29	148,862 (19.4)	137,251 (18.9)
30 – 39	150,756 (19.6)	146,658 (20.2)
40 – 49	161,353 (21.0)	159,925 (22.1)
50 – 59	139,100 (18.1)	137,416 (19.0)
60 – 69	112,033 (14.6)	109,267 (15.1)
70 – 79	75,537 (9.8)	64,483 (8.9)
≥80	52,391 (6.8)	29,913 (4.1)

The sum of the percentages exceeds the 100 percent and exceeds total number of patients, as participants could change age category during follow up.

Prevalent antidepressant prescriptions

From 1996 to 2012 (Figure 1a), prevalent antidepressant prescribing doubled (from 35.5 per 1,000 patients in 1996 – 1997 to 69.8 per 1,000 patients in 2012). The absolute rise in prevalence of SSRIs was largest and increased from 18.2 per 1,000 patients in 1996 – 1997 to 38.4 per 1,000 patients in 2012. In addition, prevalence of TCAs remained stable and the prevalence of other antidepressants almost tripled over time.

In the sex-stratified analysis (Figure 1b), prevalence was higher and increased more over time in females than in males (p -value = 0.005). In addition, although prevalence was higher in the older aged (Figure 1c), the increase in prevalent prescribing of antidepressants was similar over the age strata (p -values > 0.18). This remained similar when stratified by drug class (data not shown). In addition, patients aged 70 years and older (the elderly) were prescribed more amitriptyline and nortriptyline compared to patients between the age of 50 and 69 years (the middle-aged; Figure 1d). In the middle-aged population, the rise of prevalent prescribing of nortriptyline was less pronounced than the rise of prevalent prescribing of amitriptyline (p -value = 0.003). However, the increase in prevalent prescribing was similar for amitriptyline and nortriptyline in the elderly (p -value = 0.51).

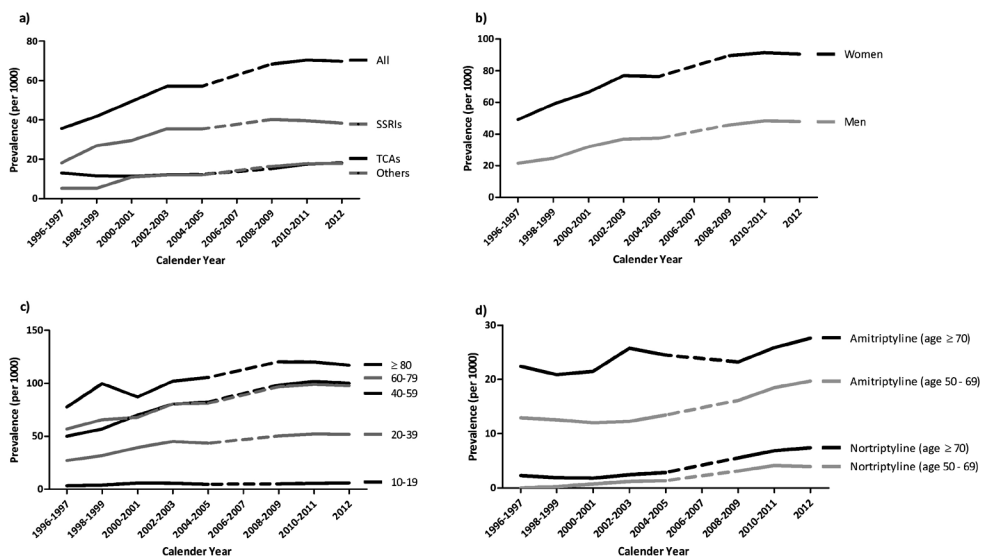


Figure 1. Prevalence of antidepressant drug prescribing over time.

a) Prevalence of antidepressant use by drug class. **b)** Prevalence of antidepressants in men and women. **c)** Prevalence of antidepressant drug prescribing by age strata. **d)** Prevalence of amitriptyline and nortriptyline in patients between age 50 and 69 and above 69 years. Data presented as the number of patients with at least one prescription in a calendar year per 1000 patients. The dotted part of the line represents the period in which prevalence could not be estimated properly. Abbreviations: SSRIs= selective serotonin reuptake inhibitors, TCAs= tricyclic antidepressants.

Incident antidepressant prescribing

Until 2000, incident prescribing of antidepressant drugs increased (Figure 2a), but decreased thereafter (from 22.6 per 1,000 PY in 2000 – 2001 to 17.1 per 1,000 PY in 2012). Of the different antidepressant drug classes, the decrease in incident prescribing of SSRIs was strongest, whereas incident prescribing of TCAs increased in more recent years and was highest in 2012 (4.3 per 1,000 PY).

Females had a higher incidence of antidepressant drug prescribing than males (Figure 2b). The decrease in incidence from 2000 – 2001 onwards was more pronounced in females than in males (p-value = 0.014). Furthermore, the incidence of antidepressant prescribing was highest in patients > 80 years, but trends over time were similar across the age strata (Figure 2c). From 2006 onwards (Figure 2d), incident prescribing of amitriptyline and nortriptyline increased both in older adults and elderly, but the difference between the two remained similar over time for both age strata (p-values > 0.16).

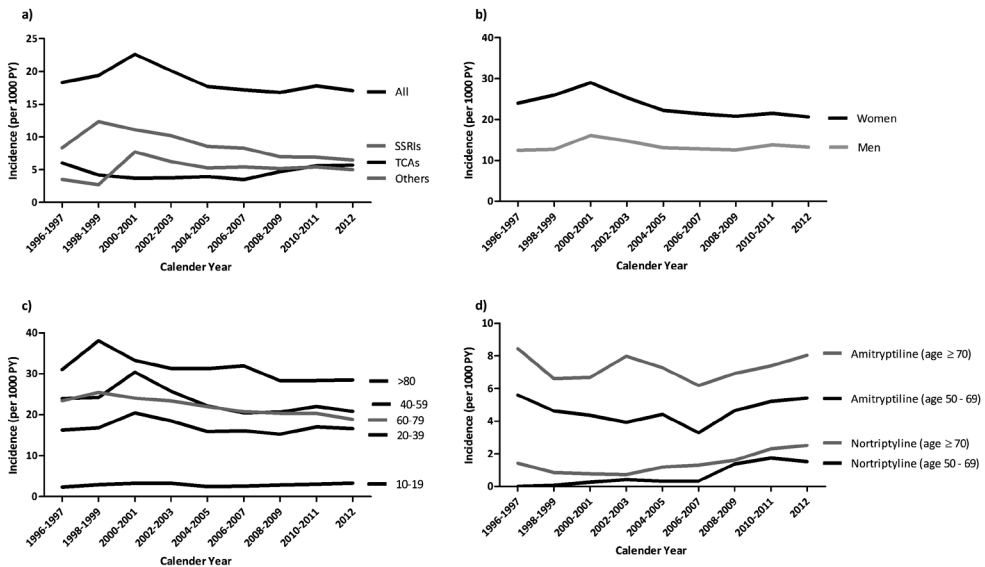


Figure 2. Incidence of antidepressant drug prescribing over time.

a) Incidence of antidepressant use by drug class. **b)** Incidence of antidepressants in men and women. **c)** Incidence of antidepressant drug use by age strata. **d)** Incidence of amitriptyline and nortriptyline in patients between age 50 and 69 and above 69 years. Data presented as the total number of incident users per 1,000 person years within a calendar year. Abbreviations: SSRIs= selective serotonin reuptake inhibitors, TCAs= tricyclic antidepressants.

Indication of prescribing

Indications registered by ICPC codes were recorded for 41 percent of the incident prescriptions during the study period, which decreased from 68 percent in 1996-1997 to 40 percent in 2012. In this subpopulation, antidepressants were mostly prescribed for depression-related

disorders. However, this percentage decreased from 65% in 1996 to 47% in 2012 (Figure 3a). In more recent years, antidepressants were increasingly prescribing for sleep disorders and neuropathic pain. The relative decrease of prescribing antidepressants for depression-related indications was least visible for SSRIs (Figure 3b). Furthermore, depression-related indications accounted only for a minor percentage (18% in 2012) of incident TCA prescriptions (Figure 3c). TCAs were mostly prescribed for sleep disorders and neuropathic pain (both 25 – 30 percent in 2012). However, this was different for nortriptyline, which was mostly prescribed for depression-related indications (31 percent in 2012; results not presented in the figure). Other antidepressants were also increasingly prescribed for indications like anxiety and sleep disorders (Figure 3d). Compared with middle-aged adults, elderly were more often prescribed antidepressants for indications different than depression (data not shown).

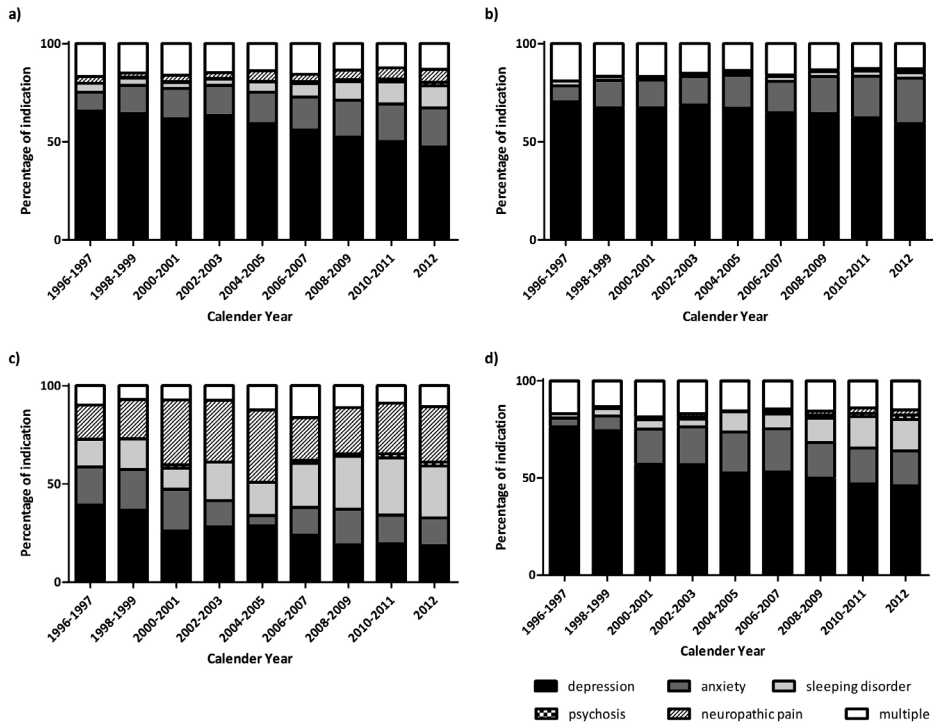


Figure 3. Indication of antidepressant prescribing over time. **a)** Indication trends of all antidepressants taken together. **b)** Indication trends of selective serotonin reuptake inhibitors. **c)** Indications trends of tricyclic antidepressants. **d)** Indications trends of other antidepressants. Data presented as the percentage of drugs prescribed for that indication. Abbreviations: SSRIs= selective serotonin reuptake inhibitors, TCAs= tricyclic antidepressants.

Discussion

Within this dynamic population-based study, we observed that prevalent antidepressant drug prescribing increased between 1996 and 2012, although incident prescribing of particularly SSRIs decreased from 2000 onwards. In females, the increase in prevalence and the decrease in incidence of antidepressant drug prescribing were more pronounced over time. In addition, the prevalence and incidence of antidepressant prescribing were higher in the older aged. However, the rise in prevalence and incidence of antidepressant prescribing was not different for a specific age-group. Over time, antidepressant drugs (in particular TCAs and other antidepressants) were increasingly prescribed for other indications than depression-related indications.

The 1994 edition of the guidelines by the Dutch College of General Practitioners stated that pharmacological treatment is only preferred for severe cases of depression [26]. However, the revised guidelines, published in 2003, were more reserved regarding the use of pharmacological treatment as first choice. This guideline preferred to start with non-pharmacological treatment [27]. Within our study population, we observed that the prevalence of antidepressants, in particular SSRIs and other antidepressants, increased. At least for the group of other antidepressants, the preference of venlafaxine and mirtazapine by the multidisciplinary guidelines (version 2008), might have contributed to the increase in prevalence of this drug class [20, 28], although the introduction of more antidepressants in this drug class on to the market may have contributed as well. In addition, our findings are in agreement with other studies conducted in Western populations [4, 11, 12]. Furthermore, we observed that from 2000 onwards, there is a trend towards a lower incidence of antidepressant prescribing, which is in line with other studies [4, 11]. This was in particular the case for the SSRIs. The revised treatment guideline from 2003, which was more reserved to initiate pharmacological treatment, might have contributed to the modest decrease in incident use [27].

The discrepancy between prevalence and incidence trends of antidepressant drug use is also described by other studies and is most likely explained by an increase in recurrent use and treatment duration [2, 12]. The difference in prevalent and incident prescribing over time between males and females has not yet been reported. The indication depression to prescribe antidepressants might explain the difference in trends between males and females, although we cannot exclude that also other indications (e.g., premenstrual syndrome) contributed to the observed difference between males and females [29, 30].

Elderly patients are of special interest, as this population has more co-morbidities and is at higher risk of polypharmacy, which increases the risk of drug-drug interactions and adverse drug reactions [10, 18, 19]. Some of the previous conducted studies showed that the increase in antidepressant drug use was mainly in elderly when compared to middle-

aged adults [8, 13]. However, within our study population, the increase in prevalence and the decrease in incidence were similar across different age strata. Similar results were found in a study conducted in British Columbia [4]. Since 2008, the interdisciplinary guidelines for the treatment of depression recommend nortriptyline instead of amitriptyline for an elderly patient diagnosed with depression [20], as nortriptyline has less cardiac side effects than other TCAs. However, no larger increase in prevalence and incidence over time was observed for nortriptyline relative to amitriptyline, which indicates that there was no clear preference for nortriptyline. The difference in indications to prescribe amitriptyline and nortriptyline might explain part of the inconsistency with the treatment guidelines. For example, amitriptyline is preferred by the guidelines of the Dutch College of General Practitioners as a treatment for neuropathic pain [31, 32]. In addition, nortriptyline was prescribed more often for depression-related indications than all TCAs together, which fits the preference by the treatment guidelines for the treatment of depression in the elderly [20].

This study has a few strengths and limitations. A strength was the large sample size, and the representativeness of the overall Dutch population [23]. The latter strength was supported by the similarity of our numbers with prescription numbers from the total Dutch population, as collected by the National Healthcare Institute [33]. This study was conducted in a general practice database. Thus, we were dependent on the quality of patient information registered by the GP. For this reason, the indication of incident antidepressants can be misclassified. In addition, the definition of an incident prescription was based on non-use during a 1-year period prior to study inclusion. Patients could still use an antidepressant prior to this period for which we did not have information. Furthermore, we used ICPC codes to define the indication of incident antidepressant drug prescriptions, but this could only be defined for a minor proportion of the total population (about 41%). A manual validation of free text of the patient records would have been the best approach, but because of the large sample size, this was not feasible. The percentage of registered indications was similar as published before in the Dutch population [34]. However, their time-window around the first antidepressant drug prescription was larger than used in our study. Nevertheless, the proportion of missing indications of use is unlikely to be related to the type of antidepressant and thus would not have influenced the results.

In conclusion, we observed that the prevalence of antidepressant prescribing increased over time, but incident antidepressant prescribing, and in particular incident SSRI prescribing, decreased from 2000 onwards in Dutch primary care. These trends over time were different for males and females, but not for different age strata. In addition, the proportion of antidepressants prescribed for depression-related indications decreased during the study period.

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2.3

Self-reported indications for antidepressant use in a population-based cohort of middle-aged and elderly

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Submitted

Abstract

Background: In clinical practice, antidepressants are prescribed for a wide range of different indications. Studies investigating indications for antidepressant prescribing mostly rely on diagnostic labels from general practitioners. However, diagnostic codes might be incomplete if not all indications were under investigation.

Objective: In the present study, we aimed to study indications for antidepressant use based on self-report. Also, we studied the presence of depressive symptoms associated with the self-reported indications in a middle-aged and elderly population.

Setting: This study was embedded in the prospective population-based Rotterdam Study (age \geq 45years).

Method: Antidepressant use (selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants [TCAs] and other antidepressants), self-reported indication for use, and presence of depressive symptoms (based on the Center for Epidemiological Studies Depression Scale) were based on interview.

Main outcome measures: Self-reported indications were based on officially approved and clinically-accepted indications extended with common off-label indications mentioned in previous literature. A score of 16 and higher on the Center for Epidemiological Studies Depression Scale was considered as an indicator for clinically-relevant depressive symptoms.

Results: We included 11,860 participants with eligible interview data. The majority of the 914 antidepressant users reported 'depression' (52.4%) as indication for treatment. Furthermore, anxiety, stress and sleep disorders were reported in SSRI and other antidepressant users (ranging from 5.9% - 13.3%). The clinically-accepted off-label indication 'pain' was common in TCA users (19.0%). Besides headache, all indications were statistically significantly associated with higher depressive symptom scores when compared to non-users.

Conclusions: Depression was the main indication for antidepressant treatment. However, our findings suggest that antidepressants are also used for off-label indications, subthreshold disorders and complex situations in the middle-aged and elderly population. Clinically-relevant depressive symptoms were observed in indications other than depression, which supports a high comorbidity of physical problems, psychological distress and depression. Nevertheless, antidepressant use should not be used as a marker of subclinical depression.

Introduction

Antidepressants are not only prescribed for depressive disorders, but also for other approved, clinically-accepted and off-label indications such as anxiety disorders, sleep disorders and neuropathic pain. Pharmacoepidemiological studies that investigated indications for antidepressant use often registered indications based on clinical diagnostic codes from medical records [1-5] or were based on diagnoses from structured interviews with general practitioners (GPs) [6, 7]. However, diagnostic codes might be incomplete if not all indications were under investigation, subthreshold psychiatric symptoms were not registered or because of diagnostic uncertainty by the GP [1-3, 5].

Studies which investigate reasons for antidepressant prescribing from a patients' perspective give insight into the original symptoms and primary condition as experienced by the patient. Besides the traditional indications, subthreshold disorders, physical comorbidities and life events have been associated with use of antidepressants [8-11]. Further characterization of these individuals and their, non-psychiatric, indications is needed.

Therefore, our objective was to investigate indications for antidepressant treatment based on patients' self-report in a population-based cohort study of middle-aged and elderly. Additionally, we aimed to assess presence of depressive symptoms, as we hypothesize that all indications might be accompanied by comorbid depressive symptoms.

Methods

Study setting

The study was conducted within the prospective population-based Rotterdam Study. The Rotterdam Study was initiated in 1990, and investigates the incidence of, and risk factors for, several age-related diseases. After extension over the years, the study comprises a total of 14,926 participants. All participants were aged 45 years or older at baseline. Detailed information on design, objectives and methods of the Rotterdam Study has been published elsewhere [12, 13].

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the "Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study)". All participants provided informed consent to participate in the study.

Study population

From 1997 onwards, participants were interviewed every 4-5 years by research assistants

about their current drug use and indication for use (N=11,860). We included participants who reported antidepressant use at one of the interview rounds. Home interviews of other participants, with complete interview data, were included as reference population of non-users.

Home interviews

Participants were asked to present all their drug containers during the home interview. Drug names, dosages, and regimen were registered by research assistants. Antidepressants were selected, based on their Anatomical Therapeutic Chemical (ATC) code (ATC code= 'N06A'), and categorized into tricyclic antidepressants (TCAs, ATC-code= 'N06AA'), selective serotonin reuptake inhibitors (SSRIs, ATC-code= 'N06AB') and other antidepressants (ATC-code= 'N06AF/AG/AX'). St John's wort was not taken into account. Moreover, participants were asked for which indications the specific drugs were taken. The symptoms or disorders mentioned by the participant were registered as 'free text', without interpretation or adjustment by the research assistants. Two researchers (NA and RN) independently categorized the complete list of symptoms and disorders into eight groups. Discrepancies were discussed to reach final consensus. The categories would represent disorders and related symptoms, and were based on officially approved and clinically-accepted indications extended with common off-label indications mentioned in previous literature (Table 1) [1, 3, 14].

As part of the home interview, presence of depressive symptoms in the week before interview were screened for with a Dutch version of the Center for Epidemiological Studies Depression Scale (CES-D) [15]. A score of 16 and higher was considered as an indicator for clinically-relevant depressive symptoms [16].

Statistical analyses

We included the first eligible interview of participants. Self-reported indications were presented for the total group of antidepressant users and stratified by antidepressant class (TCA, SSRI, other). Participants could report multiple antidepressants and indications in an interview. In a subsample analysis, we excluded participants without information regarding cognitive functioning or with possible cognitive impairment (Mini-Mental State Examination score ≤ 23 [17]), as cognitive impairment may affect the validity of self-reported data. Also, indications for treatment were stratified by age (≤ 65 , >65 years) and sex.

The median depression score and the percentage of participants with clinically-relevant depressive symptoms were presented for all indications of treatment and for non-users. Median scores and percentages for every indication category were compared to non-users or compared to the group with indication 'depression' with a Mann-Whitney U, or Pearson Chi-square test. For these analyses, we excluded participants who reported multiple

antidepressants and indications in an interview. A p-value below 0.05 was considered statistically significant and IBM SPSS Statistics (version 21.0, IBM Corp., Somers, NY, USA) was used for analyses.

Table 1. Overview of indications and their corresponding self-reported symptoms, and the registered approved or clinically-accepted antidepressants.

Category	Reported symptoms	Approved antidepressants	Clinically-accepted antidepressants ^a
Depression	Depression, anti-depressant, feeling down, discouraged	All	
Anxiety	Anxiety, panic, hyperventilation	Clomipramine, venlafaxine, duloxetine and SSRIs ^b	Imipramine
Stress	Stress, burn-out, restlessness, soothing		
Sleep disorders	Insomnia, to fall asleep, sleep		
Headache/migraine	Headache, migraine		
Pain	Pain, nerve pain, hernia, fibromyalgia, shingles	Duloxetine	TCAs (mainly amitriptyline and nortriptyline)
Other indications	Parkinson’s disease, menopause, tingling legs, general mental problems		
Unknown	No answer, unknown		

^a Clinically-accepted antidepressants are mentioned in the national therapeutic monitoring system or in national guidelines

^b Some SSRIs are only registered for specific anxiety disorders, however we consider all SSRIs registered as we cannot distinguish these specific anxiety disorders.

Abbreviations: SSRIs = selective serotonin reuptake inhibitors.

Results

Of the 11,860 participants, a total of 914 (7.7%) individuals reported to be current antidepressant user at one of the interview rounds. At the first eligible interview round, the mean age of the antidepressant users was 67.3 years (SD 10.7), 72.3% were women, and most participants were prescribed an SSRI (54.5 %).

Depression was most commonly reported as indication for treatment in the antidepressant users (52.4%, Table 2). SSRIs and other antidepressants were most often used for depression, anxiety and stress symptoms, although other antidepressants were also prescribed for sleep disorders and other indications. Of the TCA users, only 29.6% reported

depression as an indication, while stress (14.4%), sleep disorders (10.4%) and pain (18.9%) were also frequently reported. Other reported indications were menopausal complaints, tingling or restless legs, Parkinson’s disease and general mental health problems (Table 1). Percentages did not materially change when we excluded participants with possible cognitive impairment (subsample n=717, results not shown). Moreover, stratification by age showed higher percentages of depression (61.0% versus 45.0%) and anxiety-related (14.4% versus 3.9%) indications in the younger population than in the older population, while the older population had a higher percentage of stress related (9.0% vs 16.5%) and unknown indications (5.0% vs 20.8%). Stratification by gender showed comparable indications for treatment for men and women (results not shown).

Table 2. Self-reported indications for all antidepressant users and stratified by type of antidepressant.

	Total N=914 N (%)	TCA N=270 N (%)	SSRI N=498 N (%)	Other N=153 N (%)
Reported indication for use^a				
Depression	479 (52.4)	80 (29.6)	307 (61.6)	92 (60.1)
Anxiety	80 (8.8)	6 (2.2)	65 (13.1)	9 (5.9)
Stress	119 (13.0)	39 (14.4)	66 (13.3)	14 (9.2)
Sleep disorders	45 (4.9)	28 (10.4)	6 (1.2)	11 (7.2)
Headache/migraine	10 (1.1)	9 (3.3)	1 (0.2)	0 (0.0)
Pain	54 (5.9)	51 (18.9)	1 (0.2)	2 (1.3)
Other	48 (5.3)	19 (7.0)	18 (3.6)	11 (7.2)
Unknown	123 (13.5)	46 (17.0)	57 (11.4)	20 (13.1)

NOTE: number of separate antidepressants and indications do not add up to the total number of unique participants (n=914), as participants could report multiple antidepressants and indications at one interview round. ^a Reported indications for antidepressant use represent disorders and related symptoms. See Table 1. Abbreviations: TCA= tricyclic antidepressant, SSRI= selective serotonin reuptake inhibitor.

All indications, except headache, were associated with a significantly higher percentage of participants with clinically-relevant depressive symptoms or a higher median CES-D score than in the non-users (8.1%, median 2.0, interquartile range 0.0-7.0, Table 3). Of the antidepressant users with the self-reported indication depression, 36.9% also had clinically-relevant depressive symptoms as measured by questionnaire. Nonetheless, of the users who exclusively reported another indication for use, 23.4% had clinically-relevant depressive symptoms ranging from 15.9% to 29.2% over the different indication categories (Table 3). However, the percentage with clinically-depressive symptoms was significantly lower in participants who exclusively reported another indication for use, when compared to the indication ‘depression’.

Table 3. Self-reported indications for antidepressant use and presence of depressive symptoms.

	N	Median CES-D score Median (IQR)	Presence of depressive symptoms ^d N (%)
Non-use	10,797	2.0 (0.0 – 7.0)	877 (8.1)
Reported indication for use^a			
Depression	436	11.0 (3.0 – 20.8) ^b	161 (36.9) ^b
Indications except depression	410	8.0 (3.0 – 15.0) ^{b,c}	96 (23.4) ^{b,c}
Anxiety	59	5.0 (2.0 – 13.0) ^{b,c}	10 (16.9) ^{b,c}
Stress	105	9.5 (3.0 – 16.5) ^b	27 (24.7) ^{b,c}
Sleep disorders	33	7.0 (3.0 – 15.5) ^b	8 (24.2) ^b
Headache/migraine	8	1.0 (0.0 – 14.3)	2 (25.0)
Pain	48	5.0 (1.0 – 13.8) ^{b,c}	9 (18.8) ^{b,c}
Other	44	6.5 (2.3 – 13.0) ^{b,c}	7 (15.9) ^c
Unknown	113	9.0 (4.5 – 16.9) ^b	33 (29.2) ^b

^a Reported indications for antidepressant use represent disorders and related symptoms. See Table 1. ^b Significantly different from non-use ($p < 0.05$) ^c Significantly different from the indication 'depression' ($p < 0.05$) ^d Presence of depressive symptoms is based on a Center for Epidemiological Studies Depression Score of 16 or higher. NOTE: complete caseset analysis. St John's wort was not taken into account as antidepressant and excluded from the non-use group. Participants who reported multiple antidepressants and indications at one interview round were excluded. Abbreviations: CES-D= Center for Epidemiological Studies Depression Score, IQR = interquartile range.

Discussion

In line with other studies, we observed that depression was the most frequently reported indication for antidepressant use [1, 4-6]. Of those who reported depression as indication for treatment, around 40% actually reported clinically-relevant depressive symptoms based on assessment with the CES-D. Possibly, antidepressants were prescribed for mild depressive symptoms, or participants were on maintenance treatment after successful antidepressant treatment [9, 18].

As hypothesized, more than 20% of users also reported clinically-relevant depressive symptoms for indications other than depression, and had a higher depression score when compared to non-users. Two possible explanations will be discussed. First, we were able to capture mild or isolated symptoms, such as restlessness and fatigue, which do not conform to the diagnostic label depression according to the DSM-IV criteria. Yet, these are symptoms which could be part of a possible depression. Second, symptoms such as depression, social problems, distress and physical pain are highly correlated and often occur concomitantly. Depression might be a secondary indication next to the reported primary condition [6, 19-21]. Nevertheless, antidepressant use cannot be used as a marker for subclinical depressive symptoms. In most users who exclusively reported another indication, the overall percentage of depressive symptoms was significantly lower when compared to those who reported depression as indication for treatment.

In contrast, almost 80% of users with an indication other than depression did not report concurrent depressive symptoms. In this case, the reported (off-label) indications such as anxiety, pain, stress or sleeping disorders were the main reason for prescribing according to the patient. For example, we observed that almost one fifth of all TCA prescriptions were reported as being used for pain. This proportion was higher than in previous studies [1, 4], which might be due to the high average age of our population because pain is highly prevalent in the elderly [22]. The off-label indication ‘stress’ was also frequently mentioned in our study. This might relate to participants who experience psychosocial problems and distress, without clinical depressive symptoms which justify antidepressant prescribing. Previous studies already reported that, besides the traditional indications, combinations of other mental complaints, multi-morbidity, psychosocial problems and social distress are also important reasons to prescribe antidepressants [8-11, 23]. This may be particularly important in our elderly population as elderly experience more life events, physical impairment and general health complaints. This is confirmed by our stratification on age as the percentage with stress related indications is even higher in the elderly population. Although prescriptions for these indications seem off-label, no conclusions can be drawn regarding the appropriateness of the antidepressant prescribing in our study. Information from detailed individual medical records and longitudinal data would be required.

Strengths of our study are the population-based setting and the availability of interview data from participants on antidepressant use, indication for use and depression score at the same point in time. However, some limitations should be addressed. First, indications based on self-report might be biased as they relate to individual cognitive and linguistic abilities. However, results did not materially differ after exclusion of participants with possible mild cognitive impairment. Second, reported symptoms were manually categorized by two independent researchers in different indication groups. These categories might not be mutually exclusive from each other as symptoms often co-exist and are not always distinctive for one specific indication. Third, analyses were based on cross-sectional data and do not capture changes in symptoms over time.

Conclusion

Our results suggest that apart from the product-labelled indications, antidepressant use is common for self-reported off-label indications, subthreshold disorders and distress in the middle-aged and elderly population. Clinically-relevant depressive symptoms were observed for indications other than depression, which suggests that there is a high correlation between physical problems, psychological distress and depression. Nevertheless, antidepressant use should not be used as a marker of subclinical depression.

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2.4

Adherence and persistence to antidepressant drug treatment in a population-based study of older adults and elderly

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In preparation

The background is a complex, abstract composition of black and white textures. It features numerous brushstrokes of varying thickness and direction, some appearing as fine, hair-like lines and others as thick, impasto-like applications. There are also several large, irregular splatters and blotches of white paint against a dark background, and vice versa. The overall effect is one of raw, expressive energy and chaotic movement.

3

Unintended effects of antidepressants





3.1

Inhibition of serotonin reuptake by antidepressants and cerebral microbleeds in the general population

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Abstract

Background and purpose: Serotonin reuptake inhibiting antidepressants decrease platelet aggregation. This may cause an increased risk of intracerebral hemorrhage. However, the risk of subclinical microbleeds, which are highly prevalent in middle-aged and elderly people, is unknown. We studied whether serotonin reuptake inhibiting antidepressants increase the frequency of cerebral microbleeds and secondarily whether they lower the presence of ischemic vascular damage.

Methods: Within the population-based Rotterdam Study, information on antidepressant use was obtained from continuously monitored pharmacy records. Brain MRI was available in 4,945 participants (55% women, mean age 64 years) between 2005-2011. We categorized antidepressants based on affinity for the serotonin transporter: high, intermediate or low. Microbleeds (presence and location) and ischemic lesions (lacunes, white matter lesions) were rated on MRI. Logistic and linear regression, adjusted for age, sex, depressive symptoms and cardiovascular risk were used to study the association of antidepressants with microbleeds, and ischemic vascular lesions.

Results: Antidepressant use with strong serotonin reuptake inhibition was not associated with microbleed presence (odds ratio compared to non-use 1.03, confidence interval 0.75; 1.39) irrespective of microbleed location in the brain. Exclusion of antithrombotic users or persons with cortical infarcts did not change our results. Furthermore, serotonin reuptake inhibition was not related to ischemic vascular brain damage.

Conclusions: In the general population, use of serotonin reuptake inhibiting antidepressants is not related to presence of cerebral microbleeds. This strengthens the idea that the platelet inhibitor effects of antidepressant drugs with affinity for serotonin are minimal, and further supports the safety of SSRIs for non-gastrointestinal bleedings.

Introduction

The use of antidepressant medication in the general population has increased considerably in the last decades, in particular the use of selective serotonin reuptake inhibitors (SSRIs) [1, 2]. This increase in SSRI use may be explained by a broadened indication of SSRI, a different adverse effect profile and a lower toxicity compared with classic tricyclic antidepressants (TCAs) [3-5].

Yet, despite a more favorable adverse effect profile, the use of SSRIs is not entirely risk free [6-9]. SSRIs block the reuptake of serotonin by platelets and decrease serotonin platelet concentration, which may lead to impaired aggregation and prolonged bleeding times [10-14]. SSRIs have therefore extensively been studied in relation to intracerebral hemorrhages [15-22], and a recent meta-analysis of controlled observational studies showed an increased risk of intracerebral hemorrhages in SSRI users compared to non-users [23]. In addition, via the same pathophysiological pathway of reducing platelet aggregation, antidepressants with a high inhibition for serotonin reuptake may also reduce the risk of ischemic stroke, although to date this hypothesis is scarcely supported by literature [15, 16, 21, 24, 25].

Apart from major cerebrovascular events, it has not yet been investigated whether SSRIs or strong inhibitors of serotonin reuptake are associated with subclinical cerebrovascular lesions, and more particularly with subclinical bleedings. Cerebral microbleeds have increasingly been recognized on magnetic resonance imaging (MRI) in stroke patients, and mostly in association with larger intracerebral hemorrhages [26-28]. Yet, microbleeds are also highly prevalent in the general population, and microbleeds may similarly represent bleeding-prone vessels in these people. Support for this is provided in our previous studies in which we showed an association between antiplatelet drugs use and the presence of cerebral microbleeds in the general population [29, 30].

Given the association of microbleeds with symptomatic bleeds and antiplatelet drug use we hypothesized that people who use antidepressants with a great inhibition of serotonin reuptake may have a higher prevalence of cerebral microbleeds than non-users, and users of antidepressant with a low serotonin affinity. Moreover, we secondarily investigated whether the use of these drugs is associated with the presence of ischemic vascular damage on MRI, in particular a lower frequency of lacunes of presumed vascular origin [31] and lower white matter lesions (WML) volume.

Methods

Participants

The Rotterdam Study is a prospective population-based cohort study, within Ommoord, a suburb in Rotterdam, the Netherlands. The study comprises 14,926 participants, and investigates the prevalence, incidence of, and risk factors for diseases in an aging population [32]. The study started in 1990 and after baseline examination, follow-up assessments were conducted every 4-5 years including interviews and an extensive set of examinations. From 2005 onwards, brain MRI was embedded within the core protocol of the Rotterdam Study to investigate age-related brain changes on imaging [33]. The institutional review board approved the study. Between 2005 and 2011, 5,735 participants visiting the study center in that period were eligible to undergo a brain MRI. After informed consent was signed, a total of 5,074 non-demented people were scanned. After excluding participants in whom MRI was not completed (N=72) and scans with low quality (N=57), data on 4,945 participants were available for analyses.

Assessment of antidepressant drug use

We determined antidepressant drug use prior to brain MRI based on fully computerized pharmacy records from the 7 pharmacies in the Ommoord district. More than 99% of the participants have their drug prescriptions filled at these regional pharmacies. Medication records were continuously monitored from January 1st 1991 onwards. Records included the date of prescribing, the total amount of drug units per prescription, the prescribed daily number of units, the product name of the drugs and the Anatomical Therapeutic Chemical (ATC) code. The duration of treatment was calculated by counting the number of prescription days. The average prescribed daily dose was expressed in standardized defined daily doses (DDD) calculated by summing up the total number of prescribed DDDs from all prescriptions divided by the total duration.

We classified antidepressants based on their degree of serotonin reuptake inhibition. The classification is based on the dissociation constant (K_d) for the serotonin transporter. A lower dissociation constant reflects a higher affinity for the serotonin transporter and therefore a higher inhibition of serotonin reuptake. Based on previous literature, we categorized antidepressants into high (paroxetine, clomipramine, sertraline, duloxetine, fluoxetine), intermediate (escitalopram, citalopram, imipramine, fluvoxamine, amitriptyline, venlafaxine), and low (desimipramine, opipramol, nortriptyline, doxepin, dosulepin, maprotiline, moclobemide, mianserin, trazodone, nefazodone, mirtazapine) degrees of serotonin reuptake inhibition [17, 34-38].

People who used multiple antidepressants from the different groups were excluded from the main analyses (n=268), to secure a pure exposure. These users were considered switchers and were analyzed in subsequent analyses.

Brain MRI and assessments of MRI markers

Brain MRI scans were performed on a 1.5-Tesla MRI scanner (GE Healthcare Milwaukee, WI) [33]. Our multisequence MRI protocol included the following scans: T1-weighted, proton-density weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) [33]. For microbleed detection we used a custom-made accelerated three-dimensional T2*-weighted gradient-recalled echo sequence with high spatial resolution and long echo-time to enhance the detection of microbleeds [39]. Microbleeds were defined as focal areas of low signal intensity on T2*-weighted imaging. Their presence, location, and numbers were scored by 1 of 5 trained research-physicians, with good intraobserver and interobserver agreement [40]. We categorized microbleeds based on their presumed underlying etiology into lobar microbleeds (presumably reflective of cerebral amyloid angiopathy [CAA]), and deep or infratentorial microbleeds (presumably reflective of hypertensive arteriopathy) [39]. Lacunes and cortical infarcts were rated on FLAIR, proton-density-weighted and T1-weighted sequences by the same raters of microbleeds. Lacunes were defined as focal lesions between $\geq 3\text{mm}$ and $< 15\text{mm}$ in size [40]. Infarcts showing involvement of grey matter were classified as cortical infarcts. Brain tissue was segmented into grey matter, white-matter, and cerebrospinal fluid, using validated automated post-processing steps that include conventional k-nearest-neighbour brain tissue classifier extended with WML segmentation [41, 42].

Assessment of covariables

We addressed potential confounders by characterizing depressive symptoms, cardiovascular risk factors and cardiovascular medication use in our study population. Antidepressant drugs are mainly prescribed for depressive disorders. Depression has a bidirectional association with cardiovascular disease, and cardiovascular disease is related to the presence of microbleeds [43, 44].

Presence of depressive symptoms was evaluated using the Center for Epidemiological Studies Depression Scale (CESD) [45]. A score of 16 or higher was indicative of participants with clinically relevant depressive symptoms. A very high sensitivity for major depression for this score was reported in older adults in the Netherlands [46].

Participants' cardiovascular risk was assessed during the center visit preceding MRI, using interview, laboratory, and physical examinations [47]. This included presence of diabetes mellitus, smoking status (ever versus never), serum total cholesterol levels, serum high-density lipoprotein (HDL) cholesterol levels, and systolic and diastolic blood pressure. Finally, use of lipid lowering drugs (C10), antihypertensive drugs (C02, C03, C07, C08, and C09), and antithrombotic drugs (B01AA, B01AB, B01AC, and B01AX) was assessed from pharmacy records during follow-up before MRI.

Statistical analysis

We analyzed the association between use of antidepressants, their degree of serotonin reuptake inhibition (high, intermediate, low) with the presence of cerebral microbleeds (present versus absent) using multiple logistic regression, taking non-users as reference category. Analyses were repeated for microbleeds at different locations in the brain, namely strictly lobar regions and deep or infratentorial regions (with or without lobar microbleeds). Furthermore, we repeated all analyses using low and intermediate serotonin reuptake inhibition antidepressant users as reference category. Switchers were excluded from the main analyses and the subsequent analyses were repeated including switchers.

All analyses were adjusted for age and sex. We additionally adjusted for presence of depressive symptoms, diabetes mellitus, smoking, total and HDL cholesterol, systolic and diastolic blood pressure, use of lipid-lowering medication, antihypertensive medication, and antithrombotic agents. Sensitivity analyses were performed with exclusion of MRI-defined cortical infarcts or exclusion of antithrombotic drug users. Moreover, analyses were stratified for sex, the exposure was dichotomized based on the duration of treatment (cut-off was 90 days) and interaction tests with antithrombotic drug users were performed. The average prescribed daily dose, expressed in standardized DDD, was also studied dichotomized on 1.00 DDD as the cut-off to look at an effect of dose.

Furthermore, we studied the association between the degree of serotonin reuptake inhibition of antidepressants and the presence of lacunes and WML volume with, respectively, multiple logistic and linear regression. People with cortical infarcts were excluded from these analyses. Analyses were adjusted for the same factors as described above. Analyses of WML volume were additionally adjusted for intracranial volume. WML was log-transformed due to the skewed distribution.

We considered a p-value <0.05 as statistically significant, and analyses were performed with a commercially available software program (IBM SPSS Statistics for Windows, Version 21.0).

Results

Characteristics of the study population are presented in Table 1 and Supplementary Table 1. Mean age was 64.0 years (SD 11.0) and 2,724 (55.1%) were female. A total of 930 (18.8%) persons had a history of antidepressant use before MRI, and 311 (6.2%) had exclusively used antidepressants with a high degree of serotonin reuptake inhibition, 304 (6.1%) of an intermediate, and 47 (1.0%) antidepressants of a low degree. Among users, 268 (5.4%) switched between the different antidepressant drug categories. In the total study population, 957 (19.4%) had microbleeds, of whom 629 had strictly lobar and 328 deep or

infratentorial microbleeds. In the group of antidepressant drug users (n=930), 18.9% had microbleeds, which did not significantly differ from the 19.5% in the population of non-users. Of all participants in our study, lacunes were present in 370 (7.5%), and median WML volume was 3.0 ml.

Table 1. Baseline characteristics of the study population.

	N=4,945
Age, years	64.0 (11.0)
Females	2,724 (55.1)
Depressive symptoms	417 (8.6)
Diabetes mellitus	433 (8.9)
Smoking	3,436 (69.8)
Antidepressant drug users	
High degree of inhibition*	311 (6.2)
Intermediate degree of inhibition*	304 (6.1)
Low degree of inhibition*	47 (1.0)
Switchers	268 (5.4)
Presence of cerebral microbleeds	957 (19.4)
Strictly lobar	629 (13.6)
Deep or infratentorial	328 (7.6)
White matter lesion volume, mL	3.0 (1.6 – 6.5)
Lacunes	370 (7.5)
Cortical infarcts	165 (3.3)
Total cholesterol, mmol/L	5.5 (1.1)
High-density lipoprotein cholesterol, mmol/L	1.4 (0.4)
Systolic blood pressure, mmHg	138.9 (21.2)
Diastolic blood pressure, mmHg	82.2 (10.9)
History of lipid lowering drug use	1,185 (24.2)
History of antihypertensive drug use	1,696 (34.6)
History of antithrombotic drug use	1,415 (28.6)

Values represent mean (standard deviation) or number (percentage). White matter lesion volume is represented as median (interquartile range). * Degree of serotonin reuptake inhibition: High=paroxetine, clomipramine, sertraline, duloxetine, fluoxetine. Intermediate = escitalopram, citalopram, imipramine, fluvoxamine, amitriptyline, venlafaxine. Low = desimipramine, opipramol, nortriptyline, doxepin, dosulepin, maprotiline, moclobemide, mianserin, trazodone, nefazodone, mirtazapine.

Compared to non-use, the use of antidepressants with a high serotonin reuptake inhibitory potential was not associated with cerebral microbleed presence (age, sex-adjusted odds ratio [OR] 1.03, 95% CI 0.75; 1.39). In addition, no association was found for low (OR 0.76, 95% CI 0.36; 1.62) or intermediate (OR 1.04, 95% CI 0.77; 1.39) serotonin affinity antidepressants. Compared to non-use, the use of antidepressant medication with either high, intermediate, or low affinity for serotonin was neither related to lobar, nor to deep or infratentorial microbleeds (Table 2). Additionally, no association between antidepressant use and microbleeds was found for people who switched between different antidepressant

drugs (OR 0.95, 95% CI 0.68; 1.33). Additional adjustments for cardiovascular risk factors, cardiovascular medication and depressive symptoms did not change any of the results significantly (Table 2). Excluding participants with MRI-defined cortical infarcts (n=158), and excluding ever antithrombotic drug users (n=1,326) also did not materially change our results (data not shown). Moreover, the exposure split by duration and average prescribed daily dose of antidepressant drug treatment and stratification by gender did not significantly change our results (data not shown). Effect modification of antidepressant drug exposure by antithrombotic drugs was not present (p=0.96).

We did not find a higher frequency of cerebral microbleeds, irrespective of their location in the brain, when comparing the high affinity group with the combined intermediate and low affinity group (OR 1.03, 95% CI 0.68; 1.56) (Table 3).

Finally, we did not find a lower frequency of lacunes (OR 1.14, 95% CI 0.67; 1.94) nor a smaller WML volume (mean difference of WML volume 0.06, 95% CI -0.03; 0.15) for use of antidepressants with a high serotonin reuptake inhibition potential compared to non-use, neither did we find a relation when investigating the use of low and intermediate degree of serotonin reuptake inhibition (Table 4).

Table 2. Degree of serotonin reuptake inhibition for antidepressant drugs and the presence of cerebral microbleeds.

Degree of serotonin reuptake inhibition	Any microbleeds		Deep or infratentorial microbleeds		Strictly lobar microbleeds	
	n / N	Odds ratio (95% CI)	n / N	Odds ratio (95% CI)	n / N	Odds ratio (95% CI)
Model 1						
Non-use	781 / 4,015	1.00 (Reference)	270 / 3,504	1.00 (Reference)	511 / 3,745	1.00 (Reference)
Low	9 / 47	0.76 (0.36; 1.62)	2 / 40	0.51 (0.12; 2.15)	7 / 45	0.92 (0.40; 2.10)
Intermediate	65 / 304	1.04 (0.77; 1.39)	23 / 262	1.07 (0.67; 1.70)	42 / 281	1.04 (0.73; 1.47)
High	53 / 311	1.03 (0.75; 1.39)	20 / 278	1.17 (0.72; 1.90)	33 / 291	0.93 (0.64; 1.36)
Model 2						
Non-use	741 / 3,850	1.00 (Reference)	257 / 3,366	1.00 (Reference)	484 / 3,593	1.00 (Reference)
Low	8 / 45	0.70 (0.32; 1.57)	2 / 39	0.50 (0.11; 2.15)	6 / 43	0.80 (0.33; 1.96)
Intermediate	60 / 291	0.96 (0.70; 1.30)	21 / 252	0.94 (0.58; 1.54)	39 / 270	0.98 (0.68; 1.41)
High	51 / 298	0.97 (0.70; 1.35)	19 / 266	1.10 (0.66; 1.84)	32 / 279	0.88 (0.59; 1.30)

Values represent odds ratios for microbleeds in relation to antidepressant drugs with low, intermediate, and high affinity for serotonin. Non-users are the reference population for all analyses presented in Table 2. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, depression, diabetes mellitus, smoking, total and high-density lipoprotein cholesterol, systolic and diastolic blood pressure, ever use of lipid-lowering drugs, antihypertensive drugs, and antithrombotic drugs. Number of cases/total population deviate from model 1, as we performed a complete caseset analysis.

Abbreviations: n= number of cases, N= total population within the exposure category.

Table 3. Degree of serotonin reuptake inhibition for antidepressant drugs and the presence of cerebral microbleeds within drug users.

Degree of serotonin reuptake inhibition	Any microbleeds		Deep or infratentorial microbleeds		Strictly lobar microbleeds	
	n / N	Odds ratio (95% CI)	n / N	Odds ratio (95% CI)	n / N	Odds ratio (95% CI)
Low/intermediate	74 / 351	1.00 (Reference)	25 / 302	1.00 (Reference)	49 / 326	1.00 (Reference)
Model 1						
High	53 / 311	1.03 (0.68; 1.56)	20 / 278	1.14 (0.60; 2.16)	33 / 291	0.93 (0.56; 1.52)
Model 2						
High	51 / 298	1.02 (0.66; 1.58)	19 / 266	1.16 (0.59; 2.31)	32 / 279	0.91 (0.54; 1.52)

Values represent odds ratios for microbleeds in relation to antidepressant drugs with high affinity for serotonin. Users of low and intermediate degree of serotonin reuptake inhibition antidepressants are the reference population for the presented analyses in Table 3. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, depression, diabetes, smoking, total and high-density lipoprotein cholesterol, systolic and diastolic blood pressure, ever use of lipid-lowering drugs, antihypertensive drugs, and antithrombotic drugs. Number of cases/total population deviate from model 1, as we performed a complete caseset analysis.

Abbreviations: n= number of cases, N= total population within the exposure category.

Table 4. Degree of serotonin reuptake inhibition for antidepressant drugs and the presence of lacunes and white matter lesion volume.

Degree of serotonin reuptake inhibition	Lacunes		White matter lesion volume	
	n / N	Odds ratio (95%CI)	N	Difference in mean (95% CI)
Model 1				
Non-use	260 / 3,888	1.00 (Reference)	3,881	0.00 (Reference)
Low	3 / 45	0.82 (0.25; 2.74)	45	-0.05 (-0.28; 0.18)
Intermediate	23 / 288	1.20 (0.76; 1.90)	288	0.08 (-0.02; 0.17)
High	16 / 298	1.14 (0.67; 1.94)	298	0.06 (-0.03; 0.15)
Model 2				
Non-use	247 / 3,728	1.00 (Reference)	3,722	0.00 (Reference)
Low	3 / 43	0.89 (0.26; 3.02)	43	-0.04 (-0.27; 0.19)
Intermediate	22 / 275	1.13 (0.70; 1.82)	275	0.06 (-0.03; 0.16)
High	15 / 285	1.05 (0.60; 1.86)	285	0.06 (-0.03; 0.15)

Lacunes: values represent odds ratios for lacunes in antidepressant drug users with low, medium, and high affinity for serotonin compared to non-users. White matter lesions volume: values represent differences in mean log transformed white matter lesion volumes (ml) in antidepressant drug users with low, medium, and high affinity for serotonin compared to non-users. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, depression, diabetes, smoking, total and HDL cholesterol, systolic and diastolic blood pressure, ever use of lipid-lowering drugs, antihypertensive drugs, and antithrombotic drugs. Number of cases/total population deviate from model 1, as we performed a complete caseset analysis. White matter lesion volume analyses were additionally adjusted for intracranial volume and participants with unreliable white matter lesion segmentations were excluded from analyses.

Abbreviations: n= number of cases, N= total population within the exposure category.

Discussion

In the general population, we did not find an association between antidepressant drug use with a greater inhibition of serotonin reuptake and the presence of cerebral microbleeds. In addition, the degree of serotonin reuptake inhibition was not associated with presence of lacunes or WML volume.

Microbleeds are thought to precede the onset of large symptomatic hemorrhages, and may thus reflect a clinically relevant preclinical imaging marker, although evidence from longitudinal studies is still limited [26, 48, 49]. The novelty of our study lays in the fact that we investigated the use of SSRIs in relation to subclinical hemorrhagic brain lesions in the general population, in contrast to clinical studies investigating symptomatic hemorrhage. We did not observe an association between degree of serotonin reuptake inhibition and the presence of microbleeds. This is in line with the majority of previous studies on SSRIs and symptomatic brain hemorrhages [15, 18, 20], although a recent meta-analysis did find an increased risk of brain hemorrhages in SSRI users (OR cohort studies 1.68, 95% CI 1.04; 2.51) [23]. As a methodological consideration; heterogeneity in sample size, quality of the individual studies and different approaches to handle the influence of confounding may have influenced the validity of the meta-analysis to a certain degree [50].

SSRIs might increase the risk of clinical or subclinical bleedings via the following main biological mechanism. Damage to endothelial layers leads to activation of hemostatic mechanisms, and platelets adhere to damaged vessel walls. Intracellular serotonin is subsequently released into the blood stream and promotes clot formation and vasoconstriction at the site of injury. SSRIs inhibit the reuptake of serotonin by platelets from the blood, reduce intracellular serotonin concentrations, thereby decrease platelet aggregation and increase the risk of bleeding [12, 13]. Moreover, a second mechanism proposes that some SSRIs may inhibit cytochrome 450 (CYP) enzymes such as CYP 1A2, 2D6, 3A4 and 2C9. This may increase the bleeding risk by inhibition of the metabolism of certain drugs that have anticoagulant properties such as NSAIDs and antithrombotic drugs [13, 14].

Nonetheless, for both mechanisms we could argue that diminishing intraplatelet serotonin levels only affects hemostasis to a limited extent, and thus that remaining platelet function is sufficient to halt significant bleeding. Depletion of serotonin levels in platelets may well be compensated for by other adequately working hemostatic mechanisms. This would partly explain why SSRI use was more consistently associated with extra-cranial bleeds, in particular gastro-intestinal bleedings. Here, SSRI use increases serotonin levels and stimulates the production of gastric acid, which increases the risk of gastrointestinal bleedings. Bleeding complications may therefore be induced by a third mechanism which does not necessarily involve platelet dysfunction [14].

No association was found for antidepressants with an affinity for serotonin with microbleeds in either lobar or deep or infratentorial regions of the brain. Although microbleeds at both locations are representative of bleeding-prone vessels, their etiologies differ. Microbleeds in lobar regions are more likely to result from blood leaking from destructed vessel walls containing amyloid, whereas deep or infratentorial microbleeds most likely represent hemosiderin deposits as a consequence of hypertensive arteriopathy [28, 40, 43, 51]. Our findings suggest that regardless of the underlying pathology, the decrease of intracellular serotonin platelets caused by antidepressants with a strong serotonin reuptake potential is insufficient to increase the frequency of small, asymptomatic bleedings.

Finally, we did not find a protective effect of antidepressant drugs, with a high affinity for the serotonin transporter, on ischemic vascular brain lesions. This is in line with findings from previous studies in patients with ischemic stroke [15, 21], and strengthens the idea that the platelet inhibitor effects of antidepressant drug with affinity for serotonin are minimal. Two previous studies showed an increased risk of ischemic stroke in current SSRI users [16, 24]. This increased risk could be explained by a different biological mechanism which postulates that serotonin induces vasoconstriction of large vessel, and may lead to thromboembolic ischemic stroke in the presence of atherosclerosis [52]. However, in our study, we focused on silent ischemic vascular lesions, involving the small cerebral arteries, which are typically not caused by thromboembolic events.

Strengths of our study are the large sample size, population-based character of our study, and the prospectively gathered electronic pharmacy records which we used to determine antidepressant drug use. Based on a 19.5% prevalence of microbleeds in unexposed subjects, with a two-sided significance of 0.05, we had sufficient power (80%) to detect an odds ratio of 1.22 or greater. Less strong associations may not have been detected in our study, although based on the recent meta-analysis on SSRIs and symptomatic brain hemorrhages we would expect an estimate of at least this magnitude for subclinical bleedings [23]. Some limitations of our study need to be considered. The cross-sectional design of our study limits our conclusions on a causal pathway. MRI does not provide information on the timing of when cerebral microbleeds occurred, as cerebral microbleeds remain visible in the brain for an undefined period. Therefore, there is a possibility that cerebral microbleeds occurred before antidepressant use was initiated. This may have led to an underestimation of the true association presented due to non-differential misclassification of SSRI users, and further longitudinal investigations are warranted. Furthermore, confounding by indication and contra-indication poses a problem in our observational study. Depression, the most important indication to prescribe antidepressants, has a bidirectional association with cardiovascular disease, and cardiovascular diseases are associated with an increased number of microbleeds. Moreover, TCAs are relatively contra-indicated for patients with cardiovascular disease. We minimized these forms of confounding by adjusting for presence of depressive symptoms, cardiovascular risk factors, and cardiovascular medication. Also, we reclassified the antidepressant drugs based on their affinity to the serotonin reuptake transporter. Although we aimed to address all potential confounders in our study, residual confounding cannot be ruled out and may have affected our results to an extent that associations may have been overestimated.

In conclusion, this study adds important information to the previous reports on antidepressant drug use and bleeding risk. We report that, in the general population, the use of antidepressant drugs that inhibit serotonin reuptake is not related to the presence of cerebral microbleeds. This further supports the safety of these antidepressants for non-gastrointestinal bleedings. Since these results are cross-sectional, further longitudinal research regarding antidepressant drug use and the risk of microbleeds in relation to major intracerebral hemorrhage is of high interest.

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Supplementary Table 1. Baseline characteristics of the study population.

	Degree of serotonin reuptake inhibition			
	Non-users N=4,015	Low* N=47	Intermediate* N=304	High* N= 311
Age, years	64.0 (11.0)	68.5 (11.2)	65.7 (11.5)	61.4 (9.7)
Females	2,100 (52.3)	31 (66.0)	200 (65.8)	203 (65.3)
Depressive symptoms	194 (4.9)	10 (21.7)	46 (15.4)	69 (22.2)
Diabetes mellitus	337 (8.5)	3 (6.5)	32 (10.6)	28 (9.2)
Smoking	2,777 (69.4)	29 (63.0)	210 (69.8)	227 (73.2)
Presence of cerebral microbleeds	781 (19.5)	9 (19.1)	65 (21.4)	53 (17.0)
Strictly lobar	511 (13.6)	7 (15.6)	42 (14.9)	33 (11.3)
Deep or infratentorial	270 (7.7)	2 (5.0)	23 (8.8)	20 (7.2)
White matter lesion volume, mL	2.9 (1.6 – 6.4)	4.3 (1.8 – 8.0)	3.4 (1.9 – 8.5)	2.6 (1.5 – 5.3)
Lacunae	297 (7.4)	3 (6.4)	29 (9.5)	20 (6.4)
Cortical infarcts	127 (3.2)	2 (4.3)	16 (5.3)	13 (4.2)
Total cholesterol, mmol/L	5.5 (1.1)	5.5 (1.1)	5.6 (1.1)	5.7 (1.1)
High-density lipoprotein cholesterol, mmol/L	1.4 (0.4)	1.4 (0.3)	1.5 (0.5)	1.4 (0.4)
Systolic blood pressure, mmHg	139.4 (21.2)	135.5 (17.0)	139.6 (22.0)	134.8 (20.5)
Diastolic blood pressure, mmHg	82.3 (10.9)	80.1 (9.6)	82.0 (11.4)	81.8 (10.5)
History of lipid lowering drug use	927 (23.3)	17 (36.2)	86 (28.4)	85 (27.3)
History of antihypertensive drug use	1,315 (32.8)	27 (57.4)	142 (46.9)	108 (34.8)
History of antithrombotic drug use	1,110 (27.6)	15 (31.9)	116 (38.2)	85 (27.3)

Values represent mean (standard deviation) or number (percentage). White matter lesion volume is represented as median (interquartile range). * Degree of serotonin reuptake inhibition: High = paroxetine, clomipramine, sertraline, duloxetine, fluoxetine. Intermediate = escitalopram, citalopram, imipramine, fluvoxamine, amitriptyline, venlafaxine. Low = desimipramine, opipramol, nortriptyline, doxepin, dosulepin, maprotiline, moclobemide, mianserin, trazodone, nefazodone, mirtazapine.



3.2

Antidepressant use is associated with an increased risk of developing microbleeds

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Abstract

Background and purpose: Serotonin specific antidepressants may increase the risk of adverse bleeding events. In a previous cross-sectional study, we did not observe an association between antidepressant use and presence of subclinical cerebral bleedings. In the current study, we investigated longitudinally whether antidepressant use is associated with an increased risk of new subclinical cerebral microbleeds.

Methods: In total, 2,559 participants aged ≥ 45 years of the population-based Rotterdam Study, all without microbleeds at baseline, underwent baseline and repeat brain MRI between 2005 and 2013 (mean time interval 3.9 years, SD 0.5) to determine the incidence of microbleeds. Antidepressant use (yes versus no) was assessed between baseline and follow-up scan. In additional analyses antidepressants were classified as low, intermediate, or high affinity for the serotonin transporter, and alternatively as selective serotonin reuptake inhibitors (SSRIs) or non-SSRIs. We used multivariable logistic regression models to investigate the association of antidepressants with incident microbleeds.

Results: Antidepressant use was associated with a higher cerebral microbleed incidence (odds ratio [OR] 2.22, 95% CI 1.31; 3.76) than non-use. When stratified by affinity for the serotonin transporter, intermediate serotonin affinity antidepressant use was associated with an increased risk of developing microbleeds (OR 3.07, 95% CI 1.53; 6.17). Finally, SSRI and non-SSRI use were both associated with increased microbleed incidence.

Conclusions: Antidepressant use was associated with an increased risk of developing microbleeds. Our results may support findings from previous clinical studies regarding increased intracranial and extracranial bleeding risk in antidepressant users.

Introduction

Observational studies suggest that the biological effects of antidepressants [1] predispose users to symptomatic hemorrhagic adverse events, such as gastro-intestinal and intracerebral hemorrhages [2-4]. Since even symptomatic hemorrhages are not always acknowledged and reported, it is likely that the number of subclinical and thus non-recognized hemorrhages is much larger and that symptomatic hemorrhages are just the tip of the iceberg [5]. This is in line with the finding that the prevalence of intracranial microbleeds in the Rotterdam Study is much higher than that of stroke.

In the brain, reduced platelet activation due to antiplatelet drug use has been associated with a higher prevalence of subclinical microbleeds [6, 7]. The question arises whether antidepressants have comparable effects on platelet function, as it was shown that SSRIs block the reuptake of serotonin by platelets and decrease serotonin platelet concentration, which may lead to impaired aggregation and prolonged bleeding times [8]. We previously showed that in the general population, use of antidepressants, with a high serotonin affinity, did not associate with a higher frequency of subclinical microbleeds on brain MRI [9]. This study however was limited by its cross-sectional design. Therefore, we now investigated the association between antidepressant use (and their degree of serotonin reuptake inhibition) and incident cerebral microbleeds.

Methods

Participants

This study was embedded within the Rotterdam Study, a large prospective population-based cohort [10]. The study comprises 14,926 participants, and investigates the prevalence, incidence of, and risk factors for diseases in an aging population. The study started in 1990 and after baseline examination, follow-up assessments were conducted every 4-5 years including interviews, an extensive set of examinations and brain MRI [10, 11]. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the “Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study)”.

For this study, we included 3,054 participants who were affiliated with one of the pharmacies serving the study area, and underwent both baseline and repeat brain MRI between August 2005 and July 2013. Participants with microbleeds on baseline MRI were excluded (N=495), leaving a total of 2,559 participants for analyses.

Antidepressant drugs

Pharmacy records were available from 1991 onwards and provided information on prescription date of antidepressants, number of drug units, prescribed daily number of units, and Anatomical Therapeutic Chemical (ATC) code. Exposure was defined as antidepressant use between baseline and follow-up MRI, irrespective of previous antidepressant use. Non-use between the MRIs was defined as the reference group. Antidepressants were categorized based on their affinity for the serotonin transporter into low, intermediate, and high degree of serotonin reuptake inhibition, as described previously.[9] Further, antidepressants were categorized into SSRIs (ATC-code='N06AB') and non-SSRIs (respectively, all other 'N06A'). Also, the duration of treatment and the average number of prescribed defined daily doses were assessed.

Brain MRI

Participants were scanned at both time points on the same 1.5-Tesla MRI scanner (GE Healthcare, Milwaukee, WI), as described previously [11]. In short, cerebral microbleeds were rated by 5 trained research-physicians with good intraobserver and interobserver agreement ($\kappa=0.87$ and $\kappa=0.85$). Raters were blinded to clinical data, including antidepressant use. Microbleeds were defined as focal areas of low signal intensity on an accelerated 3-dimensional T2*-weighted gradient-recalled echo sequence [12]. Scans rated positive for microbleeds were included in a side-by-side comparison to determine the incidence of microbleeds [13].

Statistical analysis

We used multivariable logistic regression to investigate if any antidepressant use between baseline and follow-up MRI was associated with an increased risk of incident microbleeds, when compared with non-users. We repeated the analysis for the degree of serotonin reuptake inhibition (high, intermediate, low) – based on our a-priori hypothesis – [9] and for SSRIs and non-SSRIs, after exclusion of participants who used antidepressants from more than one group (for both classifications, $n=43, n=39$ switchers, respectively). All analyses were adjusted for age, sex, and time (in years) between baseline and repeat MRI scan. We additionally adjusted for potential confounders at baseline, including the presence of depressive symptoms based on the Center for Epidemiological Studies Depression Scale (CES-D), and a propensity score of cardiovascular risk (diabetes mellitus, smoking, total and high-density lipoprotein cholesterol, systolic and diastolic blood pressure, use of lipid-lowering (ATC-code C10), blood pressure-lowering (ATC-codes C02, C03, C07 through C09), and antithrombotic drugs (ATC-codes B01AA, B01AB, B01AC, and B01AX)). Post-hoc analyses were done to additionally adjust for all separate cardiovascular risk factors, duration of treatment, average number of prescribed defined daily doses and to test the

interaction of antidepressant with antithrombotic drug use between baseline and follow-up scan. Analyses were performed using IBM SPSS Statistics for Windows, Version 21.0, using an alpha-value of 0.05.

Results

Baseline characteristics of the study population are presented in Table 1. The mean age was 59.0 years (SD 7.8) and 1,403 (54.8) were women. The incidence of microbleeds over 3.9 years (SD 0.5) of follow-up was 3.7%.

Table 1. Baseline characteristics.

	N= 2,559
Age, years	58.7 [53.2 – 62.8]
Women	1,403 (54.8)
Depression score	3.0 [1.0 – 6.0]
Ever smoker	1,755 (68.8)
Diabetes mellitus	181 (7.2)
Total cholesterol, mmol/L	5.6 [5.0 – 6.3]
High-density lipoprotein cholesterol, mmol/L	1.4 [1.1 – 1.7]
Systolic blood pressure, mmHg	133.0 [121.0 – 146.0]
Diastolic blood pressure, mmHg	81.0 [75.0 – 88.0]
Lipid-lowering drug use	527 (20.8)
Blood pressure-lowering drug use	656 (25.9)
Antithrombotic drug use	422 (16.5)

Values represent median [interquartile range] for continuous variables and number (percentage) for categorical variables. Depression score was based on the Center for Epidemiological Studies Depression Scale (range 0-60). ATC code for lipid-lowering (C10), blood pressure-lowering (C02, C03, C07 through C09), and antithrombotic drugs (B01AA, B01AB, B01AC, B01AX).

Antidepressant use was associated with incident cerebral microbleeds (age, sex, and scan interval-adjusted odds ratio [OR] 2.22, 95% confidence interval [CI] 1.31; 3.76), compared to non-use (Table 2). When categorized by affinity for the serotonin transporter, only intermediate serotonin affinity antidepressant use was associated with an increased risk of developing microbleeds (OR 3.07, 95% CI 1.53; 6.17), also after additional adjustment for depressive symptoms and a propensity score of cardiovascular risk and cardiovascular drugs (OR 3.29, 95%CI 1.59; 6.79). Antidepressants with a high serotonin affinity were associated with incidence of microbleeds, though results did not reach statistical significance (OR 2.18, 95%CI 0.90; 5.29) (Table 2). Both SSRIs and non-SSRIs were associated with an increased risk of incident cerebral microbleeds, compared to non-use (Table 2). Additional adjustment for all separate cardiovascular risk factors and drugs did not materially change the results (not shown). Also, additional adjustments for duration and dose of antidepressant treatment

only marginally changed effect estimates, although associations were non-significant, possibly due to loss of statistical power (results not shown). We found no effect modification by antithrombotic drug use in a post-hoc analysis on the association of antidepressant use with incident microbleeds (p-value = 0.772).

Table 2. Antidepressant use and the risk of cerebral microbleeds.

	Model 1		Model 2	
	n / N	Odds ratio (95% CI)	n / N	Odds ratio (95% CI)
Non-use	75/2,260	Reference	72/2,194	Reference
Antidepressant use				
Any use	19/299	2.22 (1.31; 3.76)	19/290	2.29 (1.31; 4.02)
Degree of inhibition of serotonin reuptake				
Low	0/35	Not applicable	0/34	Not applicable
Intermediate	10/120	3.07 (1.53; 6.17)	10/116	3.29 (1.59; 6.79)
High	6/101	2.03 (0.86; 4.81)	6/97	2.18 (0.90; 5.29)
Type of antidepressant				
SSRI	8/123	2.27 (1.06; 4.85)	8/118	2.39 (1.09; 5.25)
Non-SSRI	9/137	2.28 (1.11; 4.68)	9/133	2.37 (1.13; 4.97)

Values represent odds ratios (95% confidence intervals [CI]) for incident microbleeds in antidepressant users compared to non-users. Model 1: adjusted for age, sex and scan interval. Model 2: adjusted for age, sex, scan interval, depression score based on Center for Epidemiological Studies Depression scale, and a propensity score comprised of diabetes mellitus, smoking, total and high-density lipoprotein cholesterol, systolic and diastolic blood pressure, use of lipid-lowering drugs, blood-pressure lowering drugs, and antithrombotic drugs. Complete case analysis. Number after stratifications does not add up to total number of antidepressant drug users because of exclusion of switchers. Abbreviations: n= number of cases, N= total population within the exposure category, SSRI= selective serotonin reuptake inhibitor.

Discussion

In this population-based study, we found that antidepressant use was associated with an increased risk of incident first-ever microbleeds after four years of follow up. Associations were similar for different categories of antidepressants users, and persisted after adjusting for depressive symptoms and cardiovascular risk. These findings are in line with previous cross-sectional results from other studies, although our study is the first to describe a temporal association between antidepressants and subclinical cerebral hemorrhages [4].

The increased risk of developing microbleeds in antidepressant users might be a direct consequence of the inhibiting effects on the serotonin transporter by antidepressants. Platelet motility may decrease due to reduced intra-platelet serotonin concentrations [1]. In line with this, we expected strongest associations for users in the group with a high affinity for the serotonin transporter and in SSRIs, as they selectively block serotonin reuptake and impair platelet aggregation most. Stratification on the degree of serotonin reuptake inhibition, however, yielded small subgroups and hampered our ability to study

these trends. Since we found that both SSRIs and non-SSRIs increased the risk of incident microbleeds with similar effect sizes, this suggests that the association may not be due to the affinity for the serotonin transporter. Another yet unidentified mechanism, other than platelet impairment, may cause hemorrhagic tendencies in persons using antidepressants. More likely, the lack of difference in association of high and intermediate affinity SSRIs with incident microbleeds is the result of insufficient statistical power. Also, we have to consider the possibility of reverse causality as incident microbleeds could have occurred at some time before antidepressant use during follow-up, and biologically it has been hypothesized that microbleeds may contribute to the progression of depression [14].

In our previous cross-sectional study we did not find an association between antidepressants and microbleed presence [9]. An explanation for this could be that our previous results were underestimated because of non-differential misclassification of antidepressant drug exposure, as microbleeds might have occurred before antidepressant use. Although this issue may also be present in the current study, we believe that using a narrow antidepressant drug exposure window and identifying first-ever incident microbleeds made our current longitudinal results more robust than the previous cross-sectional results.

The results of our study should be interpreted in light of some limitations. The number of incident microbleed cases during follow-up was small and limited our ability to perform microbleed subgroup analysis, for example regarding their location in the brain. Also, our results may be confounded by the indication for treatment, since depression has a bidirectional association with cardiovascular disease, and cardiovascular diseases are associated with microbleeds. We adjusted for depressive symptoms at baseline, but because we lacked data to control for depressive symptoms during follow-up potential residual confounding by depression may still be present. Also, as we mentioned reverse causality may have been present in our study. We tried to minimize the effects of reverse causality by excluding participants with prevalent microbleeds at baseline and by studying first-ever incident microbleeds.

In conclusion, antidepressant use was associated with an increased risk of developing microbleeds. Our results support findings from previous clinical studies regarding bleeding risk in antidepressants, and suggest that these risks may also apply to subclinical bleeding manifestations.

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3.3

Use of selective serotonin reuptake inhibitors and sleep quality: a population-based study

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Submitted

Abstract

Study objectives: Poor sleep is a risk factor for the development and recurrence of depression. Selective serotonin reuptake inhibitor (SSRI) use is consistently associated with good subjective sleep in clinically depressed patient populations. However, studies in the general population are lacking. Our objective was to investigate the association between SSRIs and subjective sleep in a middle-aged and elderly population in a daily practice setting.

Methods: We included participants from the prospective Rotterdam Study cohort. Participants had up to two sleep measurements assessed with Pittsburgh Sleep Quality Index ([PSQI], number of measurements=14,770). SSRI use was based on pharmacy records. We assessed the association between SSRIs and PSQI score and its sub-components, with non-users of any antidepressant as reference. Analyses were, among others, adjusted for depressive symptoms and psycholeptic drug use.

Results: We included 9,267 participants with an average baseline age of 66.3 years (SD 10.6) and 57.6% were women. SSRI use was significantly associated with a 0.78point lower PSQI score (95%CI -1.11;-0.44) which reflects better sleep, compared with non-use. The association was more prominent in continuous SSRI users (-0.71points, 95%CI -1.18;-0.24). Of the sub-components, SSRIs were associated with 0.70hour longer sleep duration (95%CI 0.56;0.85), higher sleep quality, higher sleep efficiency, and in contrast more daytime dysfunction.

Conclusions: SSRI use was associated with better subjective sleep, after adjustment for depressive symptoms and concurrent psycholeptic drug use. This suggests that – in clinical practice in the middle-aged and elderly population – the sleep quality of some persons may benefit from, continued, SSRI use.

Introduction

Sleep and depression are highly associated. The most common disturbances in the sleep pattern of a depressed person are low sleep efficiency and little deep sleep [1-4]. Poor sleep has been shown to be a risk factor for the development or recurrence of depression [2, 5-8]. On the other hand, antidepressant drugs can have positive and negative effects on sleep [9-13].

Selective serotonin reuptake inhibitors (SSRIs) are considered activating antidepressants and a risk factor for poor sleep according to most objective sleep measurements, although sedative properties and daytime somnolence have occasionally been reported for SSRIs [10, 12-16]. Studies in non-depressed individuals regarding the association between SSRIs and subjective sleep reported inconsistent results [9, 11, 12, 17-21]. Whereas, in clinically depressed patient populations, SSRI use is consistently associated with an improved subjective sleep [3, 9, 11, 22]. The favorable results in depressed populations might represent the improvement of mental health or relief of depressive symptoms [9, 22]. So far, most studies focused on subjective perception of sleep as a secondary outcome in clinical trials of antidepressants which are limited by small sample size, short follow-up or concomitant benzodiazepine use [23]. To our knowledge, to date, no population-based study investigated whether SSRIs are associated with better subjective sleep in the middle-aged and elderly population.

Therefore, our objective was to investigate the association between SSRI use and different subjective sleep parameters in a population-based cohort study. Additionally, to evaluate the effect of sleep medication and depressive symptoms, we adjusted for concurrent psycholeptic drug use or presence of depressive symptoms and studied potential effect modification.

Methods

Setting

The Rotterdam Study is a prospective population-based cohort study that investigates incidence of, and risk factors for, several age-related diseases. The study was initiated in 1990, and after extension over the years, comprises a total of 14,926 participants. All participants were 45 years or older at baseline. After baseline examination, follow-up examinations were conducted every 4-5 years. Extensive information on morbidity and mortality is available for participants on a day-to-day basis from general practitioner records. Detailed information on design, objectives and methods of the Rotterdam Study has been published elsewhere [24, 25]. The Rotterdam Study has been approved by the medical ethics committee according to

the Wet Bevolkingsonderzoek: ERGO (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sports of the Netherlands. Written informed consent was signed by all study participants.

Study population

We included participants from interview rounds between January 2002 – December 2008 and March 2009 – January 2014. These interview rounds included the Pittsburgh Sleep Quality Index (PSQI) [26]. A total of 9,897 and 6,874 participants underwent home interview during these rounds, respectively. Measurements of participants with considerable cognitive impairment (Mini-Mental State Examination score below 24) [27], measurements with less than 5 (out of 7) valid sleep components on the PSQI [26], or measurements from participants who used other antidepressants than SSRIs at the time of interview were excluded from the analyses.

Exposure definition

Antidepressant drug use was assessed on the basis of pharmacy dispensing records. Electronic pharmacy records were available from January 1st, 1991 onwards. These include the date of dispensing, the total amount of drug units per prescription, the dispensed daily number of units, the product name of the drug and the Anatomical Therapeutic Chemical (ATC) code [28]. The duration of a dispensing was calculated by dividing the total number of dispensed pills/capsules by the prescribed daily number. Treatment episodes were based on consecutive dispensings in which a treatment gap between antidepressant drug dispensings of up to 30 days was still considered as one continuous episode. Participants were considered current users if the interview date fell within an antidepressant drug treatment episode. SSRI users were defined based on the 4th level ATC-code='N06AB'. The average dose was defined as the ratio between the prescribed daily dose and the defined daily dose (PDD/DDD ratio), as determined by the World Health Organization [28]. Users of all other antidepressant drugs were excluded from analyses.

Assessment of sleep parameters

Based on the Dutch version of the PSQI we assessed subjective sleep parameters [26]. The PSQI is a self-rated questionnaire that measures sleep parameters retrospectively over a 1-month period. The questionnaire consists of seven separate components (i.e. sleep duration, sleep disturbances, sleep latency, daytime dysfunction, sleep efficiency, sleep quality, use of sleep medication) with scores ranging from 0 to 3. Based on these seven components a global PSQI score can be calculated, ranging from 0 to 21 in which a higher score corresponds to poorer sleep [26]. For our research question, we excluded the component 'use of sleep medication' from the global PSQI score, as part of our exposure of interest is equal to the component sleep medication (i.e., benzodiazepines). In the present

study, the PSQI score ranged from 0 to 18 points, with a higher score indicative of impaired sleep.

Covariables

We considered the following covariables as potential confounding factors: sex, age, educational level, employment status, body mass index (BMI), depressive symptoms, alcohol intake, and psycholeptic drug use. Except for educational level, all covariables were time-varying and defined at time of the PSQI measurements. Educational level was assessed by home interview at study entry. We categorized educational status in four groups as previously described for the Rotterdam Study and similar to the UNESCO classification (i.e. basic= primary education, low= lower vocational, lower and intermediate general, medium= intermediate vocational, higher general, high= higher vocational and university) [29, 30]. Current employment status (yes/no) was based on questionnaire data. BMI was defined as weight (in kilograms) divided by height (in meters squared), measured at the research center. At the interview rounds, depressive symptoms and alcohol intake were assessed. Depressive symptoms were assessed with a Dutch version of the Center for Epidemiological Studies Depression Scale (CES-D) [31]. A score of 16 and higher was considered as an indicator for clinically relevant depressive symptoms [32]. Alcohol intake was assessed as the average consumption of glasses of alcohol in a week. This amount was converted into grams of alcohol on an average day. Psycholeptic drug use (ATC='N05') was defined as a dispensing of antipsychotics, anxiolytics, hypnotics or sedatives within 90 days before an interview date and was based on the available pharmacy dispensing records.

Statistical analyses

Baseline was defined as the first eligible PSQI measurement of a participant included in the study. Missing values were observed, this percentage was highest for BMI (12.0%) and MMSE score (8.3%). Missing values were handled by multiple imputation using 5 imputations.

We studied the association between SSRI use and repeated measurements of the global PSQI score and its subcomponents. We used repeated measurement techniques (Generalized Estimating Equations) for our analyses, to take into account within-person correlations between visits. We chose the independent working correlation matrix according to the lowest corrected quasi likelihood under independence model criterion [33, 34]. Only the global PSQI score and sleep duration were analyzed as continuous variables. Sleep onset latency, sleep disturbances, daytime dysfunction, sleep efficiency and sleep quality were modelled as binary outcome. For the binary outcomes, the cut-off was based on their questionnaire score (0 to 1 [good sleep] versus 2 to 3 [poor sleep]).

Subsequently, we studied whether there was a dose-response relation between the average prescribed DDDs and global PSQI score. Moreover, we studied effect modification by psycholeptic drug use or by presence of depressive symptoms on the association between

SSRI use and the global PSQI score and its subcomponents. Interaction terms were added to the model and results were subsequently stratified by concurrent psycholeptic drug use or by presence of depressive symptoms.

To assess the longitudinal association between SSRI use and PSQI scores at the follow-up measurement round, we used linear and logistic regression models and adjusted for baseline PSQI scores. This enabled us to study the association between SSRI use and PSQI scores, while accounting for inter-person differences in sleep at baseline. SSRI exposure was assessed at the baseline and follow-up measurement round and classified as: incident use at the follow-up measurement (incident use), current use at both measurements (continuation of use) or only SSRI exposure at the baseline measurement round (cessation of use). All analyses were compared to non-use of any antidepressant at both measurement rounds.

All statistical models were adjusted for age and sex (model 1), or in the full model additionally adjusted for educational level, employment status, BMI, CES-D score, alcohol intake and psycholeptic drug use (model 2). Data were analyzed using IBM SPSS statistics (version 21.0, IBM Corp., Somers, NY, USA).

Results

Baseline characteristics

The total study population consisted of 9,267 participants, with a total of 14,770 PSQI measurements (Figure 1). At baseline, the study population comprised of 57.6% women had a mean age of 66.3 years (SD=10.6). Baseline characteristics are presented in Table 1.

Table 1. Baseline characteristics of the study population.

	Study population N=9,267 N (%)
Age (yr), mean (SD)	66.3 (10.6)
Women	5,338 (57.6)
Educational level ^a	
Primary	1,003 (10.8)
Lower	3,784 (40.8)
Intermediate	2,715 (29.3)
Higher	1,764 (19.0)
Currently employed	2,600 (28.1)
Body Mass Index (kg/m ²), mean (SD)	27.7 (4.3)
Depression score ^b , median (IQR)	3.0 (1.0 – 8.0)
Psycholeptic drug use	1,137 (12.3)
MMSE score, median (IQR)	28.0 (27.0 – 29.0)
Alcohol intake (gram per day), median (IQR)	7.9 (1.3 – 17.1)

Baseline characteristics (imputed) are listed as n (%), unless stated otherwise. ^a Similar to the UNESCO classification and previously described for the Rotterdam Study [29, 30]. ^b Based on the Center for Epidemiological Studies Depression Scale (range 0 -60) [31].

Abbreviations: yr= year, SD= standard deviation, IQR= Interquartile Range, MMSE= Mini-Mental State Examination

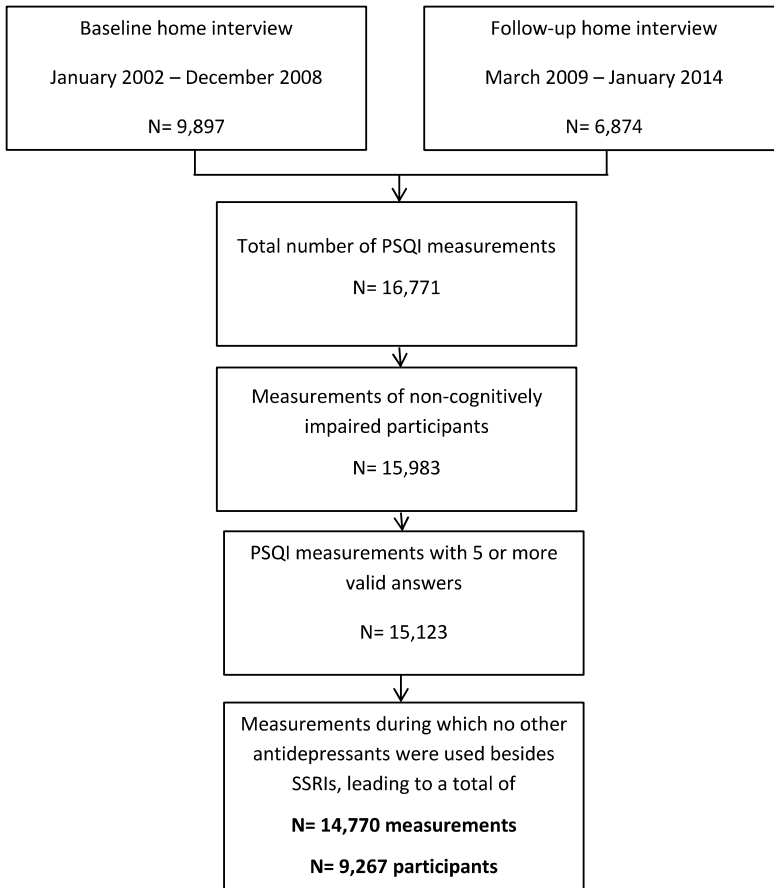


Figure 1. Flow-chart of the study population.

Abbreviations: PSQI= Pittsburg Sleep Quality Index, SSRIs= selective serotonin reuptake inhibitors

SSRIs and global PSQI

In the age- and sex-adjusted model, SSRI use was not associated with the global PSQI score (B 0.26; 95%CI -0.12; 0.63, Table 2). However, after full statistical adjustment, we observed that SSRI use was associated with a significant 0.78 point lower global PSQI score (95%CI -1.11; -0.44). Three PSQI subcomponents significantly contributed to the lower global PSQI score: longer sleep duration (B 0.70 hours, 95%CI 0.56; 0.85), better sleep quality (odds ratio [OR] 0.52, 95%CI 0.37; 0.71), and higher sleep efficiency (OR 0.65, 95%CI 0.48; 0.88) in the fully adjusted model. In contrast, SSRI use was associated with more daytime dysfunction (OR 1.48, 95%CI 1.02; 2.16).

Table 2. Association between selective serotonin reuptake inhibitor use and the global Pittsburgh Sleep Quality Index score and its subcomponents.

	Global PSQI score		Subcomponent PSQI					
	Number of measurements	B in points (95%CI)	Sleep duration B in hours (95% CI)	Sleep onset latency OR (95%CI)	Sleep quality OR (95%CI)	Daytime dysfunction OR (95%CI)	Sleep disturbances OR (95%CI)	Sleep efficiency OR (95%CI)
Non-use	14,312	Ref	Ref	Ref	Ref	Ref	Ref	Ref
SSRI use								
Model 1	458	0.26 (-0.12; 0.63)	0.49 (0.34; 0.64)	1.38 (1.08; 1.77)	1.15 (0.88; 1.52)	2.96 (2.14; 4.08)	1.95 (1.33; 2.86)	1.06 (0.79; 1.41)
Model 2	458	-0.78 (-1.11; -0.44)	0.70 (0.56; 0.85)	0.85 (0.65; 1.12)	0.52 (0.37; 0.71)	1.48 (1.02; 2.16)	0.87 (0.56; 1.34)	0.65 (0.48; 0.88)

NOTE: Global PSQI score and sleep duration are presented as B, representing higher = worse sleep or longer sleep duration. Other subcomponents are represented as odds ratio, representing higher = worse sleep. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, educational level, employment status, body mass index, Center for Epidemiological Studies Depression Scale score, alcohol intake and psycholeptic drug use. Abbreviations: PSQI= Pittsburgh Sleep Quality Index, SSRI= selective serotonin reuptake inhibitor, OR= odds ratio, ref=reference group.

A dose-response relationship was observed between the average prescribed dose and the global PSQI score (p for trend <0.001 , Figure 2). Effect modification by psycholeptic drug use was observed for the association between SSRIs and global PSQI score (p for interaction= 0.048). When stratified by concurrent use of psycholeptic drugs, SSRI use was in both groups associated with a lower global PSQI score, but point estimates were stronger in the group of concurrent psycholeptic drug use (no psycholeptic use: B -0.57 , 95%CI -0.94 ; -0.20 , psycholeptic use: B -1.09 , 95%CI -1.71 ; -0.47 , respectively, Supplementary Table 1). A longer sleep duration was also observed in both groups and point estimates were stronger in the group of concurrent psycholeptic drug users (p for interaction= 0.005). All other subcomponents were similarly associated with SSRI use when stratified by concurrent psycholeptic drug use. Furthermore, no effect modification by depression score was observed (p for interaction= 0.338), which suggest that the association between SSRIs and global PSQI score was not different in participants with or without clinically significant depressive symptoms.

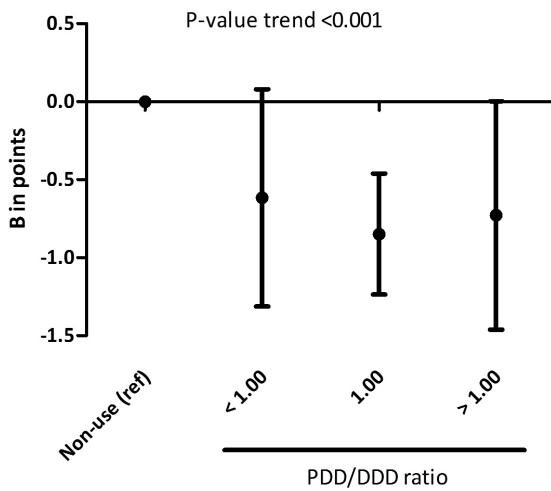


Figure 2. Association of selective serotonin reuptake inhibitor dose with global Pittsburgh Sleep Quality Index score.

Abbreviations: ref= reference group, PDD/DDD ratio= prescribed daily dose/defined daily dose.

Longitudinal analyses

Continuation of SSRI use was associated with 0.71 point lower PSQI score (95%CI -1.18 ; -0.24) and higher sleep efficiency (OR 0.48, 95%CI 0.23; 0.89) at the follow-up measurement round, when we adjusted for the baseline sleep scores and compared with non-users (Table 3).

Table 3. Longitudinal association between selective serotonin reuptake inhibitor use and the global Pittsburgh Sleep Quality Index score and its subcomponents.

	N	Global PSQI score		Subcomponents PSQI						
		B in points (95% CI)	Ref	Sleep duration B in hours (95% CI)	Ref	Sleep onset latency OR (95%CI)	Sleep quality OR (95% CI)	Daytime dysfunction OR (95% CI)	Sleep disturbances OR (95% CI)	Sleep efficiency OR (95% CI)
Non-use	5,277	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
All SSRI users										
Incident use	61	-0.06 (-0.68; 0.57)	0.27 (0.16; 0.38)	1.49 (0.80; 2.75)	0.49 (0.21; 1.14)	1.37 (0.52; 3.58)	1.71 (0.56; 5.23)	1.05 (0.50; 2.18)		
Cessation of use	58	-0.06 (-0.72; 0.60)	-0.31 (-0.42; -0.19)	1.02 (0.53; 1.98)	0.95 (0.46; 1.95)	1.11 (0.38; 3.22)	2.48 (1.00; 6.18)	1.03 (0.48; 2.19)		
Continuation of use	107	-0.71 (-1.18; -0.24)	0.48 (0.39; 0.56)	1.21 (0.74; 1.98)	0.68 (0.36; 1.25)	1.21 (0.53; 2.80)	1.10 (0.41; 2.93)	0.48 (0.23; 0.89)		

NOTE: Global PSQI score and sleep duration are presented as B, representing higher = worse sleep or longer sleep duration. Other subcomponents are represented as odds ratio (representing higher = worse sleep). Analyses adjusted for age, sex, educational level, employment status, body mass index, Center for Epidemiological Studies Depression Scale score, alcohol intake, psycholeptic drug use and baseline sleep score.
 Abbreviations: SSRI= selective serotonin reuptake inhibitor, N= number of participants, PSQI= Pittsburgh Sleep Quality Index, OR= odds ratio.

Also, continuation of SSRI use was associated with 0.48 hours longer sleep duration (95%CI: 0.39; 0.56), and this was to a lesser extent also observed in incident SSRI users (B 0.27 hours, 95% 0.16; 0.38), when compared with non-use. However, cessation of SSRI use was associated with 0.31 hours shorter sleep duration (95%CI -0.42; -0.19) and borderline significantly with more sleep disturbances (OR 2.48, 95%CI 1.00; 6.18).

Discussion

The results of this study showed a beneficiary association of SSRI use with subjective sleep. However, use of SSRIs was also associated with a higher risk of daytime dysfunction. These associations were only observed when psycholeptic drug use and presence of depressive symptoms were carefully accounted for. Consistently, these associations were also observed in longitudinal analyses of continuous users.

In clinically depressed populations, SSRI use was repeatedly associated with improved subjective sleep [9, 11, 22]. However, in these previous studies, the improved subjective sleep was possibly biased by the remitting depressive symptoms and more general improvement in mental health [9, 22]. Typically these studies focused on the change in sleep quality from start of antidepressant treatment until the end of treatment. However, results from studies in healthy participants are still inconsistent with respect to their effect of SSRIs on sleep quality [9, 11, 12, 17-22]. Our results suggest that SSRI use is associated with better subjective sleep, after we carefully accounted for presence of depressive symptoms, and ruled out possible effect modification by depressive symptoms. We observed a longer total sleep time, better sleep quality, and higher sleep efficiency. In contrast, we observed an association between SSRI use and a higher risk for daytime dysfunction. Daytime dysfunction assessed with the PSQI is based on trouble staying awake during driving, eating meals, engaging in social activity and problems with keeping up enthusiasm to get things done. An increased daytime dysfunction might represent residual depressive symptoms which diminish enthusiasm in daily life and daily activities. This would only represent residual symptoms as we already adjusted for presence of depressive symptoms with the CES-D. However, an increased daytime function could also suggest that SSRIs have sedative properties. Therefore, we think our results support the previous literature which report sedative properties and beneficial sleep effects of SSRIs in healthy participants [18, 20, 21].

Our study, embedded in a population-based cohort, in the middle-aged and elderly population has some novel aspects compared with previous studies. First, SSRI and psycholeptic drug use was allowed concurrently and associations were present in SSRI users while adjusting for psycholeptic drug use. Beneficial associations of SSRI use were present with or without psycholeptic drug use. Second, we could study the dose-response

relationship between SSRI use and global PSQI score. A significant p for trend might suggest a more valid drug effect, although the association was mainly driven by a large group of SSRI users with an average dose of one DDD. Third, we were able to adjust for baseline PSQI scores and took SSRI use at two measurement rounds into consideration, which added a longitudinal component to our analyses. This enabled us to study the association between SSRIs and PSQI scores, irrespective of inter-person differences in sleep at baseline. Moreover, we could study the effect of continuous use, incident use or cessation of SSRI treatment on subjective sleep. As our cross-sectional and longitudinal results of continuous users were in line with each other, this would suggest that our results on SSRIs and subjective sleep are robust. Especially as cessation of treatment seems to be associated with shorter sleep duration and more sleep disturbances. However, we would have expected a stronger beneficial association in incident SSRI users as well. This might suggest that continuous users represent a selected population of SSRI users on successful maintenance treatment, while other SSRI users might discontinue unsuccessful treatment. Thus, because of the association in continuous SSRI users and the fact that we used subjective sleep measures, an effect of improvement in mental health might still be present. Nevertheless, our results in the general middle-aged and elderly population are important, as a patient's own perception is relevant in the course of treatment, relief of depressive symptoms and overall well-being [11, 35].

Limitations and strengths

Strengths of our study are the large sample size, population-based character and the prospectively gathered electronic pharmacy records which we used to determine antidepressant and psycholeptic drug exposure. Some limitations of our study should be mentioned. First, the PSQI questionnaire and its separate components have not been designed and validated to be used in pharmacoepidemiological studies. However, most previous studies used the Leeds Sleep Evaluation Questionnaire or the sleep factor scores of the Hamilton Rating Scale for Depression, which are also not designed for this specific research question. Still, the PSQI is considered to be a valid questionnaire with a good test-retest reliability [26]. Second, confounding by indication might bias our results as depression itself is associated with sleep disorders. However, we observed a positive association between SSRI use and sleep quality and we were able to adjust for, and study effect modification by, depressive symptoms. Third, the numbers were low in our consecutive analyses with continuous and incident SSRI users, and interpretation should be done with caution. Fourth, ideally we would have been able to make a direct individual comparison with objective sleep measurements. Fifth, our results were based on a middle-aged and elderly population and results may not be generalizable for the complete general population. Sixth, drug exposure was based on dispensing records and not on actual intake. However, any misclassification of exposure would probably be random in this setting.

Conclusion

Within our population-based cohort study of middle-aged and elderly individuals, we observed an association between SSRI use and better subjective sleep. This association was found after carefully taking into account depressive symptoms and concurrent psycholeptic drug use, and was more prominent in continuous users. These results suggest that in the middle-aged and elderly population the sleep quality of some persons may benefit from, continued, SSRI use in daily practice.

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Supplementary table 1. Association between selective serotonin reuptake inhibitor use and the global Pittsburg Sleep Quality Index score and its subcomponents stratified by concurrent psycholeptic drug use.

	Number of measurements	Global PSQI score									
		B in points (95%CI)	Sleep duration B in hours (95% CI)	Sleep onset latency OR (95%CI)	Sleep quality OR (95%CI)	Daytime dysfunction OR (95%CI)	Sleep disturbances OR (95%CI)	Sleep efficiency OR (95%CI)			
No psycholeptic drug use											
Non-SSRI use	12,840	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
SSRI use	292	-0.57 (-0.94; -0.20)	0.57 (0.40; 0.74)	0.93 (0.67; 1.30)	0.55 (0.36; 0.83)	1.37 (0.84; 2.24)	0.84 (0.45; 1.57)	0.68 (0.45; 1.01)			
Psycholeptic drug use											
Non-SSRI use	1,473	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
SSRI use	166	-1.09 (-1.71; -0.47)	0.91 (0.65; 1.17)	0.78 (0.53; 1.16)	0.55 (0.36; 0.84)	1.59 (0.94; 2.68)	0.92 (0.51; 1.66)	0.68 (0.45; 1.04)			

NOTE: Global PSQI score and sleep duration are presented as B, representing higher = worse sleep or longer sleep duration. Other subcomponents are represented as odds ratio, representing higher = worse sleep. Adjusted for age, sex, educational level, employment status, body mass index, Center for Epidemiological Studies Depression Scale score and alcohol intake.

Abbreviations: SSRI=selective serotonin reuptake inhibitor, PSQI= Pittsburg Sleep Quality Index, OR= odds ratio, ref=reference group.



3.3

Use of selective serotonin reuptake inhibitors and sleep quality: a population-based study

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Submitted

Abstract

Study objectives: Poor sleep is a risk factor for the development and recurrence of depression. Selective serotonin reuptake inhibitor (SSRI) use is consistently associated with good subjective sleep in clinically depressed patient populations. However, studies in the general population are lacking. Our objective was to investigate the association between SSRIs and subjective sleep in a middle-aged and elderly population in a daily practice setting.

Methods: We included participants from the prospective Rotterdam Study cohort. Participants had up to two sleep measurements assessed with Pittsburgh Sleep Quality Index ([PSQI], number of measurements=14,770). SSRI use was based on pharmacy records. We assessed the association between SSRIs and PSQI score and its sub-components, with non-users of any antidepressant as reference. Analyses were, among others, adjusted for depressive symptoms and psycholeptic drug use.

Results: We included 9,267 participants with an average baseline age of 66.3 years (SD 10.6) and 57.6% were women. SSRI use was significantly associated with a 0.78point lower PSQI score (95%CI -1.11;-0.44) which reflects better sleep, compared with non-use. The association was more prominent in continuous SSRI users (-0.71points, 95%CI -1.18;-0.24). Of the sub-components, SSRIs were associated with 0.70hour longer sleep duration (95%CI 0.56;0.85), higher sleep quality, higher sleep efficiency, and in contrast more daytime dysfunction.

Conclusions: SSRI use was associated with better subjective sleep, after adjustment for depressive symptoms and concurrent psycholeptic drug use. This suggests that – in clinical practice in the middle-aged and elderly population – the sleep quality of some persons may benefit from, continued, SSRI use.

Introduction

Sleep and depression are highly associated. The most common disturbances in the sleep pattern of a depressed person are low sleep efficiency and little deep sleep [1-4]. Poor sleep has been shown to be a risk factor for the development or recurrence of depression [2, 5-8]. On the other hand, antidepressant drugs can have positive and negative effects on sleep [9-13].

Selective serotonin reuptake inhibitors (SSRIs) are considered activating antidepressants and a risk factor for poor sleep according to most objective sleep measurements, although sedative properties and daytime somnolence have occasionally been reported for SSRIs [10, 12-16]. Studies in non-depressed individuals regarding the association between SSRIs and subjective sleep reported inconsistent results [9, 11, 12, 17-21]. Whereas, in clinically depressed patient populations, SSRI use is consistently associated with an improved subjective sleep [3, 9, 11, 22]. The favorable results in depressed populations might represent the improvement of mental health or relief of depressive symptoms [9, 22]. So far, most studies focused on subjective perception of sleep as a secondary outcome in clinical trials of antidepressants which are limited by small sample size, short follow-up or concomitant benzodiazepine use [23]. To our knowledge, to date, no population-based study investigated whether SSRIs are associated with better subjective sleep in the middle-aged and elderly population.

Therefore, our objective was to investigate the association between SSRI use and different subjective sleep parameters in a population-based cohort study. Additionally, to evaluate the effect of sleep medication and depressive symptoms, we adjusted for concurrent psycholeptic drug use or presence of depressive symptoms and studied potential effect modification.

Methods

Setting

The Rotterdam Study is a prospective population-based cohort study that investigates incidence of, and risk factors for, several age-related diseases. The study was initiated in 1990, and after extension over the years, comprises a total of 14,926 participants. All participants were 45 years or older at baseline. After baseline examination, follow-up examinations were conducted every 4-5 years. Extensive information on morbidity and mortality is available for participants on a day-to-day basis from general practitioner records. Detailed information on design, objectives and methods of the Rotterdam Study has been published elsewhere [24, 25]. The Rotterdam Study has been approved by the medical ethics committee according to

the Wet Bevolkingsonderzoek: ERGO (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sports of the Netherlands. Written informed consent was signed by all study participants.

Study population

We included participants from interview rounds between January 2002 – December 2008 and March 2009 – January 2014. These interview rounds included the Pittsburgh Sleep Quality Index (PSQI) [26]. A total of 9,897 and 6,874 participants underwent home interview during these rounds, respectively. Measurements of participants with considerable cognitive impairment (Mini-Mental State Examination score below 24) [27], measurements with less than 5 (out of 7) valid sleep components on the PSQI [26], or measurements from participants who used other antidepressants than SSRIs at the time of interview were excluded from the analyses.

Exposure definition

Antidepressant drug use was assessed on the basis of pharmacy dispensing records. Electronic pharmacy records were available from January 1st, 1991 onwards. These include the date of dispensing, the total amount of drug units per prescription, the dispensed daily number of units, the product name of the drug and the Anatomical Therapeutic Chemical (ATC) code [28]. The duration of a dispensing was calculated by dividing the total number of dispensed pills/capsules by the prescribed daily number. Treatment episodes were based on consecutive dispensings in which a treatment gap between antidepressant drug dispensings of up to 30 days was still considered as one continuous episode. Participants were considered current users if the interview date fell within an antidepressant drug treatment episode. SSRI users were defined based on the 4th level ATC-code='N06AB'. The average dose was defined as the ratio between the prescribed daily dose and the defined daily dose (PDD/DDD ratio), as determined by the World Health Organization [28]. Users of all other antidepressant drugs were excluded from analyses.

Assessment of sleep parameters

Based on the Dutch version of the PSQI we assessed subjective sleep parameters [26]. The PSQI is a self-rated questionnaire that measures sleep parameters retrospectively over a 1-month period. The questionnaire consists of seven separate components (i.e. sleep duration, sleep disturbances, sleep latency, daytime dysfunction, sleep efficiency, sleep quality, use of sleep medication) with scores ranging from 0 to 3. Based on these seven components a global PSQI score can be calculated, ranging from 0 to 21 in which a higher score corresponds to poorer sleep [26]. For our research question, we excluded the component 'use of sleep medication' from the global PSQI score, as part of our exposure of interest is equal to the component sleep medication (i.e., benzodiazepines). In the present

study, the PSQI score ranged from 0 to 18 points, with a higher score indicative of impaired sleep.

Covariables

We considered the following covariables as potential confounding factors: sex, age, educational level, employment status, body mass index (BMI), depressive symptoms, alcohol intake, and psycholeptic drug use. Except for educational level, all covariables were time-varying and defined at time of the PSQI measurements. Educational level was assessed by home interview at study entry. We categorized educational status in four groups as previously described for the Rotterdam Study and similar to the UNESCO classification (i.e. basic= primary education, low= lower vocational, lower and intermediate general, medium= intermediate vocational, higher general, high= higher vocational and university) [29, 30]. Current employment status (yes/no) was based on questionnaire data. BMI was defined as weight (in kilograms) divided by height (in meters squared), measured at the research center. At the interview rounds, depressive symptoms and alcohol intake were assessed. Depressive symptoms were assessed with a Dutch version of the Center for Epidemiological Studies Depression Scale (CES-D) [31]. A score of 16 and higher was considered as an indicator for clinically relevant depressive symptoms [32]. Alcohol intake was assessed as the average consumption of glasses of alcohol in a week. This amount was converted into grams of alcohol on an average day. Psycholeptic drug use (ATC='N05') was defined as a dispensing of antipsychotics, anxiolytics, hypnotics or sedatives within 90 days before an interview date and was based on the available pharmacy dispensing records.

Statistical analyses

Baseline was defined as the first eligible PSQI measurement of a participant included in the study. Missing values were observed, this percentage was highest for BMI (12.0%) and MMSE score (8.3%). Missing values were handled by multiple imputation using 5 imputations.

We studied the association between SSRI use and repeated measurements of the global PSQI score and its subcomponents. We used repeated measurement techniques (Generalized Estimating Equations) for our analyses, to take into account within-person correlations between visits. We chose the independent working correlation matrix according to the lowest corrected quasi likelihood under independence model criterion [33, 34]. Only the global PSQI score and sleep duration were analyzed as continuous variables. Sleep onset latency, sleep disturbances, daytime dysfunction, sleep efficiency and sleep quality were modelled as binary outcome. For the binary outcomes, the cut-off was based on their questionnaire score (0 to 1 [good sleep] versus 2 to 3 [poor sleep]).

Subsequently, we studied whether there was a dose-response relation between the average prescribed DDDs and global PSQI score. Moreover, we studied effect modification by psycholeptic drug use or by presence of depressive symptoms on the association between

SSRI use and the global PSQI score and its subcomponents. Interaction terms were added to the model and results were subsequently stratified by concurrent psycholeptic drug use or by presence of depressive symptoms.

To assess the longitudinal association between SSRI use and PSQI scores at the follow-up measurement round, we used linear and logistic regression models and adjusted for baseline PSQI scores. This enabled us to study the association between SSRI use and PSQI scores, while accounting for inter-person differences in sleep at baseline. SSRI exposure was assessed at the baseline and follow-up measurement round and classified as: incident use at the follow-up measurement (incident use), current use at both measurements (continuation of use) or only SSRI exposure at the baseline measurement round (cessation of use). All analyses were compared to non-use of any antidepressant at both measurement rounds.

All statistical models were adjusted for age and sex (model 1), or in the full model additionally adjusted for educational level, employment status, BMI, CES-D score, alcohol intake and psycholeptic drug use (model 2). Data were analyzed using IBM SPSS statistics (version 21.0, IBM Corp., Somers, NY, USA).

Results

Baseline characteristics

The total study population consisted of 9,267 participants, with a total of 14,770 PSQI measurements (Figure 1). At baseline, the study population comprised of 57.6% women had a mean age of 66.3 years (SD=10.6). Baseline characteristics are presented in Table 1.

Table 1. Baseline characteristics of the study population.

	Study population N=9,267 N (%)
Age (yr), mean (SD)	66.3 (10.6)
Women	5,338 (57.6)
Educational level ^a	
Primary	1,003 (10.8)
Lower	3,784 (40.8)
Intermediate	2,715 (29.3)
Higher	1,764 (19.0)
Currently employed	2,600 (28.1)
Body Mass Index (kg/m ²), mean (SD)	27.7 (4.3)
Depression score ^b , median (IQR)	3.0 (1.0 – 8.0)
Psycholeptic drug use	1,137 (12.3)
MMSE score, median (IQR)	28.0 (27.0 – 29.0)
Alcohol intake (gram per day), median (IQR)	7.9 (1.3 – 17.1)

Baseline characteristics (imputed) are listed as n (%), unless stated otherwise. ^a Similar to the UNESCO classification and previously described for the Rotterdam Study [29, 30]. ^b Based on the Center for Epidemiological Studies Depression Scale (range 0 -60) [31].

Abbreviations: yr= year, SD= standard deviation, IQR= Interquartile Range, MMSE= Mini-Mental State Examination

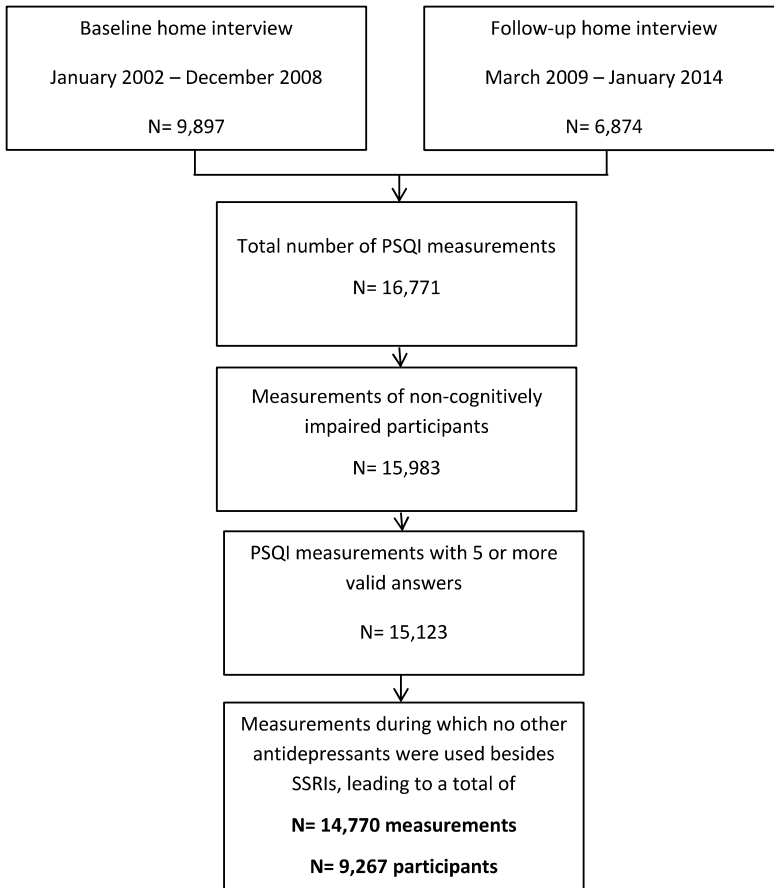


Figure 1. Flow-chart of the study population.

Abbreviations: PSQI= Pittsburg Sleep Quality Index, SSRIs= selective serotonin reuptake inhibitors

SSRIs and global PSQI

In the age- and sex-adjusted model, SSRI use was not associated with the global PSQI score (B 0.26; 95%CI -0.12; 0.63, Table 2). However, after full statistical adjustment, we observed that SSRI use was associated with a significant 0.78 point lower global PSQI score (95%CI -1.11; -0.44). Three PSQI subcomponents significantly contributed to the lower global PSQI score: longer sleep duration (B 0.70 hours, 95%CI 0.56; 0.85), better sleep quality (odds ratio [OR] 0.52, 95%CI 0.37; 0.71), and higher sleep efficiency (OR 0.65, 95%CI 0.48; 0.88) in the fully adjusted model. In contrast, SSRI use was associated with more daytime dysfunction (OR 1.48, 95%CI 1.02; 2.16).

Table 2. Association between selective serotonin reuptake inhibitor use and the global Pittsburgh Sleep Quality Index score and its subcomponents.

	Global PSQI score		Subcomponent PSQI					
	Number of measurements	B in points (95%CI)	Sleep duration B in hours (95% CI)	Sleep onset latency OR (95%CI)	Sleep quality OR (95%CI)	Daytime dysfunction OR (95%CI)	Sleep disturbances OR (95%CI)	Sleep efficiency OR (95%CI)
Non-use	14,312	Ref	Ref	Ref	Ref	Ref	Ref	Ref
SSRI use								
Model 1	458	0.26 (-0.12; 0.63)	0.49 (0.34; 0.64)	1.38 (1.08; 1.77)	1.15 (0.88; 1.52)	2.96 (2.14; 4.08)	1.95 (1.33; 2.86)	1.06 (0.79; 1.41)
Model 2	458	-0.78 (-1.11; -0.44)	0.70 (0.56; 0.85)	0.85 (0.65; 1.12)	0.52 (0.37; 0.71)	1.48 (1.02; 2.16)	0.87 (0.56; 1.34)	0.65 (0.48; 0.88)

NOTE: Global PSQI score and sleep duration are presented as B, representing higher = worse sleep or longer sleep duration. Other subcomponents are represented as odds ratio, representing higher = worse sleep. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, educational level, employment status, body mass index, Center for Epidemiological Studies Depression Scale score, alcohol intake and psycholeptic drug use. Abbreviations: PSQI= Pittsburgh Sleep Quality Index, SSRI= selective serotonin reuptake inhibitor, OR= odds ratio, ref=reference group.

A dose-response relationship was observed between the average prescribed dose and the global PSQI score (p for trend <0.001 , Figure 2). Effect modification by psycholeptic drug use was observed for the association between SSRIs and global PSQI score (p for interaction= 0.048). When stratified by concurrent use of psycholeptic drugs, SSRI use was in both groups associated with a lower global PSQI score, but point estimates were stronger in the group of concurrent psycholeptic drug use (no psycholeptic use: B -0.57 , $95\%CI$ -0.94 ; -0.20 , psycholeptic use: B -1.09 , $95\%CI$ -1.71 ; -0.47 , respectively, Supplementary Table 1). A longer sleep duration was also observed in both groups and point estimates were stronger in the group of concurrent psycholeptic drug users (p for interaction= 0.005). All other subcomponents were similarly associated with SSRI use when stratified by concurrent psycholeptic drug use. Furthermore, no effect modification by depression score was observed (p for interaction= 0.338), which suggest that the association between SSRIs and global PSQI score was not different in participants with or without clinically significant depressive symptoms.

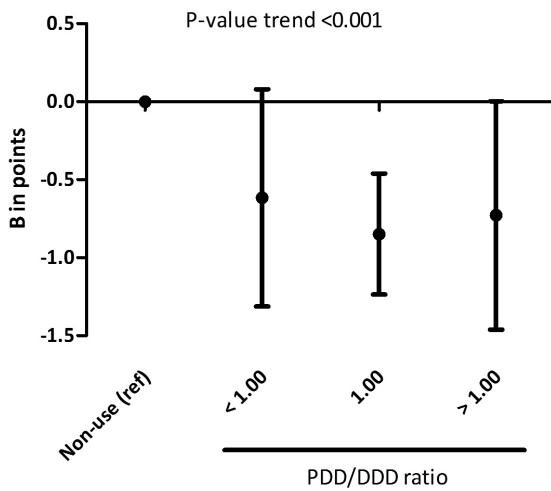


Figure 2. Association of selective serotonin reuptake inhibitor dose with global Pittsburgh Sleep Quality Index score.

Abbreviations: ref= reference group, PDD/DDD ratio= prescribed daily dose/defined daily dose.

Longitudinal analyses

Continuation of SSRI use was associated with 0.71 point lower PSQI score ($95\%CI$ -1.18 ; -0.24) and higher sleep efficiency (OR 0.48 , $95\%CI$ 0.23 ; 0.89) at the follow-up measurement round, when we adjusted for the baseline sleep scores and compared with non-users (Table 3).

Table 3. Longitudinal association between selective serotonin reuptake inhibitor use and the global Pittsburgh Sleep Quality Index score and its subcomponents.

	N	Global PSQI score		Subcomponents PSQI						
		B in points (95% CI)	Ref	Sleep duration B in hours (95% CI)	Ref	Sleep onset latency OR (95%CI)	Sleep quality OR (95% CI)	Daytime dysfunction OR (95% CI)	Sleep disturbances OR (95% CI)	Sleep efficiency OR (95% CI)
Non-use	5,277	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
All SSRI users										
Incident use	61	-0.06 (-0.68; 0.57)	0.27 (0.16; 0.38)	1.49 (0.80; 2.75)	0.49 (0.21; 1.14)	1.37 (0.52; 3.58)	1.71 (0.56; 5.23)	1.05 (0.50; 2.18)		
Cessation of use	58	-0.06 (-0.72; 0.60)	-0.31 (-0.42; -0.19)	1.02 (0.53; 1.98)	0.95 (0.46; 1.95)	1.11 (0.38; 3.22)	2.48 (1.00; 6.18)	1.03 (0.48; 2.19)		
Continuation of use	107	-0.71 (-1.18; -0.24)	0.48 (0.39; 0.56)	1.21 (0.74; 1.98)	0.68 (0.36; 1.25)	1.21 (0.53; 2.80)	1.10 (0.41; 2.93)	0.48 (0.23; 0.89)		

NOTE: Global PSQI score and sleep duration are presented as B, representing higher = worse sleep or longer sleep duration. Other subcomponents are represented as odds ratio (representing higher = worse sleep). Analyses adjusted for age, sex, educational level, employment status, body mass index, Center for Epidemiological Studies Depression Scale score, alcohol intake, psycholeptic drug use and baseline sleep score.
 Abbreviations: SSRI= selective serotonin reuptake inhibitor, N= number of participants, PSQI= Pittsburgh Sleep Quality Index, OR= odds ratio.

Also, continuation of SSRI use was associated with 0.48 hours longer sleep duration (95%CI: 0.39; 0.56), and this was to a lesser extent also observed in incident SSRI users (B 0.27 hours, 95% 0.16; 0.38), when compared with non-use. However, cessation of SSRI use was associated with 0.31 hours shorter sleep duration (95%CI -0.42; -0.19) and borderline significantly with more sleep disturbances (OR 2.48, 95%CI 1.00; 6.18).

Discussion

The results of this study showed a beneficiary association of SSRI use with subjective sleep. However, use of SSRIs was also associated with a higher risk of daytime dysfunction. These associations were only observed when psycholeptic drug use and presence of depressive symptoms were carefully accounted for. Consistently, these associations were also observed in longitudinal analyses of continuous users.

In clinically depressed populations, SSRI use was repeatedly associated with improved subjective sleep [9, 11, 22]. However, in these previous studies, the improved subjective sleep was possibly biased by the remitting depressive symptoms and more general improvement in mental health [9, 22]. Typically these studies focused on the change in sleep quality from start of antidepressant treatment until the end of treatment. However, results from studies in healthy participants are still inconsistent with respect to their effect of SSRIs on sleep quality [9, 11, 12, 17-22]. Our results suggest that SSRI use is associated with better subjective sleep, after we carefully accounted for presence of depressive symptoms, and ruled out possible effect modification by depressive symptoms. We observed a longer total sleep time, better sleep quality, and higher sleep efficiency. In contrast, we observed an association between SSRI use and a higher risk for daytime dysfunction. Daytime dysfunction assessed with the PSQI is based on trouble staying awake during driving, eating meals, engaging in social activity and problems with keeping up enthusiasm to get things done. An increased daytime dysfunction might represent residual depressive symptoms which diminish enthusiasm in daily life and daily activities. This would only represent residual symptoms as we already adjusted for presence of depressive symptoms with the CES-D. However, an increased daytime function could also suggest that SSRIs have sedative properties. Therefore, we think our results support the previous literature which report sedative properties and beneficial sleep effects of SSRIs in healthy participants [18, 20, 21].

Our study, embedded in a population-based cohort, in the middle-aged and elderly population has some novel aspects compared with previous studies. First, SSRI and psycholeptic drug use was allowed concurrently and associations were present in SSRI users while adjusting for psycholeptic drug use. Beneficial associations of SSRI use were present with or without psycholeptic drug use. Second, we could study the dose-response

relationship between SSRI use and global PSQI score. A significant p for trend might suggest a more valid drug effect, although the association was mainly driven by a large group of SSRI users with an average dose of one DDD. Third, we were able to adjust for baseline PSQI scores and took SSRI use at two measurement rounds into consideration, which added a longitudinal component to our analyses. This enabled us to study the association between SSRIs and PSQI scores, irrespective of inter-person differences in sleep at baseline. Moreover, we could study the effect of continuous use, incident use or cessation of SSRI treatment on subjective sleep. As our cross-sectional and longitudinal results of continuous users were in line with each other, this would suggest that our results on SSRIs and subjective sleep are robust. Especially as cessation of treatment seems to be associated with shorter sleep duration and more sleep disturbances. However, we would have expected a stronger beneficial association in incident SSRI users as well. This might suggest that continuous users represent a selected population of SSRI users on successful maintenance treatment, while other SSRI users might discontinue unsuccessful treatment. Thus, because of the association in continuous SSRI users and the fact that we used subjective sleep measures, an effect of improvement in mental health might still be present. Nevertheless, our results in the general middle-aged and elderly population are important, as a patient's own perception is relevant in the course of treatment, relief of depressive symptoms and overall well-being [11, 35].

Limitations and strengths

Strengths of our study are the large sample size, population-based character and the prospectively gathered electronic pharmacy records which we used to determine antidepressant and psycholeptic drug exposure. Some limitations of our study should be mentioned. First, the PSQI questionnaire and its separate components have not been designed and validated to be used in pharmacoepidemiological studies. However, most previous studies used the Leeds Sleep Evaluation Questionnaire or the sleep factor scores of the Hamilton Rating Scale for Depression, which are also not designed for this specific research question. Still, the PSQI is considered to be a valid questionnaire with a good test-retest reliability [26]. Second, confounding by indication might bias our results as depression itself is associated with sleep disorders. However, we observed a positive association between SSRI use and sleep quality and we were able to adjust for, and study effect modification by, depressive symptoms. Third, the numbers were low in our consecutive analyses with continuous and incident SSRI users, and interpretation should be done with caution. Fourth, ideally we would have been able to make a direct individual comparison with objective sleep measurements. Fifth, our results were based on a middle-aged and elderly population and results may not be generalizable for the complete general population. Sixth, drug exposure was based on dispensing records and not on actual intake. However, any misclassification of exposure would probably be random in this setting.

Conclusion

Within our population-based cohort study of middle-aged and elderly individuals, we observed an association between SSRI use and better subjective sleep. This association was found after carefully taking into account depressive symptoms and concurrent psycholeptic drug use, and was more prominent in continuous users. These results suggest that in the middle-aged and elderly population the sleep quality of some persons may benefit from, continued, SSRI use in daily practice.

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Supplementary table 1. Association between selective serotonin reuptake inhibitor use and the global Pittsburg Sleep Quality Index score and its subcomponents stratified by concurrent psycholeptic drug use.

	Number of measurements	Global PSQI score									
		B in points (95%CI)	Sleep duration B in hours (95% CI)	Sleep onset latency OR (95%CI)	Sleep quality OR (95%CI)	Daytime dysfunction OR (95%CI)	Sleep disturbances OR (95%CI)	Sleep efficiency OR (95%CI)			
No psycholeptic drug use											
Non-SSRI use	12,840	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
SSRI use	292	-0.57 (-0.94; -0.20)	0.57 (0.40; 0.74)	0.93 (0.67; 1.30)	0.55 (0.36; 0.83)	1.37 (0.84; 2.24)	0.84 (0.45; 1.57)	0.68 (0.45; 1.01)			
Psycholeptic drug use											
Non-SSRI use	1,473	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
SSRI use	166	-1.09 (-1.71; -0.47)	0.91 (0.65; 1.17)	0.78 (0.53; 1.16)	0.55 (0.36; 0.84)	1.59 (0.94; 2.68)	0.92 (0.51; 1.66)	0.68 (0.45; 1.04)			

NOTE: Global PSQI score and sleep duration are presented as B, representing higher = worse sleep or longer sleep duration. Other subcomponents are represented as odds ratio, representing higher = worse sleep. Adjusted for age, sex, educational level, employment status, body mass index, Center for Epidemiological Studies Depression Scale score and alcohol intake.

Abbreviations: SSRI=selective serotonin reuptake inhibitor, PSQI= Pittsburg Sleep Quality Index, OR= odds ratio, ref=reference group.



3.4

Antidepressants and the risk of hyponatremia: a population-based study

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In preparation





3.5

Use of selective serotonin reuptake inhibitors and bone mineral density change: a population-based longitudinal study in middle-aged and elderly individuals

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Submitted

The background of the page is a complex, abstract composition of various shades of gray, black, and white. It features numerous brushstrokes, splatters, and smudges, creating a textured and layered appearance. The overall effect is that of a heavily used and perhaps discarded piece of paper or canvas, with some areas appearing more saturated and others more faded or overexposed. The composition is dense and chaotic, with no discernible geometric shapes or patterns.

4

General discussion

In this chapter, we will discuss the main findings of this thesis and put them into a broader perspective. We aimed to characterize use of antidepressants (**chapter 2**) and their possible unintended effects (**chapter 3**) in daily practice in an ageing population. Furthermore, some important methodological considerations which we encountered will be discussed. Finally, we will try to translate our results to implications for clinical practice and provide some directions for future research.

Main findings

Characteristics of antidepressant use in daily practice

Use of antidepressants – especially selective serotonin reuptake Inhibitors (SSRIs) – increased excessively in the last decades [1-3]. Within the Rotterdam Study (**chapter 2.1**) and with data from the Integrated Primary Care Information database (IPCI [**chapter 2.2**]), we also demonstrated a steep increase in antidepressant use in the period between 1991 and 2012. Prevalent antidepressant use doubled during this period and the steepest increase was observed for use of SSRIs. In line, first choice of treatment shifted from tricyclic antidepressants (TCAs) to SSRIs and other antidepressants in later years. Moreover, the prevalence was even higher in the older age categories. Previously, concerns have been raised regarding these high rates of antidepressant use in the population. It has been hypothesized that antidepressants are too easily prescribed for indications such as mild depressive symptoms and other off-label indications, without any sound scientific evidence [4, 5]. In contrast, better adherence to the treatment guidelines – which request long term treatment – could also explain the increased prevalence [1, 6]. Therefore, we studied multiple characteristics of antidepressant use which could possibly explain the trends in prevalence.

We found that the incidence of antidepressant use over the years did not explain the patterns of prevalent prescribing. Incidence rates in **chapter 2.1** decreased over time, but may be biased by a saturation effect or depletion of susceptibles in an inception cohort such as the Rotterdam Study population. However, incidence rates of antidepressant use also decreased in the dynamic patient population of IPCI as reported in **chapter 2.2**, and previous literature also reported a declining or stable incidence over the years [7-9]. Next, an extension of the indications for antidepressant use to more chronic conditions might explain the increasing prevalence. In **chapter 2.2**, indications for treatment changed over the years as antidepressants were increasingly prescribed for sleeping disorders, multiple indications and neuropathic pain (only in TCAs). In contrast, the indication ‘depression’ was less commonly registered in later years.

However, given that indications based on diagnostic codes were only registered in 41% of antidepressant users in **chapter 2.2**, we also studied indications for antidepressant use based on self-report in **chapter 2.3**. Indications registered with diagnostic codes in general practitioners' healthcare databases may be incomplete because of diagnostic uncertainty, off-label drug use or subthreshold psychiatric symptoms which were not registered or may be difficult to recognize from free text in automated medical records [10-14]. In **chapter 2.3**, depression was still most frequently mentioned as indication for treatment in our study (based on data between 1997 and 2008). However, especially in TCA users the indication profile was very heterogeneous with depression, stress, sleeping disorders and pain commonly reported as possible indication for treatment. For SSRIs and other antidepressants, the majority of users reported psychiatric symptoms such as depression, anxiety, stress and sleep disorders. Furthermore, almost all indications were associated with a statistically significantly higher presence of depressive symptoms assessed with the Center for Epidemiological Center Depression Scale (CES-D) when compared to non-users. This suggests that these symptoms are highly correlated or often occur concomitantly [15-18]. Previous studies already established that combinations of mental complaints, multimorbidity, psychosocial problems and social distress are important reasons to prescribe antidepressants [4, 19-22]. Especially in our middle-aged and elderly study population – with their potential accumulation of life events and physical impairment – these could be important reasons to prescribe antidepressants. A possible shift to prescribing for general mental and physical health problems and other (off-label) indications could contribute to the increased prevalence of antidepressant use over the years [4, 5, 21]. However, more longitudinal patient-specific information is needed to draw firm conclusions.

An increased duration of treatment might also explain the increased prevalence of antidepressant use [3, 23]. Guidelines recommend at least 6 months of treatment after relief in depressive symptoms to prevent relapse [24-26]. However, many users discontinue antidepressants earlier than recommended and much focus has been put on proper adherence and persistence ['compliance'] to maintenance treatment [27, 28]. In **chapter 2.4**, a median persistence of 137 days was reported, thus the largest part of the antidepressant users did not reach the recommended duration of treatment. Female gender, SSRI and other antidepressant use, dependent living situation, concurrent benzodiazepine use and presence of depressive disorders or anxiety disorders were all associated with a longer duration of treatment. These factors might all relate to the presence of a psychiatric disorder with a more severe, chronic or relapsing character [3, 10, 29]. Also, as discussed, our wide range of indications for antidepressant use in the elderly population (in **chapter 2.3**) may be associated with complaints of a more chronic character. Furthermore, over the 20-year study period, first choice of treatment shifted from TCAs to SSRIs and other antidepressants, and the latter two groups were also associated with a longer duration of treatment in later

years or when compared to use of TCAs. We also reported a steeper increase in prevalent adequate antidepressant treatment (i.e. exclusion of incidental users [‘single fillers’] and at least 4 dispensings in a year), which might suggest that duration of treatment did indeed increase over the years. However, no firm conclusions can be drawn as to whether this increase in duration is a good or bad development. It is unknown whether antidepressant prescribing according to the guidelines has improved, or whether they are inappropriately continued.

Benefit-risk considerations and possible unintended effects of antidepressants

Considerations regarding benefit-risk should be taken into account when we discuss possible inappropriate use of antidepressants. The efficacy of antidepressants has been established in the treatment of major depressive disorders [30], and compared to placebo, it has been suggested that the benefits of antidepressants may be minimal in patients with minor depression or mild depressive symptoms [30, 31]. Even if proven effective, the numbers needed to treat were estimated at 7 for SSRIs and 9 for TCAs in primary care [32]. Thus, a substantial group of patients does not benefit from antidepressant use. Hence, safety of antidepressant use should be firmly established. SSRIs were a revolution when they came onto the market, especially because of their safety profile [2, 33, 34]. However, SSRIs are not risk free as more and more adverse drug reactions (ADR) are attributed to the use of SSRIs [35].

Therefore, we studied possible unintended effects of antidepressants in a middle-aged and elderly population. This population is at increased risk of ADRs and drug-drug interactions [36, 37], while they are large-scale consumers of antidepressants and other psychotropic drugs [38, 39]. Moreover, relatively little is known regarding drug safety, as elderly are underrepresented in clinical trials [40]. In the following paragraphs, we will further elaborate on the unintended effects that we investigated in **chapter 3**.

Chapter 3.1 and 3.2 both focus on the association between antidepressant use and cerebral microbleeds defined on MRI. We did not observe an association between antidepressants with a high affinity for the serotonin transporter and presence of cerebral microbleeds in **chapter 3.1**. In contrast, we did observe an association between use of all antidepressants and occurrence of cerebral microbleeds in **chapter 3.2**. The latter study probably had a better design to evaluate the temporal association between use of antidepressants and microbleeds. However, in that study, we observed an association for the total group of antidepressants and not only for antidepressants with a high affinity for the serotonin transporter. This might suggest that another mechanism than the proposed one should explain an increased occurrence of microbleeds. The originally proposed mechanism hypothesizes that SSRIs block reuptake of serotonin by blood platelets. Thereby, platelet functionality may be decreased due to reduced intra-platelet serotonin concentrations,

and bleeding times may be prolonged [41, 42]. Potentially, residual confounding by later depression may explain our results, as we were able to control for depressive symptoms at baseline, but not during follow-up. Also, we should consider reverse causation in our study as incident microbleeds could have occurred at some time before antidepressant use during follow-up. Biologically it has been hypothesized that microbleeds may contribute to the progression of depression [43]. We think that large longitudinal studies are needed on the association between antidepressants and cerebral microbleeds with a smaller time interval between MRI and with a better ability to adjust for the occurrence of depression to confirm or refute our results.

In **chapter 3.3**, we showed a beneficial association between use of SSRIs and subjective sleep. SSRIs seem to have sedative properties, as they were associated with a longer total sleep time, better sleep quality, higher sleep efficiency and more daytime dysfunction. The cross-sectional and longitudinal results were in line, which further supports the robustness of our results. However, as the results were most prominent in continuous users and not in incident users, this may indicate that only the sleep quality of some persons may benefit from SSRI use. Participants – who benefit from the SSRI – most likely continue intake. Therefore, with our study in a population-based setting in which we were able to account for depressive symptoms and benzodiazepine use, we filled an important gap in literature. In previous literature, subjective sleep is almost consistently better in SSRI users or improves during treatment, but this might represent a relief in depressive symptoms as sleep and depression are highly correlated [44-47]. This is confirmed by the fact that studies in non-depressed individuals reported inconsistent results [45-53]. Ideally, further studies should make a direct individual comparison between subjective and objective sleep measurements in a population-based setting.

Chapter 3.4 concerns a study on antidepressant-induced hyponatremia, a known but not yet completely investigated ADR. Previous literature on SSRI-induced hyponatremia, consisting of case-reports, incidence studies and observational studies, has consistently shown an association [35, 54-59]. However, studies on its association with TCAs and other antidepressants are scarce and results are inconsistent [35, 58, 60-63]. The hypothesized mechanism – syndrome of inappropriate antidiuretic hormone secretion (SIADH) – could also apply to certain serotonin specific TCAs and other antidepressants [55, 62, 64, 65]. Nevertheless, we did not observe a statistically significant association between TCAs, other antidepressants and hyponatremia. Besides, confounding by indication probably influenced our results, as past use of TCAs and other antidepressants was also associated with a non-significantly higher risk of hyponatremia. These drugs might be prescribed to participants with specific comorbidities (e.g. diabetes mellitus) which could increase the susceptibility to hyponatremia. This was not the case for SSRIs, they were consistently associated with hyponatremia in new users and during the first 30 days of use. Based on the literature

already available on SSRI-induced hyponatremia [55, 58, 60, 66], the fact that SSRI-induced hyponatremia can have a reported occurrence between the 0.06% up to 40%, with a higher occurrence in the elderly [57, 58], and the serious consequences of even mild hyponatremia [67, 68], we think that – especially in a frail elderly population – sodium measurements could be of value for new SSRI users in the first 30 days after initiation of treatment. This could be added to the already existing guidelines, from the HARM-wrestling criteria [69], for sodium measurements in concurrent users of thiazides and SSRIs in the elderly (aged 70 years and over) in the Netherlands.

In **chapter 3.5**, we did not observe an association between use of SSRIs and bone mineral density (BMD), or decline in BMD. Based on a proposed biological mechanism [70, 71], previous cross-sectional studies and (inconsistent) longitudinal studies [72-80], we would have expected an association between SSRIs and BMD or change in BMD. SSRIs are thought to play a role in bone metabolism by modulation of serotonin levels, and peripheral serotonin is hypothesized to decrease osteoblast proliferation [70]. However, centrally acting and peripheral serotonin work in opposing manners, and although most animal and cell studies reported a negative effect on BMD, they were not consistent [71, 81-84]. Previous cross-sectional studies were mostly limited by their measurement of BMD at one point in time and exposure assessment based on interview data [72-77]. In longitudinal studies, only interview data was available and duration of SSRI treatment was not always taken into account [78-80]. Bone remodeling is a slow process [85] and potent bone remodeling drugs such as denosumab take one to six months to enhance BMD [86, 87]. Therefore, it is questionable whether these cross-sectional studies demonstrated a real drug effect or represented residual confounding – most likely – by depression. Although observational studies are always subjected to possible bias and residual confounding, we took duration of use into account and were able to adjust for presence of depressive symptoms. Thus, based on our results, the inconsistent longitudinal studies and undefined proposed mechanism, we think that SSRIs are not negatively associated with BMD or that such an effect is minimal.

Methodological considerations

Exposure assessment

Important considerations should be taken into account when determining drug exposure. We used three methods to assess exposure: prescriptions from general practitioner (GP) medical records, pharmacy dispensing data and interview data. In observational research, pharmacy records are often considered as the best indicator for real drug use, since extensive information is available on a day-to-day basis, including duration and daily or cumulative dose of the dispensings. Moreover, recall bias is not an issue with prospectively gathered

drug exposure, and dispensings represent 'actual intake' better than prescriptions from GP or specialists because patients may decide not to fill their prescriptions at a pharmacy. Especially in longitudinal study designs – with interest in a potential role of cumulative exposure of interest – dispensing data are more informative and reliable when patients keep coming back for their medicines.

Besides the studies described in **chapters 2.2, 2.3 and 3.4**, we used dispensing data to assess our exposure of interest. Analyses in **chapter 2.2 and 3.4** were performed within the IPCI database, with prescription data from GP medical records. We used the IPCI database because of the large number of antidepressant users, representativeness of the total Dutch population, and the large number of hyponatremic events. **Chapter 2.3** was based on interview data since our outcome of interest (indication for use) was based on the same interview. All other exposures of interest were determined based on dispensings or episodes of antidepressant use. Dispensing data from Dutch pharmacy records include variables such as date of dispensing, total number of tablets dispensed, total number of defined daily doses and the dosage regimen. With this information the duration of an individual dispensing can be defined and based on these individual dispensings a drug treatment episode can be composed. In clinical practice, consecutive dispensings are never collected exactly after each other. Patients collect their dispensing before or after the end of the previous dispensing, leading to overlap or a gap between dispensings. Overlapping dispensings were not accounted for as we assumed that gaps compensate for the overlap between dispensings in people who use drugs long term or chronically. However, this is only an assumption and might not always account for all cases. If we would take the overlap into account the total duration of an episode of use would increase [88]. However, differences in treatment length between the two methods are smaller when a larger gap is allowed between the consecutive dispensings (i.e. at least 90 days) [88]. In **chapter 2.1 and 2.4**, we choose 90 days as the maximally allowed gap length between dispensings. We choose 90 days as a cut-off as we tried to focus on episodes of depression. Short gaps might not represent initiation of new treatment, but might characterize problems during the current treatment episode [88]. In other chapters – where we focused on ADRs related to the use of antidepressants – we considered 7 or 30 days as maximum allowable gap length between the dispensings. In this case, we were not primarily interested in depressive episodes, but in actual current drug exposure at time of the event. Allowance of a bigger gap between dispensings would introduce a higher chance of misclassification of exposure at time of the event. Nevertheless, misclassification would be similar for all antidepressant users and would probably be non-differential [at random] for cases and controls. There is no golden standard in assessment of drug exposure and the definitions of treatment episodes in pharmacoepidemiological research. At start of a study, these important considerations (e.g. type of treatment and exposure of interest) should be taken into account when determining exposure based on pharmacy records.

Classification of antidepressant use

As discussed before, antidepressants should not be prescribed without sound reason. ADRs are common with antidepressant use, especially in a population such as the elderly [37]. Studies in a real-life setting are needed to investigate the safety of antidepressants in a specific population such as the elderly. However, when studying ADRs, some considerations should be taken into account.

Antidepressants are a very heterogeneous drug class. They not only have different applications in clinical practice [10], but also have different mechanisms of action. They are subdivided by the World Health Organization based on their main mechanism of action: TCAs, SSRIs, monoamine oxidase inhibitors (MAO's, A or non-selective), and other antidepressants [89]. However, as the World Health Organization Collaborating Centre for Drug Statistics Methodology already points out: 'The various antidepressants have different modes of action, and the classification will not reflect the exact mode of action of the various antidepressants' [90]. This makes it difficult to study unintended effects for the different groups. Most ADRs are related to the pharmacological effect of the drug (type A), thus related to the mechanism of action. These ADRs are dependent on their binding properties for transporters and receptors, are predictable and dose dependent [91, 92]. Since the current classification of antidepressants does not reflect the exact mode of action, the question remains how we should then classify antidepressants in drug safety research.

First, ideally, we would like to study each antidepressant as an individual agent (as done in clinical trials). However, because of relatively low numbers of users of most individual drugs and the rare occurrence of some ADRs, this is often not feasible in observational studies. Second, an alternative categorization has been proposed by Derijks *et al.* [93]. They already pointed out discrepancies in the traditional categorization and proposed a new categorization based on the pharmacological binding properties of the antidepressants. Clomipramine, venlafaxine, nortriptyline and maprotiline would be re-classified into another cluster. Clomipramine and venlafaxine have a high affinity for the serotonin transporter, while they are originally classified as TCA or other antidepressant (i.e. serotonin noradrenalin reuptake inhibitor), respectively. Nortriptyline and maprotiline actually have a less heterogeneous binding profile than the other TCAs and have a specific affinity for the NE transporter, serotonin_{2c} and histamine₁ receptor [93]. Derijks *et al.* already reported that their new classification would better predict type A ADRs in clinical practice [94], but of course, only further studies can confirm or refute that. Third, the exposure of interest can be categorized based on the proposed mechanism of action of a specific ADR. For example, an increased risk of abnormal bleedings has been established for serotonin specific antidepressants (mostly SSRIs) [95-97]. SSRIs block the uptake of serotonin into the platelets and thereby impair platelet aggregation [41, 42, 96, 98]. This physiological mechanism has been studied extensively. Therefore, in **chapter 3.1 and 3.2**, where we

studied the association between antidepressants and presence and occurrence of cerebral microbleeds, antidepressants – the exposure of interest – were categorized based on their affinity for the serotonin transporter.

However, in all other chapters regarding drug safety, we used the traditional categorization of antidepressants from daily practice. We used these definitions in **chapters 3.3 to 3.5** for multiple reasons. First, the underlying mechanisms for the unintended effects mentioned in these chapters were still inconclusive [62, 65, 70, 71]. Second, already existing clinical guidelines are specific for these groups, such as the national HARM-wrestling guidelines on sodium assessment after concurrent use of SSRIs and thiazides in the elderly [69]. Third, our research questions were only relevant for a specific class of antidepressants. For example, SSRIs were only studied in relation to sleep quality as TCAs are often prescribed as sleep medication – because of their sedating effect – in clinical practice [10, 51]. Thus, we mostly used the classical categorization for multiple reasons. Still, it is important to emphasize the possible differences between the mechanisms of action within an antidepressant drug class. These considerations can help in decision-making to prescribe and switch from a specific antidepressant in daily practice.

Bias and confounding

In all observational studies, bias and confounding may influence the study findings. The most common biases in epidemiological research are selection bias and information bias. Selection bias was minimal in our studies as all data (Rotterdam Study and IPCI database) are population-based [99-101]. However, in a prospective cohort study such as the Rotterdam Study a healthy volunteer bias may be considered as a sort of selection bias [102]. IPCI covers a complete population of community-dwelling people because in the Netherlands, every inhabitant is designated to a single general practitioner and also hospital in- and outpatient care is routed via the GP. Information bias is also unlikely as data were gathered prospectively without prior knowledge of the research questions. Antidepressant exposure was based on pharmacy or prescriptions records which could lead to some misclassification of exposure if patients do not swallow their pills. However, we assume bias is non-differential as misclassification will not be different for diseased and controls. Misclassification of outcome might have been present in our study on hyponatremia. Cases of hyponatremia were defined based on medical records, with a serum sodium level below 130 mmol/l, and/or with a hospital admission with diagnosis of hyponatremia. However, detection of hyponatremia might have been different for antidepressant users and non-users. GPs might monitor patients on SSRIs for low serum sodium levels, while hyponatremia can often occur unrecognized in other patients. We tried to minimize bias by performing a sensitivity analyses in IPCI which included only hyponatremia cases defined at hospital admission, and not by (GP) laboratory measurements.

However, in the chapters in this thesis, confounding by indication was our main issue. Confounding by indication occurs when an indication is an independent risk factor for the event among non-exposed persons, but is also associated with the exposure of interest [103]. Studies with use of antidepressants as exposure of interest almost always have to deal with confounding by indication, i.e. depression. Depression itself is associated with many of our outcomes of interest, i.e. cerebral microbleeds, sleep quality and BMD [43, 104-106]. It has been hypothesized that depression contributes to the progression of microbleeds [43]. Also, depression and sleep quality are highly correlated. Insomnia is a risk factor for depression, while depression is a risk factor for poor sleep [104, 105, 107]. Finally, depression has also been associated with a low BMD. A direct physiological effect has been proposed by which depression lowers BMD, next to a less active physical pattern and immobility [106]. For hyponatremia, depression is not considered a risk factor. However, other indications for antidepressant use could be risk factors for hyponatremia. For example, neuropathic pain – most commonly present in diabetes mellitus patients – is an off-label indication for use of antidepressants while diabetes mellitus itself is a risk factor for hyponatremia [108, 109]. To summarize, confounding by indication can influence our results in all chapters on drug safety. We tried to minimize confounding by indication in several ways: 1) All analyses within the Rotterdam Study were adjusted for presence of depressive symptoms. 2) We took different groups of antidepressants as exposure of interest. For example, we observed an association between all antidepressants (low to high affinity for serotonin transporter) and occurrence of cerebral microbleeds. This might suggest that not the affinity for serotonin, but another variable or mechanism might explain the results, i.e. the underlying depression. 3) We selected past users as reference population instead of non-users. If the indication for treatment and accompanying specific patient characteristics will be associated with the outcome of interest, also past users might have an elevated risk. However, as depression is a transient recurrent disorder, this is a time-dependent confounding factor. Probably other characteristics of patients with a history of depression can also contribute to an elevated risk (e.g. a high number of comorbidities, polypharmacy). In **chapter 3.4**, we observed an association between past TCA users and hyponatremia. This might indicate that not the TCA, but the indication – in this case maybe neuropathic pain in specific patient populations – might explain the elevated risk of hyponatremia.

Clinical Implications and directions for future research

Our results provide additional insights into utilization and safety of antidepressants in the middle-aged and elderly population in clinical practice. Results from daily practice are very useful as antidepressants are not always prescribed according to the guidelines, and ADRs in the elderly are difficult to predict on the basis of clinical trials alone.

Guidelines of the Dutch General Practitioners Association (NHG) justify antidepressant use for major depressive disorder, anxiety disorder and as second option in the treatment of dysthymia [25, 110]. However, our results suggest that antidepressants are prescribed for a wider range of (off-label) indications. Antidepressant use for neuropathic pain, mild depressive symptoms, sleeping disorders and stress are off-label, and solid unbiased evidence of efficacy for these indications from randomized-controlled clinical trials is inconsistent or missing [30-32, 111, 112]. Thus, unjustified antidepressant prescribing seems common in the middle-aged and elderly population in daily practice. In contrast, a study by Piek *et al.* reported that most antidepressant use in primary care was justified in the Netherlands [113]. Only 5% had no current justification for antidepressant use. However, they studied antidepressant use in a population who screened positive for affective disorders. Prescriptions for other indications – than depression and anxiety – might still be unjustified. As randomized-controlled trials for registration of off-label indications are sparse, evidence from observational research and clinical practice should also be taken into account – to assess the risks and benefits for other indications – when prescribing an antidepressant to an individual patient [112].

Surprisingly, only 5% overtreatment was observed by Piek *et al.* and for a large part this was because of unjustified continuation of treatment. Users only had a justified reason for antidepressant treatment earlier in time [113]. Relatively, more chronic or long-term antidepressant users may explain the longer duration of treatment. However, problems with initiation and early discontinuation of treatment are also still a problem in daily practice [27, 28, 114]. For example, single dispensings were common in our population. People who discontinue antidepressant use after one dispensing probably changed their mind regarding the need for treatment or experienced ADRs. In the case of ADRs, treatment should be switched to another antidepressant. Moreover, after initiation of treatment, Dutch guidelines recommend that effectiveness is determined after 4 to 6 weeks of treatment. After good response (i.e. decrease in depressive symptoms), antidepressant use should continue for at least another 6 months of treatment. Multiple years or chronic use of antidepressants are only justified in patients with chronic or recurrent major depressive disorder [25]. In the continuation phase of treatment there is room for improvement. Our median duration of treatment was 137 days, and although persistence was better for psychiatric indications and in SSRI users, other indications for antidepressants are also often chronic and require long-term treatment. We would suggest that more extensive information provided by the GP, better monitoring and check-ups can help to continue maintenance treatment [115-117]. Unfortunately, we can only provide some recommendations and we cannot draw any firm conclusions based on our results. We would need more information regarding considerations made by the patient and GP, and more information on patient-doctor communication.

Furthermore, we would like to make a recommendation for clinical practice. Based on our results from **chapter 3.4**, we would suggest that – in the elderly population – sodium measurements could be of value in the first 30 days of treatment and for new SSRI users. Although we only defined an increased relative risk for incident and short term SSRI users, high rates of SSRI-induced hyponatremia (between 0.06% and 40%) and conclusive previous literature would argue for an extension of the guidelines. For example, in line with the HARM-wrestling criteria for sodium measurements in concurrent users of thiazides and SSRIs in the elderly (aged 70 years and over) [69].

Directions for future research

We already addressed issues with the initiation and continuation phase of antidepressant use in daily practice. However, since duration of treatment seems to increase over the years [1, 3], inappropriate long-term use should also be studied in more detail. Discontinuation of treatment should be done with caution (i.e. a gradual decrease in dose) and the patient should be properly informed. Acute or even tapered discontinuation of treatment can cause mild or severe withdrawal symptoms, which can be perceived as a recurrent depressive episode [118-120]. Moreover, patients can be afraid to stop treatment because of the fear for relapse. Nevertheless, according to the guidelines chronic use is only justified in a small group of patients at high risk of chronic or recurrent depressive episodes [24, 25, 121], while also other patients seem to continue antidepressant use in clinical practice [122]. Besides, important disadvantages of long-term use are the costs, and the risk of ADRs and drug-drug interactions. Especially in an ageing population, a high number of concomitantly used drugs is undesirable, particularly if the daily intake includes one or more psychotropic drugs. Also, effectiveness of antidepressant use in the elderly population in daily practice should be further established. Antidepressants are not only prescribed for traditional major depressive and anxiety disorders. Evidence for effective treatment of antidepressants for these indications or for this specific population of elderly is not firmly established. More evidence from clinical practice might help to further improve evidence-based prescription of antidepressants in the Dutch elderly population.

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5

Appendices

Summary

Recently, it was estimated that almost 1 million persons in the Netherlands were prescribed an antidepressant in 2013. This is approximately 5.8% of the total Dutch population. Antidepressant use increased excessively since the introduction of selective serotonin reuptake inhibitors (SSRIs) on the market in the late 80's. Multiple explanations for this steep increase have been proposed such as better detection and treatment of depression, widening of the indications for prescription, milder adverse drug profile for SSRIs and a longer duration of treatment. Nevertheless, concerns have been raised regarding these high levels of antidepressant use in the general population. Efficacy of antidepressants has not been established for all indications and antidepressants go together with multiple adverse drug reactions (ADRs). Especially in specific populations – such as the elderly – evidence of efficacy and risk for ADRs from randomized controlled clinical trials is limited and elderly are at increased risk of ADRs and drug-drug interactions. Therefore, within this thesis, the aim was to characterize antidepressant use in the last two decades in the elderly Dutch population. Moreover, we investigated unintended effects related to antidepressant use in the elderly in daily practice.

Utilization of antidepressants

Chapter 2 consists of four subchapters which all study different characteristics of antidepressant use in the general older Dutch population in clinical practice. In **chapter 2.1**, we reported that the prevalence of antidepressant use increased over a 20-year period within the Rotterdam Study. The steepest increase was observed for SSRIs, and we also observed a shift to SSRIs and other antidepressants as first choice of treatment when compared to tricyclic antidepressants (TCAs). In contrast, the incidence of antidepressant use decreased over the years. These opposing patterns were possibly explained by a longer duration of treatment (i.e. smaller risk at discontinuation and more adequate treatment). Results in **chapter 2.2** from a Dutch general practitioners health care database (Integrated Primary Care Information project) confirm these results. Prevalent antidepressant use, especially SSRIs, showed a steep increase in the last 15 years. However, specifically the incidence of SSRIs decreased from 2000 onwards. Levels of antidepressant use were even higher in the elderly population when compared to the younger population. Still, an increase in prevalence was similar over the different age categories. In addition, trends of indications for treatment were determined based on International Classification of Primary Care (ICPC) diagnostic codes. A shift from traditional indications (i.e. depression and anxiety) to other indications such as neuropathic pain and sleeping disorders was observed over the years in incident antidepressant users.

Chapter 2.3 further focused on indications for antidepressant use between 1997 and 2008. Indications for treatment were determined based on self-report and took all possible symptoms and disorders into account. Depression was still the main indication for antidepressant treatment. Anxiety, sleep problems and stress were often mentioned as reasons for use of SSRIs or other antidepressants, while pain was a common indication in TCA users. Moreover, all indications were associated with a significantly higher level of clinically-relevant depressive symptoms. Our results suggest that antidepressants are used for off-label indications, subthreshold disorders and complex situations – with a high comorbidity of physical problems and psychological distress – in the middle-aged and elderly Dutch population. To conclude, **chapter 2.4** focused on adherence and persistence to antidepressant treatment in a daily practice setting. Numbers of early dropout or single filling of a dispensing was with 23% – especially in non-psychiatric indications – high in our study. Moreover, with a median of 137 days of treatment, persistence of treatment was according to the treatment guidelines (i.e. multiple months of treatment continuation after remission) not optimal. Especially for non-psychiatric indications during the initiation and continuation phase of antidepressant drug treatment the persistence can be improved considerably. Nevertheless, adherence to antidepressant treatment was good in our older Dutch population.

Unintended effects of antidepressants

In **chapter 3**, unintended effects of antidepressants were studied in an elderly Dutch population. **Chapter 3.1** and **3.2** both focused on the association between antidepressants and the presence or occurrence of cerebral microbleeds. We only observed an association between use of antidepressants and the occurrence of cerebral microbleeds in **chapter 3.2**. With this longitudinal design we could better study the temporal association between exposure to antidepressants and cerebral microbleeds. We observed that all antidepressants were associated with an increased risk of incident microbleeds and this suggests that the association may not be due to the hypothesized mechanism which depends on the affinity for the serotonin transporter. Reverse causality or residual confounding by incident depression could explain our results. In **Chapter 3.3**, we studied the association between use of SSRIs and subjective sleep measurements. SSRI use was associated with a better sleep when compared to non-use after careful adjustment for depressive symptoms and concurrent benzodiazepine use. SSRIs seemed to have sedative properties as they were associated with a 0.72 hour longer sleep duration, higher sleep quality, higher sleep efficiency and more daytime dysfunction. Results were consistent in cross-sectional and longitudinal analyses, although the association was more prominent in continuous SSRI users. Apparently, these results suggest that in daily practice the sleep quality of some persons may benefit from, continued, SSRI use. In **chapter 3.4** we studied a well-known but

not yet completely investigated ADR, namely antidepressant-induced hyponatremia. We only observed an association for new users of SSRIs and during the first 30 days of SSRI use with an increased risk of hyponatremia. This might confirm that SSRI-induced hyponatremia is an ADR that is transient over time. Based on the proposed mechanism – the syndrome of inappropriate antidiuretic hormone secretion (SIADH) – we would also expect an increased risk of hyponatremia in users of certain serotonin specific TCAs and other antidepressants. However in our study, neither use of TCAs, nor use of other antidepressants as a class was associated with an increased risk of hyponatremia. Thus, with our results we could only confirm and complement previous evidence on SSRI-induced hyponatremia. **Chapter 3.5** focused on the association between use of SSRIs and bone mineral density or change in bone mineral density. Strengths of our study were the longitudinal design and the fact that we were able to take duration of treatment into account. Herewith, we could add important knowledge to the available literature. We observed no association between use of SSRIs and, change in, bone mineral density. Thus – based on our results – we would suggest that SSRIs are not negatively associated with BMD or that such an effect is minimal.

Conclusions

To summarize, within this thesis, we aimed to study characteristics and unintended effects of antidepressant use in clinical practice in an ageing population. The main findings from the studies in this thesis are further discussed and put in a broader perspective in **chapter 4**. Our results suggest that antidepressants are prescribed for a wide range of (off-label) indications and there is room for improvement in the initiation and maintenance phase of treatment in our middle-aged and elderly population in daily practice. Therefore, possible inappropriate antidepressant use in the elderly population in daily practice should be targeted in future research. Especially in a specific population such as the elderly in which a high level of concomitantly used psychotropic drugs is undesirable. More evidence from clinical practice might help to further improve evidence-based prescription of antidepressants in the Dutch elderly population.

Samenvatting

Bijna één miljoen mensen gebruikten in 2013 een antidepressivum. Dat is 5,8% van de Nederlandse bevolking. Het gebruik van antidepressiva is eind jaren '80 sterk gestegen na de introductie van selectieve serotonineheropnameremmers (SSRIs). Tot nu toe zijn er veel verschillende verklaringen geopperd voor deze excessieve toename in het gebruik van SSRIs, zoals een betere detectie en behandeling van depressie, uitbreiding van de indicaties en een milder bijwerkingenprofiel. Niettemin is er veel bezorgdheid over dit hoge percentage van antidepressivagebruikers. Het gebruik gaat vaak gepaard met bijwerkingen en de effectiviteit is niet bewezen voor alle indicaties waar antidepressiva in de dagelijkse praktijk voor worden voorgeschreven. Vooral in een specifieke populatie zoals ouderen, is er bij geneesmiddelengebruik een hoger risico op bijwerkingen en geneesmiddeleninteracties. Bovendien is deze oudere populatie vaak ondervertegenwoordigd in klinische studies waardoor bewijs over effectiviteit en bijwerkingen niet overvloedig is. In dit proefschrift werd het gebruik van antidepressiva in de afgelopen 20 jaar gekarakteriseerd in een populatie van Nederlandse ouderen. Daarnaast werden de mogelijke bijwerkingen bij ouderen bestudeerd in de dagelijkse praktijk.

Gebruik van antidepressiva

Hoofdstuk 2 bestaat uit vier verschillende subhoofdstukken waarin verschillende aspecten van gebruik van antidepressiva door ouderen in de dagelijkse praktijk worden beschreven. In **hoofdstuk 2.1** zagen we dat de prevalentie van het gebruik van antidepressiva toeneemt in een periode van 20 jaar binnen het Erasmus Rotterdam Gezondheid Onderzoek (Rotterdam Studie). De sterkste toename zagen we in het gebruik van SSRIs en tevens zagen we dat de eerste keuze voor een geneesmiddel verschoof van tricyclische antidepressiva (TCA) naar SSRI. In tegenstelling daarmee vonden we dat de incidentie van het gebruik van antidepressiva daalde naarmate de tijd vorderde. Dit contrast zou mogelijk verklaard kunnen worden door een langere gebruiksperiode; mensen stoppen minder snel met het antidepressivum en het gebruik is adequater. De resultaten in **hoofdstuk 2.2** van een huisartsen-database (Integrated Primary Care Information project) bevestigen de voorgaande uitkomsten. Prevalent antidepressivagebruik – voornamelijk SSRIs – steeg enorm over de afgelopen 15 jaar, maar juist de incidentie van SSRI-gebruik daalde na 2000. Het aantal antidepressivagebruikers was hoger in de groep ouderen vergeleken met de jongeren, maar de toename in prevalentie was voor beide populaties gelijk. Bovendien onderzochten we de indicaties voor het gebruik van antidepressiva op basis van diagnostische codes. Incidente gebruikers kregen hun antidepressivum steeds vaker voorgeschreven voor andere indicaties dan depressie, zoals neuropatische pijn en slaapproblemen, met name bij gebruik van TCAs. **Hoofdstuk 2.3** richtte zich verder op indicaties voor antidepressivagebruik in de periode

van 1997 tot 2008. De indicaties voor het gebruik van antidepressiva waren gebaseerd op zelfrapportage en bevatten alle mogelijke symptomen en stoornissen. Depressie was de belangrijkste indicatie voor antidepressivagebruik. Gebruikers van SSRIs en overige (nieuwe) antidepressiva noemden angst, slaapproblemen en stress vaak als reden voor gebruik, terwijl TCA-gebruikers vaak pijn rapporteerden. Alle indicaties waren geassocieerd met een significant frequentere aanwezigheid van klinisch-relevante depressieve symptomen vergeleken met niet-gebruikers. De resultaten suggereren dat antidepressiva worden voorgeschreven voor *off-label* indicaties, losse kernsymptomen die niet voldoen aan de DSM-criteria voor depressie, complexe situaties – met een hoge comorbiditeit van fysieke en psychologische problemen – in onze populatie van middelbare en hogere leeftijd. In het laatste subhoofdstuk, **hoofdstuk 2.4**, werden de therapietrouw en persistentie van antidepressivagebruik in de dagelijkse praktijk bestudeerd. Het percentage mensen dat meteen stopt of nooit begon, en dus maar een enkel recept ophaalde, was met 23% erg hoog. Dit waren voornamelijk gebruikers van antidepressiva zonder een psychiatrische indicatie. De persistentie van antidepressivagebruik was met een mediaan van 137 dagen gebruik niet optimaal volgens de richtlijnen, die adviseren om de behandeling bij een goede respons bij voorkeur 6 maanden voort te zetten. Vooral voor niet-psychiatrische indicaties kunnen de initiatie en persistentie van antidepressivagebruik verbeterd worden. Daarmee vergeleken was de therapietrouw, met 90%, erg goed in onze oudere populatie.

Bijwerkingen van antidepressiva

In **hoofdstuk 3** worden meerdere bijwerkingen besproken van antidepressiva bij gebruik in een oudere populatie. In **hoofdstukken 3.1** en **3.2** zijn de resultaten van de associatie tussen antidepressivagebruik en de aanwezigheid of het ontstaan van cerebrale microbloedingen vastgelegd. Alleen in **hoofdstuk 3.2** toonden we een associatie aan tussen antidepressivagebruik en het ontstaan van cerebrale microbloedingen. Vergeleken met de cross-sectionele opzet van **hoofdstuk 3.1** was de longitudinale opzet van deze studie beter geschikt om de tijdsrelatie tussen het gebruik van antidepressiva en cerebrale microbloedingen te bepalen. De resultaten toonden aan dat alle antidepressiva het risico op cerebrale microbloedingen verhoogden. Dit zou betekenen dat het mechanisme dat ten grondslag ligt aan het verhoogde risico waarschijnlijk niet samenhangt met de affiniteit voor de serotonine-transporter maar er sprake lijkt te zijn van een onbekend mechanisme, tenzij omgekeerde causaliteit of versturende factoren de resultaten verklaren. In **hoofdstuk 3.3** hebben we gekeken naar de associatie tussen het gebruik van SSRIs en slaapkwaliteit. Het gebruik van SSRIs was geassocieerd met een betere slaapkwaliteit, nadat factoren als depressieve symptomen en gelijktijdig benzodiazepine gebruik meegenomen werden in de analyses. Het lijkt erop dat SSRIs een sederende werking hadden: ze waren geassocieerd met een langere slaaptijd, een hogere slaapkwaliteit, hogere slaapefficiëntie en meer verstoring

van het ritme overdag. De resultaten waren in de cross-sectionele en longitudinale analyses consistent en de effecten waren vooral aanwezig in de groep continue SSRI-gebruikers. De resultaten tonen aan dat in de dagelijkse praktijk sommige mensen profijt kunnen hebben van continu SSRI-gebruik voor een betere slaapkwaliteit. In **hoofdstuk 3.4** hebben we een bekende bijwerking van antidepressiva bestudeerd, namelijk hyponatriemie tijdens gebruik van SSRIs. Wij zagen alleen een associatie tussen het gebruik van antidepressiva en hyponatriemie voor nieuwe SSRI-gebruikers en tijdens de eerste 30 dagen van SSRI-gebruik. Dit suggereert dat hyponatriemie geassocieerd met SSRI-gebruik een bijwerking is die van voorbijgaande aard is. Gebaseerd op het voorgestelde mechanisme – syndroom van inadequate secretie van antidiuretisch hormoon – zouden we ook een verhoogd risico op hyponatriemie verwachten voor bepaalde TCAs en overige antidepressiva die ook serotonine-specifiek zijn. Dit kwam in onze studie niet naar voren; met onze studieresultaten hebben we aldus voorgaande studies over door SSRI-veroorzaakte hyponatriemie bevestigd en aangevuld. **Hoofdstuk 3.5** beschrijft een onderzoek naar het gebruik van SSRIs en de associatie met botdichtheid en een verandering in botdichtheid. In cross-sectionele studies zijn SSRIs consequent geassocieerd met een lagere botdichtheid, terwijl longitudinale studies inconsistente resultaten laten zien. De belangrijkste toegevoegde waarden van onze studie ten opzichte van eerdere publicaties waren de longitudinale studie-opzet en het feit dat we daarbij gegevens hadden over de duur van antidepressivagebruik. We vonden geen enkele associatie tussen SSRI-gebruik en botdichtheid of een afname in botdichtheid. Gebaseerd op onze resultaten kunnen we concluderen dat SSRIs niet negatief geassocieerd zijn met botdichtheid, al kunnen we niet uitsluiten dat er sprake is van een zeer gering effect.

Samenvattend: in dit proefschrift hebben we geprobeerd om karakteristieken en bijwerkingen van antidepressivagebruik in de dagelijkse praktijk in een oudere populatie te bestuderen. De belangrijkste bevindingen van de studies in het proefschrift worden verder besproken in **hoofdstuk 4**. Onze resultaten tonen aan dat antidepressiva worden gebruikt voor uiteenlopende indicaties die geregistreerd, beschreven in behandelrichtlijnen of mogelijk *off-label* zijn. Bovendien is er ruimte voor verbetering bij de initiatie en onderhoudsbehandeling met antidepressiva in onze populatie van middelbare en hogere leeftijd. Meer resultaten van onderzoek uit de dagelijkse praktijk zou het *evidence-based* voorschrijven van antidepressiva in de Nederlandse oudere populatie verder kunnen verbeteren en mogelijk ongewenst gebruik van psychotrope geneesmiddelen kunnen verminderen.

List of publications

Manuscripts based on this thesis

- 2.1 **Aarts N**, Noordam R, Hofman A, Tiemeier H, Stricker BH, Visser LE. Utilization patterns of antidepressants between 1991 and 2011 in a population-based cohort of middle-aged and elderly. *Eur Psychiatry*. 2014 Aug;29(6):365-70.
- 2.2 Noordam R, **Aarts N**, Verhamme KM, Sturkenboom MC, Stricker BH, Visser LE. Prescription and indication trends of antidepressant drugs in the Netherlands between 1996 and 2012: a dynamic population-based study. *Eur J Clin Pharmacol*. 2015 Mar 15; 71(3):369-75.
- 2.3 **Aarts N**, Noordam R, Hofman A, Tiemeier H, Stricker BH, Visser LE. Self-reported indications for antidepressant drug use in a population-based cohort of middle-aged and elderly. *Submitted*.
- 2.4 **Aarts N**, Noordam R, Hofman A, Tiemeier H, Stricker BH, Visser LE. Persistence of antidepressant drug treatment in a population-based study of older adults and elderly. *In preparation*.

- 3.1 **Aarts N***, Akoudad S*, Noordam R, Hofman A, Ikram MA, Stricker BH, Visser LE, Vernooij MW. Inhibition of serotonin reuptake by antidepressants and cerebral microbleeds in the general population. *Stroke*. 2014 Jul;45(7):1951-7.
- 3.2 Akoudad S*, **Aarts N***, Noordam R, Hofman A, Ikram MA, Tiemeier H, Stricker BH, Vernooij MW, Visser LE. Antidepressant use is associated with an increased risk of developing microbleeds. *Accepted for publication in Stroke*.
- 3.3 **Aarts N**, Zuurbier LA, Noordam R, Hofman A, Tiemeier H, Stricker BH, Visser LE. Use of selective serotonin reuptake inhibitors and sleep quality: a population-based study. *Submitted*.
- 3.4 **Aarts N**, van Blijderveen JC, Rodenburg EM, Noordam R, Sturkenboom MC, Stricker BH, Visser LE. Antidepressants and the risk of hyponatremia: a population-based study. *In preparation*.
- 3.5 Ham AC*, **Aarts N***, Noordam R, Rivadeneira F, Ziere G, Zillikens MC, Tiemeier H, van der Velde N, Hofman A, Uitterlinden AG, Stricker BH, Visser LE. Use of SSRIs and bone mineral density change: a population-based longitudinal study in middle-aged and elderly individuals. *Submitted*.

Other manuscripts

- Noordam R, **Aarts N**, Hofman A, van Schaik RH, Stricker BH, Visser LE. Association between genetic variation in the ABCB1 gene and switching, discontinuation, and dosage of antidepressant therapy: results from the Rotterdam Study. *J Clin Psychopharmacol*. 2013 Aug;33(4):546-50.

- Cheung K, **Aarts N**, Noordam R, van Blijderveen JC, Sturkenboom MC, Ruiters R, Visser LE, Stricker BH. Antidepressant use and the risk of suicide: a population-based cohort study. *J Affect Disord*. 2015 Mar;15(174):479-84.
- Noordam R, Direk N, Sitlani CM, **Aarts N**, Tiemeier H, Hofman A, Uitterlinden AG, Psaty BM, Stricker BH, Visser LE. Identifying genetic loci associated with antidepressant drug response with drug-gene interaction models in a population-based study. *J Psychiatr Res*. 2015 Mar;62:31-7.
- Maljuric NM*, Noordam R*, **Aarts N**, Niemeijer MN, van den Berg ME, Hofman A, Kors JA, Stricker BH, Visser LE. Use of selective serotonin reuptake inhibitors and the heart-rate corrected QT interval in a real-life setting: the population-based Rotterdam Study. *Br J Clin Pharmacol*. 2015 May 13.
- Noordam R, van den Berg ME, Niemeijer MN, **Aarts N**, Leening MJ, Deckers JW, Hofman A, Rijnbeek PR, Eijgelsheim M, Kors JA, Stricker BH, Visser LE. Assessing prolongation of the heart rate corrected QT interval in users of tricyclic antidepressants: advice to use Fridericia rather than Bazett's correction. *J Clin Psychopharmacol*. 2015 Jun;35(3):260-5.
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- Noordam R, **Aarts N**, Keyser CE, Hofman A, Stricker BH, Visser LE. Antidepressants with a high serotonin reuptake transporter affinity and serum lipid levels in a population-based study in older adults. *J Psychopharmacol*. 2015 Jul 6.
- Noordam R, **Aarts N**, Peeters RP, Hofman A, Stricker BH, Visser LE. Selective serotonin reuptake inhibitors decrease pancreatic insulin secretion in older adults and increase the risk of insulin dependency in type 2 diabetes patients. *Accepted for publication in Journal of Clinical Psychiatry*.
- Noordam R, **Aarts N**, Leening MJ, Tiemeier H, Franco OH, Hofman A, Stricker BH, Visser LE. Use of antidepressants and the risk of myocardial infarction in middle-aged and older adults: a matched case-control study. *Accepted for publication in European Journal of Clinical Pharmacology*.
- Noordam R*, van den Berg ME*, Niemeijer MN, **Aarts N**, Hofman A, Tiemeier H, Kors JA, Stricker BH, Eijgelsheim M, Visser LE, Rijnbeek PR. Antidepressants and heart-rate variability in a general middle-aged and elderly population: the Rotterdam Study. *Submitted*.
- Jovanonova O, **Aarts N**, Noordam R, Zillikens MC, Hofman A, Tiemeier H. Vitamin D serum levels are cross-sectionally but not prospectively associated with late-life depression. *Submitted*.
- Rodenburg EM, **Aarts N**, van Blijderveen JC, Visser LE, Hoorn EJ, Liamis G, Sturkenboom MC, Stricker BH. Benzodiazepine-induced hyponatremia and interaction with thiazide diuretics. A population-based study. *In preparation*.

PhD portfolio

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1. PhD training

Research skills

- 2011 Popular Regression Models, Netherlands Institute for Health Sciences (NIHES), Rotterdam, the Netherlands.
- 2011 Genetics for Dummies, Molecular Medicine, Rotterdam, the Netherlands.
- 2011 Short course in Scientific English, Erasmus Medical Center, Rotterdam, the Netherlands.
- 2012 Survival analysis, Netherlands Institute for Health Sciences (NIHES), Rotterdam, the Netherlands.

Specific courses

- 2012 Antidepressants, PAOFarmacie, Zeist, the Netherlands.
- 2013 Workshop Netherlands Adherence Research Platform, Utrecht, the Netherlands.
- 2014 Postdoc retreat, Postdoc Career Development Initiative, Utrecht, the Netherlands.
- 2014 Mindfulness, Ekayana psychology practice, Rotterdam, the Netherlands.

Presentations

- 2012 'Incident use, discontinuation and switching of antidepressant drugs in the Rotterdam study' (poster), 28th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE), Barcelona, Spain.
- 2012 'Association of different antidepressant drug therapies with sleep parameters' (oral), Dutch Medicines Days, Luntenen, the Netherlands
- 2013 'Association between patient, treatment and clinical characteristics with adherence and persistence of antidepressant drugs in an aging population'(poster), 29th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) 2012, Montreal, Canada.

- 2013 'Association between antidepressant use and sleep quality: a population-based study in elderly' (poster), 29th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE), Montreal, Canada.
- 2013 'Serotonergic antidepressants and presence of cerebral microbleeds in the general population: the Rotterdam Scan Study' (oral), Dutch Medicines Days, Ede, the Netherlands.
- 2013 'Utilization patterns of antidepressants between 1991 and 2012 in a population-based cohort of Dutch elderly' (poster), Dutch Medicines Days, Ede, the Netherlands.
- 2014 'Determinanten van therapietrouw tijdens behandeling met antidepressiva' (oral), symposium Praktijk Research In Samenwerking Met Apothekers, Amersfoort, the Netherlands.
- 2014 'Antidepressiva gebruik tussen 1991 en 2011 in een populatie van oudere volwassenen' (oral), symposium Praktijk Research In Samenwerking Met Apothekers, Amersfoort, the Netherlands.

(Inter)national conferences and symposia

- 2011 – 2015 Research seminars, Department of Epidemiology, Erasmus MC – University Medical Center Rotterdam, Rotterdam, the Netherlands.
- 2012 28th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) 2012, Barcelona, Spain.
- 2012 Dutch Medicines Days, Lunteren, the Netherlands.
- 2012 15th Annual Meeting European Society for Patient Adherence Compliance and Persistence, Gent, Belgium.
- 2013 Science Days Internal Medicine Department, Antwerp, Belgium
- 2013 Dutch Medicines Days, Ede, the Netherlands.
- 2014 Symposium Praktijk Research In Samenwerking Met Apothekers, Amersfoort, the Netherlands.

2. Teaching

Supervising practicals

- 2012 – 2015 Pharmacoepidemiology, Netherlands Institute for Health Sciences (NIHES), Rotterdam, the Netherlands.

Supervising Master of Science students

- 2012 – 2014 K. Cheung, 'Antidepressant use and the risk of suicide: a population-based cohort study', Department of Epidemiology, Erasmus MC – University Medical Center Rotterdam, Rotterdam, the Netherlands.
- 2013 – 2014 N.M. Maljuric, 'Use of selective serotonin reuptake inhibitors and prolongation of the heart-rate corrected QT interval in a real-life setting: results from the population-based Rotterdam Study', Department of Epidemiology, Erasmus MC – University Medical Center Rotterdam, Rotterdam, the Netherlands.

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Curriculum Vitae

Nikkie Aarts werd op 16 januari 1987 geboren te Amsterdam. Het VWO-diploma behaalde zij aan het Montessori Lyceum Amsterdam. In 2005 startte zij met de Bachelor Voeding en Gezondheid aan de Wageningen Universiteit. De Master Voeding en Gezondheid, met de specialisatie Epidemiologie en Public Health behaalde zij tevens aan de Wageningen Universiteit. Als onderdeel van deze Master heeft zij 6 maanden onderzoek gedaan naar de effecten van eiwit-suppletie bij patiënten met taaislijmziekte in Little Rock, Arkansas, Verenigde Staten.

In 2011 verhuisde ze naar Rotterdam om daar te beginnen aan haar promotietraject aan het Erasmus MC bij de afdelingen Inwendige Geneeskunde en Epidemiologie. Dit promotieonderzoek stond onder leiding van prof.dr. Bruno H.Ch. Stricker en dr. Loes E. Visser in het kader van het ZonMw programma 'Priority Medicines Elderly'. Het doel was om verschillende aspecten van antidepressivagebruik door ouderen in de dagelijkse praktijk te bestuderen. Nikkie richtte zich onder andere op karakteristieken van het gebruik en de bijwerkingen van antidepressiva, waarvan de resultaten zijn beschreven in dit proefschrift.

Op dit moment woont Nikkie weer in Amsterdam en werkt ze als onderzoeker op de afdeling Medische Ethiek en Filosofie van de Geneeskunde aan het Erasmus MC, waar zij ethische en maatschappelijke problemen in kaart brengt rondom de wereldwijde ambities van het bedrijf myTomorrows binnen het NWO-project: 'Nice to meet? Meeting unmet medical needs: a social innovation to facilitate early access to investigational drugs'.

