Adverse drug reactions of antipsychotics in frail older patients

Astrid van Strien

Adverse drug reactions of antipsychotics in frail older patients

Colofon

Dit proefschrift is mede mogelijk gemaakt door:
de Raad van bestuur van het Jeroen Bosch Ziekenhuis, 's-Hertogenbosch

Foto omslag: Marcel Fischer - Fischer Fotografie - Boxtel
Ontwerp & Lay-out: isontwerp.nl - Eindhoven
Drukwerk: Gildeprint - Enschede
ISBN: 978-94-92303-13-4
Lettertype: Hurme Geometric Sans

VRIJE UNIVERSITEIT

Adverse drug reactions of antipsychotics in frail older patients

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. V. Subramaniam,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op donderdag 14 september 2017 om 15.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door
Astrid Maria van Strien
geboren te Alphen aan den Rijn

promotor:	prof.dr. R.J. van Marum
copromotoren:	dr. C.J.P.W. Keijsers
	dr. H.J. Derijks

Voor mijn opa en oma

Table of contents

1.

General introduction and aim and outline of the thesis

General Introduction

1.

Epidemiology

In the Netherlands 17.7% of the total population is older than 65 years and an increase of the aging population is expected in the next few years.[1] A variety of psychiatric behavioural symptoms commonly occur in people of advanced age.[2] Delirium and dementia are the most common primary causes of psychotic symptoms in older patients. The prevalence of behavioural symptoms in patients with dementia rises above 80% in nursing homes.[2] Both delirium as behavioural problems in dementia can be reasons for physicians to prescribe antipsychotic drugs. In the Netherlands there are more than 300.000 antipsychotic users, of which more than 88.000 older than 65 years.[3] This all shows that antipsychotic drugs are widely used since their introduction in the 1950's to relieve psychotic symptoms.

Ever since the introduction of antipsychotics their use has been criticised, especially in patients with dementia. The first double-blind withdrawal study was carried out in 1966 by Barton, who found no deterioration after withdrawal in 85% of patients with dementia, leading to his conclusion that "our trial suggests that about 80 percent of elderly demented patients are receiving tranquillizers unnecessarily".[4] Literature reviews about the use of antipsychotics in dementia suggest that they are "modestly effective" in treating agitation and that no single neuroleptic is non-inferior.[5] The first meta-analysis that compared thioridazine or haloperidol with a placebo in agitated dementia patients showed that only 18 out of 100 dementia patients benefited from antpsychotic treatment.[5] In Dutch nursing homes antipsychotics are prescribed four times more often than to older people living independently.[6] It should be noted that the use of antipsychotic medication for patients with dementia decreased 8% in nursing homes between 2003 and 2011.[7] This decrease is probably due to initiatives to treat behavioural symptoms non pharmacological.[7] Despite this small decrease in prescription rates, there are still more than 300.000 users in the Netherlands.[7]

In Dutch nursing homes, physicians, nurses, and family caregivers generally

consider the possible benefits of antipsychotics to outweigh the risk of side effects.[8] The main reasons to start therapy are still agitation and aggression. The interviewed nursing home physicians and nurses expect almost half of their patients with dementia and behavioural disturbances to benefit from antipsychotic therapy. Serious side effects were expected to occur only sporadically.[8] To summarize, although the prescribing physicians consider these drugs as rather safe and effective, this can be questioned as shown above.

Pharmacokinetics of antipsychotics

A better understanding of causes of antipsychotic side effects can be considered from a pharmacokinetic and pharmacodynamic perspective. Most side effects seem to be a group effect and not limited to a single drug.

To start with the pharmacokinetics, haloperidol is worldwide the most prescribed antipsychotic and will be used as example of the group antipsychotics. Side effects of haloperidol are sedation, falls and extrapyramidal effects, which includes parkinsonism. It is unknown why some elderly develop antipsychotic induced parkinsonism (AIP) at a low dosage haloperidol and others do not. There are different hypothesis that could explain the age related sensitivity to antipsychotics: 1) an increased serum concentration for a given dose (peripheral pharmacokinetic hypothesis), 2) increased brain access and distribution for a given serum concentration (central pharmacokinetic hypothesis) or 3) decreased endogenous dopamine in elderly, a decreased number of dopamine-2 receptors in the brain or a different receptor occupancy (central pharmacodynamics).[9] To start with the first, a study in 150 elderly patients did not support the hypothesis of the peripheral pharmacokinetic explanation. In this study, 46% of the patients treated with haloperidol, in dose varying from 0.3-5.0 mg/day, developed AIP.[10] The study found a significant but moderate relationship between dose and serum concentration. The moderate association between dose and concentration may result from cytochroom P450 (CYP)-2D6 polymorphism, since this is the major enzyme that contributes to the biotransformation of haloperidol.[11] The second hypothesis is the central pharmacokinetic hypothesis. Within the central pharmacokinetic hypothesis, transport across the blood-brain barrier (BBB) is an important factor. The blood-brain barrier, a single layer of capillary endothelial cells joined together at tight junctions, regulates access of xenobiotics (including antipsychotics) to the central nervous system.[12] Loosening of these junctions would theoretically increase access of antipsychotics into the brain. The relationship between serum and cerebrospinal fluid (CSF) concentration of haloperidol has not earlier been assessed

in an elderly population and still many questions remain. Regarding the third hypothesis, there is a decrease in endogenous dopamine level and the absolute number of dopamine neurons and the density of dopamine D2 receptors have been shown to decrease with age.[9]
In summary, the pharmacokinetic of haloperidol is still largely unknown and this is probably one of the causes why it cannot be predicted why some patients develop side effects and some do not.

Pharmacodynamics of antipsychotics

Several side effects of antipsychotics occur more often in elderly patients and are more harmful and sometimes even lethal in elderly patients. Antipsychotics are prescribed and studied for decades; however, the last two decades evidence from post marketing research in large populations becomes available and shows more uncommon and rare side effects. This raises questions on their safety. This is why, in 2005 Health authorities, the Food and Drug Administration, have warned against use of atypical antipsychotics in elderly patients with dementia, because of an increased risk of mortality.[13] Of a total of seventeen placebo controlled trials with atypical antipsychotics in elderly demented patients with behavioural disorders, fifteen showed numerical increases in mortality in the drug-treated group compared to the placebo-treated patients.[13] These studies enrolled a total of 5,106 patients, and several analyses have demonstrated an approximately 1.6-1.7 fold increase in mortality in these studies. Examination of the specific causes of these deaths revealed that most were either due to heart related events (e.g., heart failure, sudden death) or infections (mostly pneumonia).[13] In contrast, a recent meta-analysis of randomised controlled trials did not show that conventional antipsychotics in general and haloperidol in particular increase the risk of mortality in elderly patients. This questions earlier observational findings and the warning based on these findings.[14]
Although increased mortality is still discussed, there are probably a lot of rare side effects that are not discovered yet. Antipsychotics do have a lot of well known side effects, of which the underlying mechanism is frequently known. Even so there are side effects with unknown mechanism. In addition to unknown pharmacokinetic as described above, still much more is unknown regarding the patients pharmacodynamic profile and side effects. Effects and side effects ofantipsychotics are related to dopaminergic (D-2), noradrenergic (α-1), histaminergic (H1) and cholinergic (muscarine) receptor blockade.[15] The antipsychotic effect and extrapyramidal side effects are caused by blockade of the dopamine-2-receptors. Blockade of the noradrenergic receptors (α-1) can

cause orthostatic hypotension and to a lesser extent hypotension and hypnosedation. Strong hypnosedation is due to histaminergic blockade. Anticholinergic side effects are e.g. dry mouth, constipation, urinary retention, sedation en confusion. Haloperidol is the strongest dopamine-2-blocker with little α-1, H1, muscarine or 5HT2 receptor antagonism.[15] To give an example, a well-known and well understood side effect is parkinsonism, which is a direct result of the pharmacodynamics namely blockade of the dopaminergic receptor. Nearly half of a group of elderly patients using haloperidol experienced parkinsonism.[10] These side effects result in an impaired quality of life.[16]
An example of a less understood adverse drug effect is the increased risk of infection. The use of antipsychotics is associated with infections like pneumonia.[17] Risk of bacterial infections were higher in nursing home residents newly initiated on conventional antipsychotics than in those initiating atypical antipsychotic medication and there seems to be a dose response relationship.[18] Although an increased risk of bacterial infection like pneumonia is shown, it is still very unclear why this happens, and whether this is also the case for e.g. urinary tract infections, another very common infection in the older population. There are no reasons to believe that a urinary tract infection differs from other infections in the pathophysiological mechanism, although still unrelieved. Next to that, other urinary tract problems such as incontinence and urine retention are reported with both typical and atypical antipsychotics. It has been hypothesized as being a form of extrapyramidal side effects, or due to anticholinergic side effects. As underlying mechanism, peripheral α1-adrenergic blockade may act synergistically to cause incontinence or retention.[19]

It was only until the last two decades that important side effects on the cardiovascular system were still unknown e.g. cerebrovascular accidents, venous trombo-embolism, myocardial infarction and cardiovascular mortality. In older patients a decreased risk of hospitalization was found for acute coronary syndrome.[20] In older users of antipsychotics, there seems to be an increased risk in cerebrovascular accidents.[21-24] Underlying mechanisms are still unknown. Potential mechanisms earlier proposed to explain the association between antipsychotics and cerebrovascular events include thromboembolic effects, altered platelet function, cardiovascular effects (eg. orthostatic hypotension, arrhythmias) and the atherosclerotic effects of deregulation of glucose and lipid metabolism.[22] Evidence of an association between the use of antipsychotics and the risk of venous thromboembolism (VTE) is contradictory.[25-28] Virchow's triad was first described in 1856 and composed of the following factors which

contributed to formation of venous thrombosis: an endothelial lesion, venous stasis and a hypercoagulable state.[29] To date it is unknown what the underlying mechanism is for increased (cerebro)vascular events in older users of antipsychotics and if the underlying mechanism is related to one of the factors Virchow found. In addition, there currently is no literature about the effect of haloperidol on thrombogenesis in older people.
To summarize, side effects can be a logical result of the pharmacodynamics of antipsychotic drugs or with an unknown pathophysiological mechanism. Although antipsychotic drugs are already prescribed for half a century, still new side effects are discovered.

Taken all above together, variation in effects and side effects between patients can be explained by pharmacokinetic and pharmacodynamic components. Better understanding of causes and consequences of side effects in antipsychotic users is needed to develop effective and safe treatment strategies tailored to the individual older patient.

How to recognize and measure side effects in antipsychotic users

It is important that physicians and patients are aware of possible side effects. Rating scales can be used for measurement and recognition of side effects. To date, there has been no clear review of rating scales, and their psychometric characteristics, used to assess the side effects of antipsychotics. Several rating scales have been developed to evaluate the side effects of antipsychotics. However, these scales mostly evaluate a single side effect, for example parkinsonism or sexual functioning, and are often used for drugs other than antipsychotics alone, such as the rating scales for drug-induced parkinsonism.[30] There have been few studies of scales evaluating multiple side effects, although the use of one scale instead of several separate scales can have advantages (e.g., less time consuming) and might provide a better insight into the overall side effect profile. While psychometric characteristics are of major importance in a research setting and usability is of secondary importance, ease of use is important in a clinical setting.

Aim and outline of the thesis

The objectives of this thesis are:

1. to extend our knowledge of the pharmacokinetics and pharmacodynamics of haloperidol, the most prescribed antipsychotic worldwide,
2. to investigate side effects of antipsychotics in clinical practice in older patients, where there is a gap in scientific evidence for this group,
3. to qualify available rating scales for side effects in antipsychotic users.

Aim 1. Pharmacokinetics and pharmacodynamics

In elderly there is a large, not well understood, inter-individual variation in effect and side effects (in particular antipsychotic induced parkinsonism) of haloperidol. We investigated two possible explanations. First, differences in drug metabolism resulting from polymorphism of cytochroom P450 CYP2D6. Second, if variability in transport over the blood-brain barrier is the explanatory factor for inter-individual variation in response of haloperidol in elderly patients **(chapter 2.1).** To reveal the underlying mechanism of (cerebro)vascular events in non-psychotic older patients, we investigated the effects of haloperidol on thrombogenesis factors (**chapter 2.2**).

Aim 2. Side effects in older patients

In **chapter 3** we focus on side effects of antipsychotic medication in frail older patients in clinical practice. Falls constitute a leading cause of injuries, hospitalisation and deaths among older patients. The association between the use of psychotropic medication and falls was studied in **chapter 3.1**. An increased risk of pneumonia was associated with the start of antipsychotic therapy. The question arose if there was an association between antipsychotic drug use and urinary tract infection, a major cause of morbidity and mortality in older people (**chapter 3.2** and **chapter 3.3**).

Aim 3. Recognition and measurement of side effects

In the last part the focus is on the recognition and measurement of side effects in antipsychotic users. As shown earlier, antipsychotics have many different side effects, which can result in an impaired quality of life and early treatment discontinuation. In **chapter 4** we show the results of a systematic review on the clinical use and psychometric characteristics of rating scales used to assess multiple side effects in patients treated with antipsychotics.

Finally, the results of the studies are summarized and put into a broader perspective.

References

1. www.cbs.nl. Available at: www.cbs.nl. Accessed January, 2017.
2. Zuidema SU, Derksen E, Verhey FR, et al. Prevalence of neuropsychiatric symptoms in a large sample of Dutch nursing home patients with dementia. Int J Geriatr Psychiatry 2007;22:632-8.
3. GIPdatabank Nederland. Available at: https://www.gipdatabank.nl/databank.asp?tabel=01-basis&geg=gebr&item=N05. Accessed January, 2017.
4. Barton R, Hurst L. Unnecessary use of tranquilizers in elderly patients. Br J Psychiatry 1966;112:989-90.
5. Schneider LS, Pollock VE, Lyness SA. A metaanalysis of controlled trials of neuroleptic treatment in dementia. J Am Geriatr Soc 1990;38:553-63.
6. Stichting Farmaceutische Kengetallen Nederland. Available at: https://www.sfk.nl/nieuws-publicaties/PW/2015/antipsychotica-vier-keer-vaker-in-verpleeghuizen. Accessed January, 2017.
7. Zuidema SU, Koopmans RTCM, Schols JMGA, et al. Trends in psychofarmaca gebruik bij patienten met dementie. Tijdschrift voor Ouderengeneeskunde 2015;april.
8. Cornege-Blokland E, Kleijer BC, Hertogh CM, et al. Reasons to prescribe antipsychotics for the behavioral symptoms of dementia: a survey in Dutch nursing homes among physicians, nurses, and family caregivers. J Am Med Dir Assoc 2012;13:80.e1,80.e6.
9. Uchida H, Mamo DC, Mulsant BH, et al. Increased antipsychotic sensitivity in elderly patients: evidence and mechanisms. J Clin Psychiatry 2009;70:397-405.
10. Knol W, van Marum RJ, Jansen PA, et al. Parkinsonism in elderly users of haloperidol: associated with dose, plasma concentration, and duration of use. J Clin Psychopharmacol 2012;32:688-93.
11. Brockmoller J, Kirchheiner J, Schmider J, et al. The impact of the CYP2D6 polymorphism on haloperidol pharmacokinetics and on the outcome of haloperidol treatment. Clin Pharmacol Ther 2002;72:438-52.
12. Bradbury MW. Hugh Davson--his contri bution to the physiology of the cerebrospinal fluid and blood-brain barrier. Cell Mol Neurobiol 2000;20:7-11.
13. FDA. Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances. Washington, DC, Department of Health and Human Services. 2005. Available at: http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm053171. Accessed January, 2017.
14. Hulshof TA, Zuidema SU, Ostelo RW, et al. The Mortality Risk of Conventional Antipsychotics in Elderly Patients: A Systematic Review and Meta-analysis of Randomized Placebo-Controlled Trials. J Am Med Dir Assoc 2015;16:817-24.
15. Moleman P. Praktische psychofarmacologie. Houten, the Netherlands: Bohn Stafleu Van Loghum 1998:210-296.
16. Schouten HJ, Knol W, Egberts TC, et al. Quality of life of elderly patients with antipsychotic-induced parkinsonism: a cross-sectional study. J Am Med Dir Assoc 2012;13:82.e1,82.e5.
17. Knol W, van Marum RJ, Jansen PA, et al. Antipsychotic drug use and risk of pneumonia in elderly people. J Am Geriatr Soc 2008;56:661-6.
18. Huybrechts KF, Schneeweiss S, Gerhard T, et al. Comparative safety of antipsychotic medications in nursing home residents. J Am Geriatr Soc 2012;60:420-9.

19. Saddichha S, Kumar M. Antipsychotic-induced urinary dysfunction: anticholinergic effect or otherwise?. BMJ Case Rep 2009;2009:10.1136/bcr.02.2009.1547.
20. Kleijer BC, Koek HL, van Marum RJ, et al. Risk of acute coronary syndrome in elderly users of antipsychotic drugs: a nested case-control study. Heart 2012;98(15):1166-71.
21. Hsieh PH, Hsiao FY, Gau SS, et al. Use of antipsychotics and risk of cerebrovascular events in schizophrenic patients: a nested case-control study. J Clin Psychopharmacol 2013;33:299-305.
22. Kleijer BC, van Marum RJ, Egberts AC, et al. Risk of cerebrovascular events in elderly users of antipsychotics. J Psychopharmacol 2009;23:909-14.
23. Mittal V, Kurup L, Williamson D, et al. Risk of cerebrovascular adverse events and death in elderly patients with dementia when treated with antipsychotic medications: a literature review of evidence. Am J Alzheimers Dis Other Demen 2011;26:10-28.
24. Percudani M, Barbui C, Fortino I, et al. Second-generation antipsychotics and risk of cerebrovascular accidents in the elderly. J Clin Psychopharmacol 2005;25:468-70.
25. Parker C, Coupland C, Hippisley-Cox J. Antipsychotic drugs and risk of venous thromboembolism: nested case-control study. BMJ 2010;341:c4245.
26. Liperoti R, Pedone C, Lapane KL, et al. Venous thromboembolism among elderly patients treated with atypical and conventional antipsychotic agents. Arch Intern Med 2005;165:2677-82.
27. Kleijer BC, Heerdink ER, van Marum RJ. Antipsychotics and venous thrombosis. Dutch experience differs. BMJ 2010;341:c5631.
28. Kleijer BC, Heerdink ER, Egberts TC, et al. Antipsychotic drug use and the risk of venous thromboembolism in elderly patients. J Clin Psychopharmacol 2010; 30:526-30.
29. Dutta TK, Venugopal V. Venous thromboembolism: the intricacies. J Postgrad Med 2009;55:55-64.
30. Knol W, Keijsers CJ, Jansen PA, et al. Systematic evaluation of rating scales for drug-induced parkinsonism and recommendations for future research. J Clin Psychopharmacol 2010;30:57-63.

2.

Pharmacokinetics and pharmacodynamics of haloperidol

2.1

Astrid M. van Strien, Annemieke Vermeulen Windsant – van den Tweel, Petra M. Leliveld – van den Heuvel, Manuela di Biase, Adriaan J. van den Brule, Rob J. van Marum

Published as Letter to the Editors
J Clin Psychopharmacol. 2014 Aug;34(4):516-7

Correlation of haloperidol levels in blood and cerebrospinal fluid: a pharmacokinetic study

2.1

Abstract

Introduction: Haloperidol is the first choice antipsychotic medication in treatment of delirium. In older patients there is a large, not well understood, inter-individual variation in effect and side effects (in particular antipsychotic induced parkinsonism). There are three possible explanations. First, differences in pharmacokinetics, e.g. cytochroom P450 CYP2D6 contributes to the biotransformation of haloperidol. Second, variation in transport over the blood-brain barrier (BBB). Last, the number of dopamine-2 (D2) receptors in the brain.

Methods: This cross-sectional study included 20 older patients above 64 years (average 78.9 years), with an elevated risk to develop delirium who were prescribed haloperidol 1 mg/day during five days before an elective surgery performed under spinal anaesthesia. Introductory the surgery, cerebrospinal fluid (CSF) (2 ml) and a blood sample (2 ml) were taken. Sample analysis was done by a validated liquid chromatography – mass spectrometry. The correlation of CYP-2D6 polymorphism vs. serum and serum vs. CSF concentration of haloperidol was investigated by linear regression analysis subsequently.

Results: Serum and CSF concentrations of haloperidol averaged 0.52 µg/litre (range 0.17-0.99 µg/litre) and 0.04 (range <0.01-0.09 µg/litre)(ratio averaged 11.45%). The correlation of CSF and serum concentration was significant ($r=0.85$, $p<0.05$). The large variation in serum concentrations (factor 6) could not be explained by differences in drug metabolism resulting from polymorphism of CYP2D6 ($p=0.59$).

Conclusions: Variability in transport over the BBB is not the explanatory factor for inter-individual variation in response. CYP2D6 polymorphisms do not explain the large inter-individual variation in serum haloperidol concentrations. An alternative explanation is the number of remaining dopamine-2 receptors.

Introduction

Haloperidol is commonly prescribed to older patients for the treatment of acute and chronic psychotic symptoms or behavioural symptoms in dementia. It's use is associated with adverse effects such as antipsychotic induced parkinsonism (AIP) and tardive dyskinesia.[1,2] AIP is characterized by the presence of tremor, rigidity, and bradykinesia. These symptoms are associated with impaired quality of life of older patients treated with haloperidol.[3] It is unknown why some older patients develop AIP at a low dosage haloperidol and others do not. There are different hypotheses that could explain the age related sensitivity to antipsychotics: an increased serum concentration for a given dose (peripheral pharmacokinetic hypothesis), increased brain access and distribution for a given serum concentration (central pharmacokinetic hypothesis), or decreased endogenous dopamine in older patients, a decreased number of dopamine-2 receptors in the brain or different receptor occupancy.[4]

A study in 150 older patients did not support the hypothesis of the peripheral pharmacokinetic explanation. In this study, 46% of the patients treated with haloperidol, in dose varying from 0.3-5.0 mg/day, developed AIP.[5] The study found a significant but moderate relationship between dose and serum concentration. Both dose and serum concentrations of haloperidol were not associated with occurrence of AIP. The moderate association between dose and concentration may result from cytochroom P450 (CYP)-2D6 polymorphism since this is the major enzyme that contributes to the biotransformation of haloperidol.[6] Within the central pharmacokinetic hypothesis, transport across the blood-brain barrier (BBB), is an important factor.

The blood-brain barrier, a single layer of capillary endothelial cells joined together at tight junctions, regulates access of xenobiotics (including antipsychotics) to the central nervous system.[7] Loosening of these junctions would theoretically increase access of antipsychotics into the brain. Central concentration of many drugs, including antipsychotics, is also regulated by P-glycoprotein (P-gp), which restricts the permeability of the BBB indirectly by pumping drugs back into the peripheral circulation.[8, 9] Decreased BBB P-gp is found with aging and there is decreased P-gp function in Alzheimer's disease.[10, 11]

The relationship between serum and cerebrospinal fluid (CSF) concentration of haloperidol has not been prescribed earlier in an elderly population. The aim of this investigation therefore was to study this correlation in elderly patients. A secondary aim was to investigate if inter-individual variation in serum concentration can be explained by CYP2D6 polymorphisms.

Methods

Patient selection and study procedure

The study was conducted in a population of patients visiting the pre-operative screening and delirium prevention outpatient clinic (DEPOS) from the department of geriatric medicine of the Jeroen Bosch Hospital, a large teaching hospital in 's-Hertogenbosch, the Netherlands between January 2012 and January 2013. In case of an increased risk of a delirium, haloperidol 1mg/day for five days pre-operative was prescribed by the geriatrician, according to hospital protocol. Inclusion criteria were: age above 64 years old, elective surgery under spinal anaesthesia, adequately started with haloperidol 1 mg/day according hospital protocol, mentally competent and written informed consent. Approval was obtained from the regional Medical Research Ethics Committee. Informed consent was asked by one of the researchers. Elective surgery under spinal anaesthesia made it possible to obtain 2 ml CSF for research goals without patient burden such as a lumbar puncture. A blood sample (2 ml) was drawn by the anaesthesiologist in addition.

Processing of the samples

Serum and CSF samples were stored at -20°C until further processing. A published LC-MS/MS method[12] was adapted to perform the analysis of the samples. The quantification limit of haloperidol levels was 0.02 ng/ml. Only one patient had a haloperidol CSF concentration below this quantification limit. We defined that patient at a CSF concentration of 0.01 ng/ml.

CYP P450 2D6 analysis

Genotyping of the CYP P450 2D6 gene was performed by realtime PCR using the Taqman Drug metabolism Genotyping assays (Applied Biosystems) for 2D6*3, *4, *6, *7, *9, *10 en *41. For determination of 2D6 gene amplifications and deletions (*5) separate analyses were performed using Taqman Copy Number Assay CYP 2D6 (Applied Biosystems) and Taqman Copy Number Reference Assay RNaseP (Applied Biosystems). After DNA extraction (MP96, Roche Diagnostics) of blood samples, PCR was performed on an ABI Prism 7500FAST Sequence Detection System (Applied Biosystems) according to manufacturer's conditions.

The CYP2D6 genotyping were classified into groups with no active gene (poor metabolizers), 1 active gene (intermediate metabolizers), 2 active genes (extensive metabolizers), or more than 2 active genes (ultrarapid metabolizers).

Data analysis

Using the Statistical Package for the Social Sciences (IBM® SPSS 20®) frequencies and distributions were extracted. The correlation coefficient (r) was calculated with Pearson's R. R square was used to express the percentage of explained variance between CSF and serum. We corrected in multiple linear regression analysis for age and gender to identify the adjusted R.

The correlation between CYP-2D6 polymorphism versus serum concentration was investigated by linear regression analysis. Possible explanations for variance in serum concentrations at the same dose haloperidol are interaction with comedication, gender or age. Age was a continuous variable. We made categories of strong and weak CYP2D6 inhibitors and strong and weak CYP2D6 inducers according to the P450 interaction table.[13] A multiple regression analysis with these variables was performed.

Results

Table 1 summarizes the results of this study. Twenty patients were included. Median age was 80 years and ranged from 68 to 91 years. Four (20%) patients were female. Eighteen patients used a dosage of 1 mg haloperidol a day for a period of five days before CSF and serum concentrations were measured. Patient eleven used 1 mg haloperidol a day for a period of five days and the day before the operation she used 2 mg haloperidol. Patient sixteen used a dosage of 2 mg haloperidol a day for a period of five days before CSF and serum concentrations were measured.

Serum and CSF concentrations of haloperidol averaged 0.52 µg/litre (range 0.17-0.99 µg/litre) and 0.04 (range <0.01-0.09 µg/litre (ratio averaged 11.45%). The correlation of CSF and serum concentrations was significant ($r=0.85$, $r^2=0.73$, $p<0.01$)(Figure 1). The CSF concentrations of haloperidol were mainly explained (by 73%) by the serum haloperidol concentration. When age is added in the model $r^2=0.77$. This means that age explains a small additional part of the correlation between CSF and serum. There was no significant correlation between age and CSF concentrations. No differences in CSF concentration were found between males and females.

In 15 patients informed consent to perform CYP2D6 polymorphism analysis was obtained. One patient had no active genes (poor metabolizer), 9 patients had 1 active gene (intermediate metabolizers) and 5 patients had 2 active genes

Table 1. Haloperidol concentration in serum and CSF (microgram/litre)

Patient	Age (years)	Gender	Concentration of haloperidol in blood (µg/litre)	Concentration of haloperidol in cerebro-spinal fluid (µg/litre)	CYP 2D6 alleles
1	80	F	0.808	0.069	Hom 2D6wt(EM)
2	87	M	0.402	0.044	Het 2D6*3(IM)
3	91	M	0.331	0.036	-
4	83	M	0.600	0.066	-
5	71	M	0.568	0.044	Het 2D6*41(EM)
6	70	M	0.580	0.038	Het 2D6*4(IM)
7	71	M	0.999	0.086	Hom 2D6wt(EM)
8	69	M	0.656	0.044	Het 2D6*41(EM)
9	83	M	0.459	0.050	Hom 2D6*41(IM)
10	82	F	0.394	0.052	-
11[1]	83	F	0.759	0.057	Het 2D6*4/41(IM)
12	84	M	0.167	0.010	-
13	78	M	0.488	0.035	Het 2D6*4(IM)
14	73	M	0.495	0.051	Het 2D6*4/*41(IM)
15	81	F	0.487	0.042	Het 2D6*5(IM)
16	79	M	0.430	0.042	Hom 2D6*4(PM)
17[2]	80	M	0.430	0.042	-
18	68	M	0.363	0.031	Hom 2D6wt(EM)
19	80	M	0.359	0.023	Het 2D6*5(IM)
20	80	M	0.556	0.040	Het 2D6*4(IM)
Median	80		0.516	0.045	

[1] *Used 1mg haloperidol a day for a period of five days and the sixth day 2mg haloperidol*

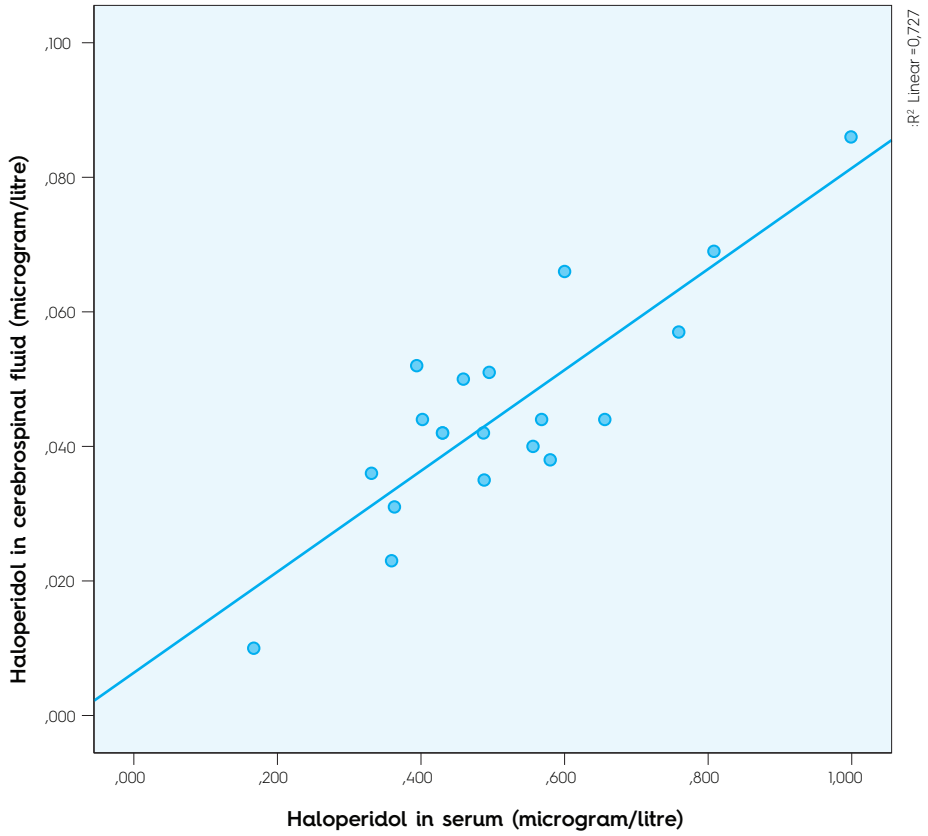
[2] *Used 2mg haloperidol a day for a period of five days*

Hom: homozygote; Het: heterozygote; wt: wild type; -No informed consent was obtained

EM= extensive metabolizer, IM= intermediate metabolizer, PM= poor metabolizer

(extensive metabolizers). The large variation in serum concentrations (factor 6) could not be explained by differences in drug metabolism resulting from polymorphism of CYP-2D6 (p=0.59). No patients used strong CYP2D6 inhibitors or strong CYP2D6 inducers.[13] Patient 2 and 15 used darifenacin, patient 6 used mirtazapin, patient 11 used venlafaxine and patient 13 used citalopram, all weak CYP2D6 inhibitors.[13] Introduction of comedication use to the model could not explain the large variation in serum concentrations (p=0.61).

Figure 1. Correlation of CSF and serum concentration was r=0.853



Discussion

This study shows a strong and significant correlation between the serum concentration and CSF concentration of haloperidol in older patients. Sex or age did hardly influence this relation nor did co-medication or CYP polymorphism explain the serum concentration.

As far as we know, only one study was published studying haloperidol concentrations in CSF and in serum, however, not in older patients, but in younger schizophrenic patients. Rimon et al. analysed 12 chronic neuroleptic-non responsive schizophrenic patients (mean age 39 years) after 1 month on 60 mg haloperidol daily. CSF concentrations of haloperidol were significantly correlated ($r=0.55$ and $p<0.01$) with and averaged 4.3% of the serum concentrations.[14]

In our study CSF concentration of haloperidol were stronger correlated to the plasma concentration ($r=0.85$) however twice as high relative concentrations were measured (11.5% versus 4.3% of serum concentration in the study of Rimon et al.). One of the hypotheses of variability of response to haloperidol, variability in transport over the blood-brain barrier, seems to be not an explanatory variable given these results. A possible explanation for a higher ratio between CSF and serum concentrations of haloperidol in our study (11.5% compared to 4.3%) could be age. It might be possible that older patients have a more permeable blood-brain barrier than younger people, although the fact that no correlation of age (in our study aged 68-91 years old) and CSF concentrations ($p=0.09$) was found, and the fact that adding age to the model did hardly increase correlation, we could not underline that hypothesis. It should be taken into account that the range in age in this study population was quite small to do a proper analysis on age, so this could still be a possible hypothesis. The higher ratio could also be related to the much lower doses used, haloperidol 1 versus 60 mg/day. This seems less likely to be the explanation, because haloperidol is not a substrate of P-glycoprotein (P-gp). P-gp is an efflux pump expressed at the blood-brain barrier (BBB) and limits drug access into the central nervous system. A previous study found that antipsychotic induced parkinsonism (AIP) could not be explained at all by dose or blood concentration of haloperidol.[5] Taken together, although by age still some variation in CSF concentration might be explained by future research, the main explanation appears to be plasma concentration of haloperidol, which is in line with a previous study. So the inter-individual variability of CSF concentrations is unlikely to have a major role in the inter-individual response to haloperidol at the level of AIP.

Cytochrome P450 (CYP) 2D6 contributes to the biotransformation of haloperidol.

A pharmacokinetic study showed reduced haloperidol through concentration and haloperidol total clearance correlated significantly with the number of active CYP2D6 genes.[6] Our results show inter-individual variation in concentrations of haloperidol in serum at the same dose haloperidol. CYP2D6 is not the explanatory factor for inter-individual variation in serum, co-medication with weak CYP2D6 inhibitors neither.

Than what could be the explanation instead? The concentration and density of dopamine transporter have consistently been reported to decline with age. This is a possible explanation for inter-individual variation in effect and side effects of antipsychotic medication. In young patients with schizophrenia, occupancy of more than 80% of striatal D2 receptors with antipsychotics has been associated with extrapyramidal symptoms. This suggests that a minimum of 20% of the receptor population must be free for physiologic transmission to overcome extrapyramidal symptoms. With ageing there is a decline in D2 receptors, so a greater percentage of receptors must be free to provide an adequate level of physiologic transmission in older patients.[4] Older persons would be expected to require a higher occupancy of the D2 receptor for the same effect. Older persons would show a decrease in the threshold for extrapyramidal symptoms. This would lead to a lower dose requirement for elderly.

Taken together, this study shows that the main explanation for CSF concentration variation is the plasma concentration, not age or gender. Why this plasma concentration differs largely in patients with identical haloperidol dosages and why with the same CSF concentration some patients develop AIP and some do not is still unclear, but might be caused by pharmacodynamic differences such as dopamine-2 receptor occupancy and needs future research. This study contributes to a better understanding of the different factors of inter-individual variation to haloperidol and in the end might lead to more evidence based prescribing for older patients.

Acknowledgements: We like to thank Natasja Runderkamp for performance of the CYP P450 2D6 analyses, the Department of Anesthesiology and Renate Paanakker en Peter de Crom for their cooperation.

References

1. Kamble P, Chen H, Sherer JT, Aparasu RR. Use of antipsychotics among elderly nursing ho me residents with dementia in the US: an analysis of National Survey Data. Drugs Aging 2009;26(6):483-92.
2. Testad I, Auer S, Mittelman M, Ballard C, Fossey J, Donabauer Y, et al. Nursing home structure and association with agitation and use of psychotropic drugs in nursing home residents in three countries: Norway, Austria and England. Int J Geriatr Psychiatry 2010; Jul;25(7):725-31.
3. Schouten HJ, Knol W, Egberts TC, Schobben AF, Jansen PA, van Marum RJ. Quality of life of elderly patients with antipsychotic-induced parkinsonism: a cross-sectional study. J Am Med Dir Assoc 2012; Jan;13(1):82.e1,82.e5.
4. Uchida H, Mamo DC, Mulsant BH, Pollock BG, Kapur S. Increased antipsychotic sensitivity in elderly patients: evidence and mechanisms. J Clin Psychiatry 2009; Mar;70(3):397-405.
5. Knol W, van Marum RJ, Jansen PA, Egberts TC, Schobben AF. Parkinsonism in elderly users of haloperidol: associated with dose, plasma concentration, and duration of use. J Clin Psychopharmacol 2012; Oct;32(5):688-93.
6. Brockmoller J, Kirchheiner J, Schmider J, Walter S, Sachse C, Muller-Oerlinghausen B, et al. The impact of the CYP2D6 polymorphism on haloperidol pharmacokinetics and on the outcome of haloperidol treatment. Clin Pharmacol Ther 2002; Oct;72(4):438-52.
7. Bradbury MW. Hugh Davson--his contribution to the physiology of the cerebrospinal fluid and blood-brain barrier. Cell Mol Neurobiol 2000; Feb;20(1):7-11.
8. Brenner SS, Klotz U. P-glycoprotein function in the elderly. Eur J Clin Pharmacol 2004; Apr;60(2):97-102.
9. Akamine Y, Yasui-Furukori N, Ieiri I, Uno T. Psychotropic drug-drug interactions involving p-glycoprotein. CNS Drugs 2012; Nov;26(11):959-73.
10. van Assema DM, Lubberink M, Bauer M, van der Flier WM, Schuit RC, Windhorst AD, et al. Blood-brain barrier P-glycoprotein function in Alzheimer's disease. Brain 2012; Jan;135(Pt 1):181-9.
11. van Assema DM, Lubberink M, Boellaard R, Schuit RC, Windhorst AD, Scheltens P, et al. P-glycoprotein function at the blood-brain barrier: effects of age and gender. Mol Imaging Biol 2012; Dec;14(6):771-6.
12. Hoja H, Marquet P, Verneuil B, Lotfi H, Dupuy JL, Penicaut B, et al. Determination of haloperidol and its reduced metabolite in human plasma by liquid chromatography-mass spectrometry with electrospray ionization. J Chromatogr B Biomed Sci Appl 1997; Jan 24;688(2):275-80.
13. P450 drug interaction table, division of clinical pharmacology, Indiana University. Available at: http://medicine.iupui.edu/clinpharm/DDIs/table.aspx. Accessed January, 2017.
14. Rimon R, Averbuch I, Rozick P, Fijman-Danilovich L, Kara T, Dasberg H, et al. Serum and CSF levels of haloperidol by radioimmunoassay and radioreceptor assay during high-dose therapy of resistant schizophrenic patients. Psychopharmacology (Berl) 1981;73(2):197-9.

2.2

Astrid M. van Strien, Edmée J.M. Schrijver, Carolina (Karen) J.P.W. Keijsers, Nathalie C. Péquériaux, Prabath W.B. Nanayakkara, Hieronymus (Jeroen) J. Derijks, Rob J. van Marum

Published as letter to the Editors
J Clin Psychopharmacol 2017 May, 5.

Haloperidol does not activate thrombogenic factors in older, non-psychotic hospitalised patients

2.2

Abstract

Introduction: This study evaluates the effects of haloperidol on thrombogenesis factors in older users.

Methods: Randomised groups of non-psychotic older patients received haloperidol or placebo. To measure the effect of haloperidol on coagulation, the following markers were measured at day 1 and day 6: Fibrinogen, D-Dimer, P-selectin, von Willebrand factor and osteoprotegerin. Repeated measures ANOVA were performed.

Results: 16 haloperidol and 18 placebo patients were compared: no significant changes in the laboratory markers were found.

Conclusions: No relationship between the short term use of low dose haloperidol and change in thrombogenesis factors was found in older patients.

Introduction

Worldwide, haloperidol is the antipsychotic drug used most often to treat delirium in (older) patients admitted to hospital.[1] In 2005, the Food and Drug Administration issued a warning about the increased mortality rate in elderly users of antipsychotics.[2] Although the pathophysiological mechanism is unknown, the increased death rate might be due to vascular problems. For example, users of antipsychotic drugs are at increased risk of cerebrovascular accidents[3] and venous thromboembolism.[4,5] Potential mechanisms for the association between antipsychotics and cerebrovascular events include thrombo-embolic effects, altered platelet function, cardiovascular effects, and the atherosclerotic effects of metabolic dysregulation.[3] Markers of thrombogenesis are activated in untreated patients with an acute psychosis,[6] which suggests that the psychosis itself may be responsible for the increased risk of morbidity and mortality. However, there is no clear explanation for the increased mortality seen in non-psychotic elderly patients with dementia.

The main aim of this study was to investigate whether factors of thrombogenesis are activated in older, non-psychotic hospitalised patients treated with haloperidol.

Methods

Setting

Patients were a subset of patients included in a randomised, stratified, double-blind, placebo-controlled trial ("Haloperidol prophylaxis in older emergency department patients", HARPOON study).[7] This subset consisted of all patients recruited at the Jeroen Bosch Hospital, a teaching hospital in the Netherlands, between June 2014 and March 2015.

Design

In this RCT, non-psychotic elderly received haloperidol 1 mg two times daily or placebo. Patients were included if they presented to the emergency department, had an age ≥ 70 years, an increased risk of developing a delirium, but no delirium, and were admitted at internal or surgical departments. Primary outcome was the effect of haloperidol versus placebo on coagulation. The following markers were measured: Fibrinogen and D-Dimer as thrombogenesis markers, platelet activation (P-selectin) and endothelial cell activation markers von Willebrand factor and osteoprotegerin. Venous blood was collected on

day 1 (baseline) and day 6. All the laboratory markers were analysed at once at the end of the inclusion period.

Statistics

The effect of haloperidol versus placebo on coagulation and the effect of time, namely day 1 versus day 6 was analysed using repeated measures ANOVA's to take potential non-significant baseline differences into account and to distinguish between "within groups" (day 1 versus 6) and "between groups" (haloperidol versus placebo) effects. IBM® SPSS 22® was used.

Ethics

This study was approved by the Ethical Committee and all participants provided written informed consent.

Results

For this study 52 patients were randomised, 3 patients withdrew consent, 3 patients stopped per protocol and 12 patients had no blood sample drawn at day 6. Ultimately, 16 haloperidol patients and 18 placebo patients were included in the analysis. None of these patients developed a delirium. Table 1 on page 36 shows the baseline characteristics.

Table 2 (page 36) shows the main results. There were no significant changes in the thrombogenesis factors between the two groups. However, time, namely day 1 versus day 6, caused significant decrease in P-selectin ($F(1, 32) = 4.460$, p 0.043) and increase in Fibrinogen ($F(1, 32) = 6.606$, p 0.015), but not for the other factors.

Table 1. Baseline characteristics

	Haloperidol (n=16)	Placebo (n=18)
Age (years, SD)	84.7 (7.2)	83.8 (7.1)
Gender (female n, %)	6 (37.5%)	14 (77.8%)
Admitted at a department (n, %)		
Surgical	10 (62.5%)	9 (50%)
Internal	6 (37.5%)	9 (50%)
Potentially relevant comedication (n, %)		
Aspirin/Persantin/Clopidogrel	5 (31.2%)	8 (44.4%)
NSAID's	0 (0%)	0 (%)
SSRI	0 (0%)	2 (11.1%)
Low molecular weight heparins (LMWH)	0 (0%)	1 (5.6%)
Vitamin K antagonist or NOAC	4 (25%)	6 (33.3%)
Total amount of drugs (mean, SD)	7.3 (3.8)	8.7 (3.1)

Table 2. Main results

	Groups				Statistics	
	Haldol (n=16)		Placebo (n=18)		ANOVA Between	ANOVA Within
	Day 1, before first dose	Day 6, after ten doses	Day 1, before first dose	Day 6, after ten doses	(haldol-placebo)[a]	(day 1-6)[a]
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p-value	p-value
Fibrinogen (g/l)	4.30 (1.18)	4.75 (0.99)	4.49 (1.29)	5.24 (1.10)	0.299	**0.015**
D-dimer (ug/ml)	2.77 (2.26)	1.95 (0.81)	5.53 (6.41)	2.69 (4.42)	0.099	0.078
P-selectine (ng/ml)	75.94 (29.99)	72.69 (19.87)	83.67 (37.81)	72.17 (29.67)	0.716	**0.043**
Von Willebrand factor (%)	236.93 (95.22)	272.39 (81.41)	259.74 (122.04)	274.14 (71.51)	0.672	0.113
Osteoprotegerine (pg/ml)	1798.13 (872.18)	1743.25 (663.29)	1541.33 (850.33)	1326.06 (630.95)	0.178	0.156

[a] *Repeated measures ANOVA, main effect haldol-placebo.*

Discussion

Our study did not show any effect of haloperidol treatment on levels of thrombogenic factors, although overall Fibrinogen levels were increased and P-selectin levels decreased on day 6 relative to baseline. P-selectin plays an essential role in the initial recruitment of leucocytes to the site of injury during inflammation and decreases with recovery. The high levels of Fibrinogen and D-Dimer at baseline may be due to infection or fractures, and levels were expected to decrease as the patient recovered in hospital. This does not explain the increase in Fibrinogen on day 6. Because all patients were non-delirious, delirium cannot explain these results.
Our results are in line with previous studies. We found no direct evidence that thrombogenesis was activated in elderly users of antipsychotic drugs. A laboratory study also failed to find a clear pattern of changes in fibrinogen and C-reactive protein in patients chronically treated with antipsychotic drugs.[8] However, another study reported a higher overall coagulation potential and overall hemostatic potential in patients with schizophrenia receiving long-term antipsychotic therapy, whereas the fibrinolytic potential was lower.[9] A strong temporal relationship was found between antipsychotic use and cerebrovascular accidents, with the highest association in the first week.[3] Also for venous thrombo-embolism the strongest association was found in new users of antipsychotics.[4] Our study did not show any effect of haloperidol treatment on levels of thrombogenic factors in the first week after start.

This was the first study to investigate thrombogenesis in older haloperidol users. The study design corrected for known and unknown confounders, all patients were non-psychotic, and potentially relevant co-medication was equally divided over the groups; however, the small sample size means that we might have missed small effects on coagulation factors. Another limitation is that patients were admitted for different reasons and some thrombogenic factors were already activated at baseline. Depending on genetic factors like Protein C or S deficiency or Factor V Leiden, some people may be vulnerable to thrombotic events even from moderate risks (a few days of bed rest) while others will require a more serious trigger.

These results may not be generalisable, it is unknown whether these results are applicable to home dwelling elderly. Moreover, D-dimer levels were not normally distributed and there were a number of outliers, which means that the

D-dimer results should be interpreted with caution.
We found no significant differences in laboratory factors of thrombogenesis in non-psychotic older patients receiving haloperidol or placebo. Thus the underlying cause of the increase in cerebrovascular events seen in haloperidol users remains to be established.

Acknowledgements: We like to thank Renate Paanakker, Desiree Dudink en Peter de Crom for their cooperation in data collection and patient inclusion.

References

1. Inouye SK. Delirium in older persons. N Engl J Med 2006;354:1157-65.
2. FDA. Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances. Washington, DC, Department of Health and Human Services. 2005. Available at: http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm053171. Accessed December, 2016.
3. Kleijer BC, van Marum RJ, Egberts AC, et al. Risk of cerebrovascular events in elderly users of antipsychotics. J Psychopharmacol 2009;23:909-14.
4. Parker C, Coupland C, Hippisley-Cox J. Antipsychotic drugs and risk of venous thromboembolism: nested case-control study. BMJ 2010;341:c4245.
5. Hatta K, Kishi Y, Wada K, et al. Antipsychotics for delirium in the general hospital setting in consecutive 2453 inpatients: a prospective observational study. Int J Geriatr Psychiatry 2014;29:253-62.
6. Masopust J, Maly R, Andrys C, et al. Markers of thrombogenesis are activated in unmedicated patients with acute psychosis: a matched case control study. BMC Psychiatry 2011;11:2.
7. Schrijver EJ, de Vries OJ, Verburg A, et al. Efficacy and safety of haloperidol prophylaxis for delirium prevention in older medical and surgical at-risk patients acutely admitted to hospital through the emergency department: study protocol of a multicenter, randomised, double-blind, placebo-controlled clinical trial. BMC Geriatr 2014;14:96,2318-14-96.
8. Carrizo E, Fernandez V, Quintero J, et al. Coagulation and inflammation markers during atypical or typical antipsychotic treatment in schizophrenia patients and drug-free first-degree relatives. Schizophr Res 2008;103:83-93.
9. Chow V, Reddel C, Pennings G, et al. Global hypercoagulability in patients with schizophrenia receiving long-term antipsychotic therapy. Schizophr Res 2015;162:175-82.

3.

Side effects in clinical practice of antipsychotic medication in frail elderly

3.1

Astrid M. van Strien, Huiberdina L. Koek, Rob J. van Marum, Mariëlle H. Emmelot-Vonk

Published as
Maturitas. 2013 Apr;74(4):357-62

Psychotropic medications, including short acting benzodiazepines, strongly increases the frequency of falls in elderly

Abstract

Objectives: Falls in the elderly are common and often serious. The aim of this study was to examine the association between the use of different classes of psychotropic medications, especially short acting benzodiazepines, and the frequency of falling in elderly.

Study design: This retrospective cohort study was performed with patients who visited the day clinic of the department of geriatric medicine of the University Medical Center Utrecht in the Netherlands between 1 January 2011 and 1 April 2012.

Measurements: Frequencies of falling in the past year and medication use were recorded. Logistic regression analysis was performed to assess the relationship between the frequency of falling in the past year and the use of psychotropic medications.

Results: During this period 404 patients were included and 238 (58.9%) of them had experienced one or more falls in the past year. After multivariate adjustment, frequent falls remained significantly associated with exposure to psychotropic medications (Odds Ratio [OR] 1.96; 95% Confidence Interval [CI] 1.17-3.28), antipsychotics (OR 3.62; 95% CI 1.27-10.33), hypnotics and anxiolytics (OR 1.81; 95% CI 1.05-3.11), short-acting benzodiazepines or Z-drugs (OR 1.94; 95% CI 1.10-3.42) and antidepressants (OR 2.35; 95% CI 1.33-4.16).

Conclusions: This study confirms that taking psychotropic medication, including short-acting benzodiazepines, strongly increases the frequency of falls in elderly. This relation should be explicitly recognised by doctors prescribing for older people, and by older people themselves. If possible such medication should be avoided for elderly patients especially with other risk factors for falling.

Introduction

The World Health Organisation describes a fall as "an event which results in a person coming to rest inadvertently on the ground or floor or other lower level".[1] Approximately 28-35% of people aged 65 and over fall each year, increasing to 32-42% for those over 70 years of age. Approximately 30-50% of people living in long term care institutions fall each year and 40% of them experience recurrent falls.[1] Falls constitute a leading cause of injuries, hospitalisation and deaths among the elderly.[2] The annual costs associated with falls and fall-related complications are substantial.[3] The costs related to fall injuries are expected to rise steeply over the next 50 years as a result of the increase in the elderly population.[4] Fall risk is multifactorial, with many intrinsic and extrinsic factors. Prescribed medications are an important contributor to falls in seniors.[5] In a meta-analysis that included studies between 1966 and 1996, Leipzig et al. found an association between the use of most classes of psychotropic drugs, cardiac and analgesic drugs and falls.[6, 7] The general message that psychotropic drugs increase falls is already well accepted. However, the contribution of specific psychotropic drugs to fall frequency in elderly has not been quantified precisely until now. The older patient is more frail than normal adults and thus more prone to the negative effects of psychotropic drugs. Furthermore, results from different studies are inconsistent concerning benzodiazepines, as short- or intermediate acting benzodiazepines were not always associated with an increased frequency of falling.[8-10]

The aim of the current study was to evaluate the association between the use of different classes of psychotropic drugs, especially short acting benzodiazepines, and the frequency of falling in elderly patients who visited the day clinic of the department of geriatric medicine of the University Medical Center Utrecht.

Methods

Patient selection

Patients who visited the day clinic of the department of geriatric medicine of the University Medical Center Utrecht, between 1 January 2011 and 1 April 2012 were included. These outpatients were referred by the general practitioner to the department of geriatric medicine with functional decline, cognitive impairment, incontinence or impaired immobility. As part of usual care, all these

patients underwent a comprehensive geriatric assessment existing of a physical examination, cognitive and mobility tests and laboratory research. In addition patients filled out a questionnaire concerning their general health. Data of these outpatients were collected in a database by the nurses and physicians of the day clinic of the department of geriatric medicine. The Medical Ethics Committee of the University Medical Center Utrecht approved the study.

Definition of variables

The following data were extracted from the database: age, gender, type of day clinic (memory clinic, fall clinic, general day clinic), living situation and number of medications.

Living situation was dichotomized in: living independent without professional help and living with professional help (living independent with professional help, living in a senior apartment, living in a home for the elderly, living in a nursing home).

The number of medications comprised all the medications the patient was using at the time of visit to the day clinic. This included ocular, dermatologic and intercurrent medication. Polypharmacy was defined as using five or more medications a day.

Falls were described as at least one fall in the past year. The frequency of falls was registered in four subgroups: no fall, one fall, two falls, or more than two falls. Frequent falls were defined as more than two falls in the past year, non frequent falls as two or less falls in the past year.

The intensity of daily walks was categorized in: mainly at home, daily around the block, frequent a moderate distance or frequent a long distance.

Body mass index was calculated by dividing the weight by the length squared in kg/m^2.

The Patient Health Questionnaire-2 (PHQ-2) was used as screening tool for depression.[11] Each patient who visited the day clinic filled out the following two questions in the PHQ-2: 1."During the past month, have you often been bothered by feeling down, depressed, or hopeless?" and 2."During the past month, have you often been bothered by little interest or pleasure in doing things?". If the patient answered two times "no" to these two screening questions a patient was considered not depressive. Otherwise a Geriatric Depression Scale with 15 items, (GDS-15) was taken.[12] If a patient had a known diagnosis of a depression or a GDS-15 score of 6 or higher a patient was considered depressive. If a GDS-15 was not performed because there was no indication or the GDS-15 score was below 6, a patient was considered not depressive.

From all the patients who visited the memory clinic and from all the patients who visited the fall clinic or general day clinic with a suspicion of cognitive impairment, a Mini Mental State Examination (MMSE) with 30 items was taken.[13] The MMSE tests multiple cognitive domains. The first section covers orientation, memory, and attention. The second part tests ability to name, follow verbal and written commands, write a sentence spontaneously, and copy a complex figure which is a test for visuospatial and executive functions. Cognitive impairment was defined as a known diagnosis of dementia or a score on the MMSE of 24 or lower.[14] A MMSE score above 24, or when no MMSE was taken, because there was no indication, was considered as no cognitive impairment.

In this study medications were classified according to the 2006 Anatomical Therapeutic Chemical (ATC) Classification system (World Health Organisation 2003). Psychotropic medications included antipsychotics, hypnotics and anxiolytics, antidepressants and anti dementia medication. Long-acting benzodiazepines with an elimination half life of more than 20 hours included clobazam, clonazepam, nitrazepam, diazepam, fludiazepam and clorazepate. Short-acting benzodiazepines included oxazepam, temazepam, alprazolam, bromazepam, lorazepam and midazolam. Non benzodiazepine hypnotics zolpidem and zopiclon (Z-drugs) were also included in this group.
Isometric grip strength was measured using an adjustable hand held dynamometer (JAMAR dynamometer) at the hand. The subjects were standing with their shoulder adducted and neutrally rotated. The dynamometer was held freely without support, the arm was stretched. The subjects were told to put maximal force on the dynamometer. The maximal value of the left and the right hand was counted up and noted in kilograms.
Walking speed was measured by performing a 4 meter walk test. The patient was asked to walk 4 meter from one line to another while a nurse recorded the time with a timer. Gait speed was defined in meters per second.

Data analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (version 15.0; SPSS, Inc, an IBM Company, Chicago, Illinois). Differences in frequencies were tested using Pearson's chi-squared test. Differences in means were tested with the Student's t-test. A p-value of less than 0.05 was considered statistically significant. To investigate the association between the use of psychotropic drugs and the frequency of falling, logistic regression analysis was done. Outcomes were calculated with a 95% Confidence Interval

(95% CI). This was also done for the subgroups of antipsychotics, hypnotics and anxiolytics, long-acting benzodiazepines, short-acting benzodiazepines and Z-drugs, antidepressants and anti dementia medication. Age and gender adjusted odds ratio's (ORs) were calculated, as well as ORs adjusted for age, gender, cognitive impairment, depression, polypharmacy, living situation and amount of walking on a day.

Results

Table 1. Medication use according to class of psychotropic medication and the drugs that fall into each group

Medication class	Number of users
Antipsychotics Haloperidol, Risperidon, Quetiapine, Olanzapine, Zuclopentixol, Lithium and Levomepromazine	19 (4.7%)
Hypnotics and anxiolytics	91 (22.5%)
- Long-acting benzodiazepines Clobazam, Clonazepam, Nitrazepam, Diazepam, Fludiazepam and Clorazepate	20 (5.0%)
- Short-acting benzodiazepines and Z-drugs Oxazepam, Temazepam, Alprazolam, Bromazepam, Lorazepam, Midazolam, Zolpidem and Zopiclon	75 (18.6%)
Antidepressants Citalopram, Escitalopram, Fluoxetine, Paroxetine, Mirtazapine, Sertraline, Duloxetine, Venlafaxine, Amitriptyline, Nortriptyline, Clomipramine, Trazodon, Fenelzine	74 (18.3%)
Anti dementia medication Rivastigmine, Galantamine, Memantine	12 (3.0%)
Psychotropic medications total	139 (34.4%)

416 Patients visited the day clinic of the department of geriatric medicine of the Academic Hospital Utrecht between 1 january 2011 and 1 april 2012. For twelve patients it was unknown if they had fallen in the past year. Medication use within class of psychotropic medications is listed in table 1.
Psychotropic medication use was present in one third (34%) of the patients. The characteristics of the 404 included patients are shown in table 2.

Table 2. Characteristics of Patients

	Patients using psychotropic medications (n=139)	Patients not using psychotropic medications (n=265)	
	Number of patients (proportion)	**Number of patients (proportion)**	**p-value Chi-square Test**
Gender: female	106 (76.3%)	149 (56.2%)	0.001
Living situation			
Patients who live independent without professional help	35 (25.2%)	127 (47.9%)	0.001
Patients who live independent with professional help	65 (46.8%)	99 (37.4%)	0.067
Patients who live in a seniors appartment	11 (7.9%)	14 (5.3%)	0.297
Patients who live in a home for the elderly	16 (11.5%)	15 (5.7%)	0.036
Patients who live in a nursing home	12 (8.6%)	10 (3.8%)	0.041
Referred to			
Memory clinic	62 (44.6%)	156 (58.9%)	0.006
Fall clinic	21 (15.1%)	48 (18.1%)	0.446
General day clinic	56 (40.3%)	61 (23%)	0.001
How much do you walk every day?			
Mainly at home	92 (66.2%)	143 (54%)	0.030
Daily around the block	39 (28.1%)	75 (28.3)	0.868
Frequently a moderate distance	8 (5.8%)	38 (14.3%)	0.008
Frequently a long distance	0 (0.0%)	4 (1.5%)	0.142

Table 2. Continued

	Patients using psychotropic medications (n=139)	Patients not using psychotropic medications (n=265)	
	Number of patients (proportion)	**Number of patients (proportion)**	**p-value Chi-square Test**
How many times did you fall last year?			
I did not fall last year	40 (28.8%)	126 (47.5%)	0.001
One time	22 (15.8%)	44 (16.6%)	0.864
Two times	12 (8.6%)	36 (13.6%)	0.150
More than two times	63 (45.3%)	57 (21.5%)	0.001
Depression found on PHQ-2 or GDS-15	48 (34.5%)	42 (15.8%)	0.001
Cognitive impairment defined as MMSE score of 24 or below	61 (43.9%)	117 (44.2%)	0.819
	Mean (standard deviation)	**Mean (standard deviation)**	**p-value T-Test**
Age (years)	78.5 (8.8)	77.8 (8.8)	0.423
Body Mass Index (kg/m²)	26.7 (5.6)	26.2 (5.6)	0.460
MMSE (n=328)	23.4 (5.6)	22.8 (5.5)	0.971
GDS-15 (n=264)	5.3 (3.1)	3.8 (3.1)	0.001
Number of medications	8.8 (4.1)	5.1 (3.4)	0.001
Isometric grip strength (kg)	29.3 (19.9)	37.9 (19.1)	0.001
Gait speed (m/s) on the four meter walk test	0.78 (0.34)	0.90 (0.47)	0.041

Differences between groups were tested with Pearson's chi squared tests (proportions) and Student's t-tests (means). A p value less than 0.05 is considered statistically significant.

There were no significant differences in age, body mass index and MMSE between the two groups. In the group of psychotropic medication users there were more females (76.3% versus 56.2%, p-value 0.001). Patients in that group had professional help more often and lived more frequently in long term care facilities. The number of medications was 8.8 in the group of patients who used

psychotropic medications. This was remarkable higher than the 5.1 medications that the group of non users received (p-value 0.001).

The 4 meter walk test was performed in 269 patients and isometric grip strength was performed in 324 patients. Patients who used psychotropic medications had a significant lower gait speed on the 4 meter walk test (p-value 0.041) and lower isometric grip strength (p-value 0.001) compared to non users (0.8 versus 0.9 m/sec and 29.3 versus 37.9 kg).
In 264 patients (65.1%) who visited the day clinic a GDS-15 was taken. In 32.2% there was no indication for a GDS-15 because the patient answered two times "no" to the two screening questions. In 1% there was no GDS-15 because of a language barrier and in 1.7% there was no GDS-15 because of the unreliability due to severe cognitive impairment. One third (34.5%) of the patients who used psychotropic medication were found to be depressive. This was significantly more often compared to non-users (15.8%, p-value 0.001).
In 328 patients (81.2%) who visited the day clinic a MMSE was taken. In 14.9% there was no indication for a MMSE. In 2% there was no MMSE because of a language barrier and in 2% the patient did not want to cooperate. Cognitive impairment was not significantly more often present in users of psychotropic medication compared to non users (43.9% versus 44.2%, p-value 0.819). Of the 404 included patients, 238 (58.9%) had experienced one or more falls in the past year (69.7% of users versus 51.6% of non users).

After multivariate adjustment, users of psychotropic medications did not have a higher risk to fall incidentally than non-users (OR 1.54; 95% CI 0.90-2.61), but they did have a higher risk to fall more frequently (more than two falls) (OR 1.96; 95% CI 1.17-3.28) (tables 3 and 4). Antipsychotic users were not at greater risk of falling at least once compared to non-users (OR 4.39; 95% CI 0.96-20.12), but they were of greater risk of frequent falling (OR 3.62; 95% CI 1.27-10.33).

Hypnotic and anxiolytic medication use was significantly associated with frequent falls (OR 1.81; 95% CI 1.05-3.11) as well as short-acting benzodiazepines or Z-drugs use (OR 1.94; 95% CI 1.10-3.42) and antidepressant use (OR 2.35; 95% CI 1.33-4.16). The association between falls and use of anti dementia medication or long-acting benzodiazepines did not reach significance.

Table 3. Association between the use of psychotropic medications and falls (defined as at least one fall)

	OR	95% CI		OR	95% CI		OR*	95% CI	
		Lower limit	Upper limit	Age and gender adjusted	Lower limit	Upper limit	Multi-variate	Lower limit	Upper limit
Antipsychotics	6.31	1.44	27.68	6.62	1.48	29.66	4.39	0.96	20.12
Hypnotics/ Anxiolytics	2.49	1.48	4.19	2.27	1.33	3.88	1.60	0.88	2.88
Long-acting benzo-diazepines	2.17	0.77	6.08	1.87	0.65	5.35	1.28	0.42	3.87
Short-acting benzo-diazepines and Z-drugs	2.59	1.46	4.59	2.40	1.34	4.29	1.69	0.90	3.20
Anti-depressants	2.09	1.20	3.66	2.13	1.20	3.80	1.56**	0.84	2.92
Anti dementia medication	0.98	0.30	3.13	0.94	0.29	3.14	0.61***	0.17	2.14
Psychotropic medications total	2.22	1.45	3.48	2.17	1.38	3.43	1.54	0.90	2.61

*Analyses based on logistic regression analysis. Reference group: patients with no fall. OR: odds ratio. 95% CI: 95% confidence interval. *Adjusted for age, gender, cognitive impairment, depression, polypharmacy, living situation and walking distance. **Use of antidepressants was not adjusted for depression. ***Use of anti dementia medication was not adjusted for cognitive impairment.*

Table 4. Association between the use of psychotropic medications and frequent falls, defined as more than two falls in the past year and non frequent falls defined as two or less falls in the past year

	OR	95% CI		OR	95% CI		OR*	95% CI	
		Lower limit	Upper limit	Age and gender adjusted	Lower limit	Upper limit	Multi-variate	Lower limit	Upper limit
Antipsychotics	5.55	2.06	14.97	5.31	1.95	14.45	3.62	1.27	10.33
Hypnotics/ Anxiolytics	2.84	1.74	4.63	2.64	1.61	4.34	1.81	1.05	3.11
Long-acting benzo-diazepines	2.44	0.94	6.31	2.11	0.81	5.51	1.43	0.51	3.97
Short-acting benzo-diazepines and Z-drugs	2.93	1.74	4.92	2.76	1.63	4.66	1.94	1.10	3.42
Anti-depressants	3.33	1.90	5.47	3.09	1.81	5.28	2.35**	1.33	4.16
Anti dementia medication	2.40	0.76	7.61	2.47	0.77	7.92	1.67***	0.51	5.46
Psychotropic medications total	3.08	1.97	4.81	2.91	1.85	4.59	1.96	1.17	3.28

*Analyses based on logistic regression analysis. Reference group: patients with two or less falls. OR: odds ratio. 95% CI: 95% confidence interval. *Adjusted for age, gender, cognitive impairment, depression, polypharmacy, living situation and walking distance. **Use of anti-depressants was not adjusted for depression. ***Use of anti dementia medication was not adjusted for cognitive impairment.*

Discussion

The main finding of this retrospective study in geriatric outpatients was that there is a strong association between frequent falls and different classes of psychotropic medications. Our data showed the strongest association with the use of antipsychotics, hypnotics or anxiolytic medications, short-acting benzodiazepines or Z-drugs and antidepressants.

Comparison with other studies

This effect of psychotropic medications on falling is consistent with a lot of previous research summarized in systematic literature reviews.[2, 6] In this study with different falling outcomes (incidentally falling and frequent falling), we did not find an association between the different psychotropic medications and incidental falls, but we did find that the elderly using psychotropic medications were more at risk of multiple falls. This can be explained by the fact that an incidental- accident is more likely to be the underlying cause in patients with a single fall, but not in patients with multiple falls.

We found a higher risk of falling in antipsychotic users (OR 3.62; 95% CI 1.27-10.33) than others found before (OR1.3-2.8).[3,15,16] The relationship between antipsychotics and falling is probably (partly) due to the drugs' effects on gait and postural stability.[17] A lower gait speed on the 4 meter walk test and lower isometric grip strength (representing diminished mobility and muscle strength) may be one of the underlying mechanisms of this association between more frequent falling and antipsychotic medication use in elderly patients. However, little is known about the influence of psychotropic medications on gait parameters. Withdrawal of psychotropic medications improved mobility in geriatric outpatients in a study performed in 2007.[18] Despite fewer extrapyramidal side effects, atypical antipsychotic medications are not associated with fewer falls than conventional antipsychotics.[19] We had too limited power to detect differences between atypical antipsychotic medications and the older antipsychotics. Our data showed that use of short-acting benzodiazepines is a significant risk factor for frequent falls in geriatric patients. The point estimator for long-acting benzodiazepines indicates that there is a possible association, but we had limited power to demonstrate this effect. Other studies found that the increase in falls is mainly due to the use of long-acting benzodiazepines and not to medications with a shorter elimination half live.[8,20,21] A possible explanation for our findings may be that the pharmacokinetic half-life of short-acting benzodiazepines in blood may be misleadingly long for older people. Hepatic drug

clearance is reduced in elderly because of reduction in hepatic blood flow and hepatocyte mass. Other age related changes that may influence metabolism of psychotropic medications are decreased plasma albumin, decreased lean body mass and reduction in renal clearance.[22] Also the pharmacodynamic effect on the nervous system may be altered in the elderly making them more prone for negative effects of psychotropic medications.

Our finding that the use of antidepressants leads to frequent falls in the elderly is confirmed by the findings of others.[23,24] Findings from the literature suggest that selective serotonin re-uptake inhibitors and tricyclic antidepressants are both associated with increased falling, with possibly somewhat higher rates for selective serotonin re-uptake inhibitors than for tricyclic antidepressants.[23,25] Falling may be directly potentiated by the sedative and orthostatic effects of antidepressants.

A study in patients with mild Alzheimer's disease showed that cholinesterase inhibitors significantly reduced the number of falls.[26] Donepezil treatment significantly increased gait velocity and reduced gait variability, resulting in a more-stable walking pattern in the intervention group.[26] However, a meta-analysis of randomised controlled trials showed no effects of anti dementia medication on falls in cognitively impaired older adults.[27] Our study was underpowered to show a difference in falls in elderly with anti dementia medication.

Strengths and limitations

Our study has a number of strengths. Our study was performed in a frail population, representative for geriatric outpatients elsewhere. We studied the association between different classes of psychotropic medication with single, but also with multiple falls. Little data were missing in our database and medication use was verified in the patients chart.

Our study also has several limitations. As this is an observational study, it is susceptible to confounding by indication and residual confounding. Patients receiving psychotropic medications may be at higher risk of falls because of the underlying conditions treated by these medications (depression, anxiety, insomnia, agitation, and dementia). We adjusted our results for a number of possible confounders, including cognitive impairment, depression, age, gender, polypharmacy, living situation and amount of walking on a day. The increased risk was sustained even after adjustment for these multiple confounding factors. However, residual confounding might still be present. We did not have information about insomnia, poor balance, orthostatic hypotension for all the patients. As in most observational studies, we were not able to correct this possible bias.

This study did not evaluate the fall related injuries. We only had information on fall related injury from the patients who visited the falls clinic. This study did not evaluate the effect of the dosage and duration of the medication use. The database only has information on the medications being taken at the time of the visit to the day clinic. It does not provide information on the medications taken by the patients over the past year. Data on falls were self-reported by the patients and may be affected by recall bias.

Clinical implications and conclusions

In this frail population one third (34%) of the patients used psychotropic medications and several classes of these psychotropic medications were found to be strong risk factors of falling. It is probable useful to try to lower these medications. Withdrawal of psychotropic medications, especially benzodiazepines or related drugs, has shown to lower the risk of falls.[28,29] Withdrawing these medications however is challenging because of their propensity for causing dependence and rebound insomnia. Despite these challenges, specialist recommendations to cease or reduce dosage of these medications are associated with a high success rate.[30]

This study confirms that taking psychotropic medication, including short-acting benzodiazepines, strongly increases the frequency of frequent falls in elderly. This relation should be explicitly recognised by doctors prescribing for older people, and by older people themselves. If possible such medication should be avoided for elderly patients with other risk factors for falling

References

1. Violence and injury prevention: other injury topics: falls. WHO [online]. Available at:http://www.who.int/violence_injury_prevention/publications/other_injury/falls_prevention.pdf.Accessed Janurary, 2017.
2. Huang AR, Mallet L, Rochefort CM, Eguale T, Buckeridge DL, Tamblyn R. Medication-related falls in the elderly: causative factors and preventive strategies. Drugs Aging 2012; May 1;29(5):359-76.
3. Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med 2009; Nov 23;169(21):1952-60.
4. Vitry AI, Hoile AP, Gilbert AL, Esterman A, Luszcz MA. The risk of falls and fractures associated with persistent use of psychotropic medications in elderly people. Arch Gerontol Geriatr 2010; May-Jun;50(3):e1-4.
5. Neutel CI, Perry S, Maxwell C. Medication use and risk of falls. Pharmacoepidemiol Drug Saf 2002; Mar;11(2):97-104.
6. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. J Am Geriatr Soc 1999; Jan;47(1):30-9.
7. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. J Am Geriatr Soc 1999; Jan;47(1):40-50.
8. Berdot S, Bertrand M, Dartigues JF, Fourrier A, Tavernier B, Ritchie K, et al. Inappropriate medication use and risk of falls--a prospective study in a large community-dwelling elderly cohort. BMC Geriatr 2009; Jul 23;9:30.
9. Pierfitte C, Macouillard G, Thicoipe M, Chaslerie A, Pehourcq F, Aissou M, et al. Benzodiazepines and hip fractures in elderly people: case-control study. BMJ 2001; Mar 24;322(7288):704-8.
10. Sylvestre MP, Abrahamowicz M, Capek R, Tamblyn R. Assessing the cumulative effects of exposure to selected benzodiazepines on the risk of fall-related injuries in the elderly. Int Psychogeriatr 2011; Nov 8;:1-10.
11. Whooley MA, Avins AL, Miranda J, Browner WS. Case-finding instruments for depression. Two questions are as good as many. J Gen Intern Med 1997; Jul;12(7):439-45.
12. D'Ath P, Katona P, Mullan E, Evans S, Katona C. Screening, detection and management of depression in elderly primary care attenders. I: The acceptability and performance of the 15 item Geriatric Depression Scale (GDS15) and the development of short versions. Fam Pract 1994; Sep;11(3):260-6.
13. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; Nov;12(3):189-98.
14. Damian AM, Jacobson SA, Hentz JG, Belden CM, Shill HA, Sabbagh MN, et al. The Montreal Cognitive Assessment and the mini-mental state examination as screening instruments for cognitive impairment: item analyses and threshold scores. Dement Geriatr Cogn Disord 2011;31(2):126-31.
15. Jalbert JJ, Eaton CB, Miller SC, Lapane KL. Antipsychotic use and the risk of hip fracture among older adults afflicted with dementia. J Am Med Dir Assoc 2010; Feb;11(2):120-7.
16. Sterke CS, van Beeck EF, van der Velde N, Ziere G, Petrovic M, Looman CW, et al. New insights: dose-response relation-

ship between psychotropic drugs and falls: a study in nursing home residents with dementia. J Clin Pharmacol 2012; Jun;52(6):947-55.
17. Putzhammer A, Perfahl M, Pfeiff L, Hajak G. Gait disturbances in patients with schizophrenia and adaptation to treadmill walking. Psychiatry Clin Neurosci 2005; Jun;59(3):303-10.
18. van der Velde N, Stricker BH, Pols HA, van der Cammen TJ. Withdrawal of fall-risk-increasing drugs in older persons: effect on mobility test outcomes. Drugs Aging 2007;24(8):691-9.
19. Hien le TT, Cumming RG, Cameron ID, Chen JS, Lord SR, March LM, et al. Atypical antipsychotic medications and risk of falls in residents of aged care facilities. J Am Geriatr Soc 2005; Aug;53(8):1290-5.
20. Ensrud KE, Blackwell TL, Mangione CM, Bowman PJ, Whooley MA, Bauer DC, et al. Central nervous system-active medications and risk for falls in older women. J Am Geriatr Soc 2002; Oct;50(10):1629-37.
21. Ray WA, Thapa PB, Gideon P. Benzodiazepines and the risk of falls in nursing home residents. J Am Geriatr Soc 2000; Jun;48(6):682-5.
22. McLean AJ, Le Couteur DG. Aging biology and geriatric clinical pharmacology. Pharmacol Rev 2004; Jun;56(2):163-84.
23. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ 2011; Aug 2;343:d4551.
24. Gribbin J, Hubbard R, Gladman J, Smith C, Lewis S. Serotonin-norepinephrine reuptake inhibitor antidepressants and the risk of falls in older people: case-control and case-series analysis of a large UK primary care database. Drugs Aging 2011; Nov 1;28(11):895-902.
25. Sterke CS, Ziere G, van Beeck EF, Looman CW, van der Cammen TJ. Dose-response relationship between selective serotonin re-uptake inhibitors and injurious falls: a study in nursing home residents with dementia. Br J Clin Pharmacol 2012; May;73(5):812-20.
26. Montero-Odasso M, Wells J, Borrie M. Can cognitive enhancers reduce the risk of falls in people with dementia? An open-label study with controls. J Am Geriatr Soc 2009; Feb;57(2):359-60.
27. Kim DH, Brown RT, Ding EL, Kiel DP, Berry SD. Dementia medications and risk of falls, syncope, and related adverse events: meta-analysis of randomized controlled trials. J Am Geriatr Soc 2011; Jun;59(6):1019-31.
28. van der Velde N, Stricker BH, Pols HA, van der Cammen TJ. Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study. Br J Clin Pharmacol 2007; Feb;63(2):232-7.
29. Salonoja M, Salminen M, Vahlberg T, Aarnio P, Kivela SL. Withdrawal of psychotropic drugs decreases the risk of falls requiring treatment. Arch Gerontol Geriatr 2012; Jan;54(1):160-7.
30. Joester J, Vogler CM, Chang K, Hilmer SN. Hypnosedative use and predictors of successful withdrawal in new patients attending a falls clinic: a retrospective, cohort study. Drugs Aging 2010; Nov 1;27(11):915-24.

3.2

Astrid M. van Strien, Patrick C. Souverein, Carolina (Karen) J.P.W. Keijsers, Eibert R. Heerdink, Hieronymus (Jeroen) J. Derijks, Rob J. van Marum

Published as
Maturitas. 2017 Apr;98:46-50

Antipsychotic drug use associated with uncomplicated urinary tract infections in older women

Abstract

Background/Objectives: Antipsychotic drugs are frequently prescribed to elderly patients, but they are associated with serious adverse effects. The objective of the current study was to investigate the association between use of antipsychotics by elderly women and the risk of urinary tract infections (UTIs).

Design/Setting/Participants: A Cohort study. Dispense data were obtained from PHARMO Database Network for the period 1998–2008. Participants were ambulatory Dutch women (≥65 years) with current and past use of antipsychotics.

Measurements: Incidence rate of UTIs, as defined by use of nitrofurantoin, was calculated within and outside exposure to antipsychotic drugs. Cox proportional hazard regression analysis with Andersen-Gill extension for recurrent events was used to calculate crude and adjusted hazard ratios (HRs).

Results: During the study period, 18,541 women with a first prescription of an antipsychotic were identified. Current use of antipsychotics was associated with an increased risk of UTI compared to past use: (HR, adjusted for age and history of UTIs, 1.33, 95% CI 1.27-1.39). A strong temporal relationship was found, with the risk of being treated for a UTI being higher in the first week after the start of the treatment (adjusted HR 3.03, 95% CI 2.63-3.50) and decreased after 3 months (adjusted HR 1.22, 95% CI 1.17-1.28). Cumulative exposure was not associated with an increased risk of UTIs. There was no difference in effect between conventional and atypical antipsychotics.

Conclusion: Our results show an increased risk of uncomplicated UTIs during antipsychotic use in older female patients, especially in the first week after the start of treatment.

Introduction

Antipsychotic drugs are approved for the treatment of schizophrenia and bipolar disorder.[1] While they are frequently prescribed to older patients, atypical antipsychotics are often used outside their approved indication, to treat behavioural disturbances in elderly patients with dementia.[1] A recent study in the United Kingdom reports a rather high prevalence of antipsychotic drug use of 1% in a primary care setting.[2] Yet, these drugs may cause serious adverse effects. In 2008, the Food and Drug Administration reported that the use of antipsychotics to treat behavioural disorders in elderly patients with dementia was associated with an increased mortality rate.[3,4] Although the cause of this increased mortality is not completely understood, antipsychotic drug use is associated with an increased risk of cardiovascular events, such as stroke, thrombo-embolic events, and cardiac arrhythmia, and infections, such as pneumonia.[5] The risk of bacterial infections was found to be higher in nursing home residents starting conventional antipsychotics than in similar residents starting atypical antipsychotics.[6]

Although these drugs increase the risk of bacterial infection, such as pneumonia, it is unclear whether this is also the case for urinary tract infections (UTIs). Urinary tract problems, such as incontinence and urine retention, are reported in users of both typical and atypical antipsychotics.[7] These problems may be caused by extrapyramidal side effects, due to anticholinergic side effects or peripheral α1-adrenergic blockade, and may increase the susceptibility to UTIs.[7] UTIs are very common in the elderly population.[8] In the Netherlands, in primary care there are on average 70 episodes of UTIs per 1000 patients-year in women of all ages, with the highest incidence in women >60 years old.[9]

Since UTIs are a major cause of morbidity and mortality in elderly people and antipsychotic drugs are prescribed frequently to these individuals, an association between these two factors would be clinically relevant. Therefore, the aim of this study was to investigate the association between antipsychotic use in elderly women and the risk of UTIs.

Methods

Design

This population-based cohort study involved ambulatory Dutch female patients ≥65 years with current and past use of antipsychotics, with or without the occurrence of an uncomplicated UTI.

Setting

Data were obtained from the PHARMO Database Network (Pharmo Institute, Utrecht, the Netherlands; available at: http://www.pharmo.nl). The PHARMO database network includes the pharmacy dispense records of over 3 million community-dwelling residents in the Netherlands from 1998 onward. Patient information includes gender and date of birth. Because most patients in the Netherlands are registered with a single community pharmacy, records are virtually complete with regard to prescription drugs.[10] The computerized drug-dispense histories contain information about the dispensed drug, dispense date, the prescriber, amount dispensed, and the prescribed dosage regimen. The dispense date is the day the patient or caregiver picked up the prescription at the pharmacy. The duration of use of each dispensed drug can be estimated from the database by dividing the number of dispensed units by the prescribed number of units to be used per day. The database does not provide information about the indications for use of the medication or registration of non-prescription medication. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. All PHARMO-linked research is in accordance with Dutch privacy and ethical regulations.

Participants

Female patients (≥65 years) with at least one prescription of an antipsychotic drug between 1998 and 2008 were identified. Drugs starting with the four-digit ATC code N05A (with the exception of lithium) were classified as antipsychotics. The date of the first antipsychotic prescription marked the start of follow-up. Patients were then followed up until the end of the study period, the censoring date in the database, or death of the patient, whichever came first. All patients were eligible for inclusion if they had one year of prior history in PHARMO before the start of follow-up, in order to verify the history of UTI. The rationale for including female patients only was because we defined our study outcome of uncomplicated UTI on the basis of the use of nitrofurantoin, which is the first-choice drug for treating uncomplicated UTIs in women in the Netherlands, but not in men.[9]

Exposure definition

Exposure was defined as the use of antipsychotic drugs. For all patients, we classified follow-up time into periods of current use and past use of antipsychotics. To assess periods of current use, treatment episodes were constructed. Antipsychotic treatment episodes were established by summing consecutive drug deliveries by the pharmacy.[11] If an antipsychotic prescription with the same drug was collected by the patient before the theoretical end date of the previous prescription, the number of overlapping days (units at home) was added to the end date of the subsequent antipsychotic prescription. We allowed for a 14-day permissible gap between the theoretical end date of an antipsychotic prescription and the next one. We created separate treatment episodes for individual antipsychotic initially, and combined these episodes to allow concurrent use of multiple types of antipsychotic drugs. If the duration of a subsequent prescription overlapped that of a subscription for another antipsychotic, the patient was considered to have switched therapy and the remaining tablet days from the first prescription were disregarded. After the end of a treatment episode, patients were classified as past users, until a new treatment episode occurred. We chose past antipsychotic use as reference period, because the patient characteristics were then comparable in both timeframes. To allow for time-dependent updates of covariates e.g. potential confounders, periods of current and past use were split into periods of maximally 182 days. The first 14 days of past use were considered a washout period where no events were counted.
Periods of current use were further stratified according to:

I. **Duration** (of each current use episode, not cumulatively over follow-up) in 1-7, 8-14, 15-30, 31-90, >90 days;
II. **Mean number of standardized defined daily doses (DDD) per day**, this is the assumed average maintenance dose per day of a drug used for its main indication in adults and is defined by the World Health Organization (WHO).12 For example, the DDD of haloperidol is 8 mg per day for the treatment of psychosis in adults. In general, older patients receive lower doses of antipsychotic medications than younger patients. We used DDD to create comparative doses for different drugs with different potencies. The DDD was categorized into <0.125, 0.125–0.5, and >0.5 DDD.
III. **Type of antipsychotic:**
    1. Use of atypical antipsychotics (clozapine, olanzapine, quetiapine, tetrabenazine, sulpiride, tiapride, risperidone, aripiprazole);
    2. Use of conventional antipsychotics (bromperidol, chlorprothixene, droperidol,

fluphenazine, flupentixol, fluspirilene, haloperidol, lurasidone, paliperidone, penfluridol, perphenazine, periciazine, pimozide, pipamperone, sertindole, zuclopenthixol);

3. Concurrent use of more than one antipsychotic agent.

Outcome definition: recurrent events

The outcome of interest was the occurrence of uncomplicated UTI. Since the Pharmo database used does not contain medical diagnoses in general practice, the prescription of a therapeutic dosage of nitrofurantoin (50 mg 4 times a day or 100 mg 2 times a day) was used as proxy for uncomplicated UTI. In general, uncomplicated UTI is the sole indication for nitrofurantoin, except for UTI prophylaxis. In those cases the dose is lower and the duration is longer. If a patient received a second prescription of nitrofurantoin within 7 days after the first prescription ended, this was considered one event (cluster). During the event (cluster of days) the patient was not at risk of a recurrent event. As patients may experience several episodes of UTIs, we assessed the occurrence of recurrent UTIs during the whole follow-up period.

Potential confounders

Known risk factors for UTIs that could potentially confound the relationship between antipsychotic drug use and UTIs are age[13], history of UTIs[13], diabetes mellitus[9], being immune compromised[9], stroke[13], urine incontinence[13], cognitive impairment[13], disability in daily living[13], kidney stones, or anomalies of the kidney or urinary tract.[9] Age was added directly to the model as covariate.[13] Proxies were used for some risk factors: prescription of nitrofurantoin in the past year for medical history of UTI[13], use of blood glucose-lowering drugs for diabetes mellitus[9], use of immunosuppressive drugs for increased susceptibility to infection[9], use of alpha-blockers for kidney stones[9], use of urinary antispasmodics e.g. oxybutynin, tolterodine, darifenacin, for incontinence[13], rivastigmine or galantamine for cognitive impairment[13] and distigmine or carbachol for incomplete bladder emptying[9]. For stroke, a hospital diagnosis of stroke was used.[13] No data were available about disability in daily life, or anomalies of the kidney or urinary tract.

Data analysis

Incidence rates for UTIs were calculated as the number of UTIs divided by person-time in current and past exposure periods of antipsychotic use (reference period). The occurrence of an event (UTI) influences the risk of other events. This means that the analysis of recurrent events is complicated by the

dependence of the related events.
Cox proportional hazard regression analysis with Andersen-Gill extension for recurrent events was used to calculate crude and adjusted hazard ratios (HRs) for the association between current use of antipsychotics and risk of recurrent UTI. Patients with maintenance therapy of nitrofurantoin (UTI prophylaxis) were excluded from the analysis. Confounders were added sequentially to the model as follows: age, comedications as a proxy for other diagnoses, and stroke as hospital diagnosis. To adjust the model, covariates were included in the final multivariate model if they induced a change in beta coefficient of at least 10% for the individual covariates. P-values of <0.05 were considered to be statistically significant. Data analysis was conducted with STATA SE 14 and IBM SPSS for Windows, version 22 (IBM Inc., New York, NY).

Results

During the study period, 18,541 women with a first prescription of an antipsychotic drug were identified (mean age at entry into the study 81.9 years, SD 8.1). The characteristics of the study population are displayed in Table 1.

The incidence of UTIs among current antipsychotic users was 29.8/100 person-years versus 20.2/100 person-years in the reference period, during past use, yielding an incidence rate ratio (IRR) 1.47 (95% CI 1.42-1.54). Using Cox-regression analysis, current use of antipsychotics was associated with an increased risk of UTI. Adjustment for age and history of UTI lowered the magnitude of the effect, but it remained statistically significant. Current use of antipsychotics was associated with a 33% increased risk of UTIs compared with past use (adjusted HR 1.33, 95% CI 1.27-1.39). Table 2 shows the results.
The risk of getting a UTI was particularly high in the first week after start of the antipsychotic medication (adjusted HR 3.03, 95% CI 2.63-3.50) and decreased after 3 months (HR 1.22, 95% CI 1.17-1.28). The association of atypical antipsychotic drug use with UTI was dose related in a reverse way. The higher the dose of atypical antipsychotics, the lower the risk of UTI. Whereas the cumulative dose of conventional antipsychotics was dose related (adjusted HR 1.30, 95% CI 1.22-1.38 for DDD <0.25) and (HR 1.59, 95% CI 1.33-1.90 for DDD >0.5.) There was no difference in effect between conventional and atypical antipsychotics. Conventional antipsychotics showed a slightly higher point estimator (HR 1.36, 95% CI 1.30-1.43) than atypical antipsychotics (HR 1.22, 95% CI 1.13-1.30), but 95% confidence interval was overlapping.

Table 1. Characteristics of study population

Characteristic	Number (%) (n=18,541)
Mean age (SD)	81.9 (8.1)
65-74	3742 (20.2%)
75-84	7275 (39.2%)
85+	7524 (40.6%)
Comedication (6 months before index date)	
Antidiabetic drugs	2984 (16.1%)
Systemic glucocorticoids	1885 (10.2%)
Antidementia drugs	324 (1.8%)
Immunosuppressants	107 (0.6%)
Drugs for urinary frequency and incontinence	566 (3.1%)
Maintenance therapy nitrofurantoin	321 (1.7%)
Distigmine	47 (0.3%)
Alpha-blockers	144 (0.8%)
History of urinary tract infection	2521 (13.6%)
Admission (ever before index date)	
Stroke	446 (2.4%)

Table 2. Hazard ratio of uncomplicated urinary tract infections according to nitrofurantoin prescription in female antipsychotic users

	Number of UTIs	Person years
Past use of antipsychotic	3913	19398
Current use of antipsychotic	4671	15664
Analysis within current antipsychotic users		
Duration of antipsychotic use (days)		
1-7	201	335
8-14	130	307
15-30	217	616
31-90	613	1697
>90	3509	12710
Defined daily doses of antipsychotic (DDD)†		
Monotherapy atypical		
<0.125	317	1064
0.125-0.5	650	2606
>0.5	134	655
Monotherapy conventional		
<0.125	1470	4730
0.125-0.5	1754	5565
>0.5	127	491
Type of antipsychotics		
Atypical antipsychotics‡	1101	4325
Conventional antipsychotics§	3351	10786
Concurrent use of more than one antipsychotic	219	553

CI= Confidence interval; HR= Hazard ratio; UTI= urinary tract infection; Full adjusted: adjusted for age and history of urinary tract infection. †DDD= defined daily dose. Defined daily dose of haloperidol for example is 8 mg for treatment of psychosis in adults. ‡clozapine, olanzapine, quetiapine, tetrabenazine, sulpiride, tiapride, risperidone, aripiprazole. § phenothiazines, butyrophenones, indoles, thioxanthenes, diphenylbutylamine*

Crude HR (95% CI)	Age adjusted HR (95% CI)	Full adjusted* HR (95% CI)
1.00 (reference)	1.00 (reference)	1.00 (reference)
1.57 (1.50-1.63)	1.46 (1.39-1.52)	1.33 (1.27-1.39)
3.33 (2.89-3.84)	3.07 (2.66-3.54)	3.03 (2.63-3.50)
2.34 (1.96-2.78)	2.14 (1.80-2.55)	2.04 (1.71-2.43)
1.96 (1.70-2.24)	1.78 (1.54-2.04)	1.71 (1.49-1.96)
2.02 (1.85-2.20)	1.83 (1.68-1.99)	1.76 (1.61-1.91)
1.43 (1.37-1.50)	1.34 (1.28-1.40)	1.22 (1.17-1.28)
1.41 (1.26-1.58)	1.43 (1.28-1.61)	1.29 (1.15-1.45)
1.22 (1.12-1.32)	1.26 (1.16-1.37)	1.20 (1.11-1.31)
1.04 (0.88-1.24)	1.24 (1.04-1.47)	1.15 (0.97-1.36)
1.66 (1.57-1.77)	1.42 (1.34-1.51)	1.30 (1.22-1.38)
1.72 (1.63-1.82)	1.54 (1.46-1.63)	1.40 (1.32-1.48)
1.56 (1.30-1.86)	1.80 (1.51-2.15)	1.59 (1.33-1.90)
1.24 (1.16-1.33)	1.30 (1.22-1.39)	1.22 (1.13-1.30)
1.69 (1.61-1.77)	1.50 (1.43-1.57)	1.36 (1.30-1.43)
2.11 (1.84-2.42)	1.92 (1.67-2.20)	1.67 (1.46-1.91)

Discussion

To our knowledge, this is the first study to report an increased risk of UTIs in patients currently using antipsychotics. We showed that the antipsychotic-associated increased risk of UTIs occurred primarily in the first week of treatment. It is possible that these patients had delirium caused by a UTI, so that the relation in these patients would be the other way around, protopathic bias. This is less likely for patients who were prescribed an antipsychotic first and then nitrofurantoin >7 days after the start of the antipsychotic. We found UTIs to be associated with both conventional and atypical antipsychotics.

It is unclear whether the observed association between current antipsychotic use and UTIs is related to antipsychotic use or the underlying disease or delirium itself. Theoretically, both could be the case. Older female patients with behavioural disturbances of dementia may be more susceptible to UTIs because of malnutrition, wrong wiping after urination, poor hygiene, or going to the toilet less often. Urination is controlled by a complex mechanism that coordinates bladder storage, emptying, and urinary sphincter activity, by regulating smooth muscle tone in the bladder and urethra.[14] Haloperidol, a conventional antipsychotic, is the first choice antipsychotic for the treatment of delirium in Europe.[15] Conventional antipsychotics like haloperidol are in general stronger D2-receptor antagonists than atypical antipsychotics.[14] D2-receptor antagonists have been suggested to influence the capacity and residual volume of the bladder, external urethral sphincter function, and the relaxation pressure and volume of urine at micturition via inhibition of the spinobulbar reflexes.[14] The association of atypical antipsychotic drug use with UTI was dose related in a reverse way. The higher the dose of atypical antipsychotics, the lower the risk of UTI. We don't have a clear explanation for this finding. Maybe the association between antipsychotics and UTI is smaller when there is less D2-receptor antagonism. Also anticholinergic effects of antipsychotics may play a role. The retention of urine caused by these agents can lead to bacterial growth, and UTI's. However, in our sample, the prevalence of antipsychotics with a strong anticholinergic profile (thioridazine, clozapine, chlorpromazine, olanzapine was very low.[16] The association of antipsychotic drug use and different infections (pneumonia, UTI's) suggests that there is an effect of antipsychotic drugs on the immune system. Psychotropic medications have been shown to modulate immune activation. However, the effects of individual psychotropic agents on the immune system and how these might contribute to their efficacy remain largely unclear.[17]

The strengths of this study are its population-based nature, the substantial sample size, and the reliable collection of longitudinal data on antipsychotic and nitrofurantoin prescriptions. However, it also had limitations. The use of a prescription database limited the ability to determine comorbidity except by the proxy of a prescription. As we did not have access to clinical data, the presence of a UTI was based on the prescription of nitrofurantoin, which could have led to misclassification. The Dutch College of General Practitioners (NHG) Clinical guideline Urinary Tract Infections gives nitrofurantoin as the first-choice treatment for uncomplicated UTIs in non-pregnant women.[9] It is possible that there was an over-diagnosis of UTI, particularly if nitrofurantoin was started before confirmatory results of a UTI were available. This is especially relevant to the possibility that an antipsychotic was prescribed for agitation or delirium that was misattributed to a UTI.[18] In general, Dutch physicians are reluctant to prescribe antimicrobial drugs because of the risk of resistance, and treat only those patients with a proven or very high suspicion of infection.[19] For this reason, we think that the likelihood of misclassification is limited. Complicated UTIs are treated with antibiotics that reach urine and tissue, such as fluoroquinolones,[9] and so we cannot generalize our findings to complicated UTIs. The association between uncomplicated UTIs and antipsychotic use is probably an underestimation, because antibiotics such as fosfomycin and trimethoprim are also prescribed for uncomplicated UTIs.[9]

In conclusion, our results show that the risk of uncomplicated UTIs in older, female users of antipsychotics is increased after medication is started. Clinicians should be alert to the occurrence of UTIs after the start of an antipsychotic drug, especially in the first week. Further research is necessary to confirm these findings. If this is also the case for men using antipsychotics and women with complicated UTIs remains to be established in future studies.

References

1. Hollingworth SA, Siskind DJ, Nissen LM, et al. Patterns of antipsychotic medication use in Australia 2002-2007. Aust N Z J Psychiatry 2010;44:372-7.
2. Marston L, Nazareth I, Petersen I, et al. Prescribing of antipsychotics in UK primary care: a cohort study. BMJ Open 2014;4:e006135,2014-006135.
3. FDA. Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances. Washington, DC, Department of Health and Human Services. 2005. Available at: http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm053171. Accessed January, 2017.
4. FDA. Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances, conventional antipsychotics. Washington, DC, Department of Health and Human Services. 2008. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm. Accessed January, 2017.
5. Knol W, van Marum RJ, Jansen PA, et al. Antipsychotic drug use and risk of pneumonia in elderly people. J Am Geriatr Soc 2008;56:661-6.
6. Huybrechts KF, Schneeweiss S, Gerhard T, et al. Comparative safety of antipsychotic medications in nursing home residents. J Am Geriatr Soc 2012;60:420-9.
7. Saddichha S, Kumar M. Antipsychotic-induced urinary dysfunction: anticholinergic effect or otherwise?. BMJ Case Rep 2009;2009:10.1136/bcr.02.2009.1547.
8. Matthews SJ, Lancaster JW. Urinary tract infections in the elderly population. Am J Geriatr Pharmacother 2011;9:286-309.
9. Dutch College of General Practitioners (NHG) (2013) Clinical guideline (M05): Urinary Tract Infections. Available at: https://www.nhg.org/standaarden/samenvatting/urineweginfecties. Accessed January, 2017.
10. Buurma H, Bouvy ML, De Smet PA, et al. Prevalence and determinants of pharmacy shopping behaviour. J Clin Pharm Ther 2008;33:17-23.
11. Gardarsdottir H, Souverein PC, Egberts TC, et al. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. J Clin Epidemiol 2010;63:422-7.
12. WHO Collaborating Center, Definition of DDD defined daily dose. Available at: http://www.whocc.no/ddd/definition_and_general_considera/. Accessed January, 2017.
13. Caljouw MA, den Elzen WP, Cools HJ, et al. Predictive factors of urinary tract infections among the oldest old in the general population. A population-based prospective follow-up study. BMC Med 2011;9:57,7015-9-57.
14. Faure Walker N, Brinchmann K, Batura D. Linking the evidence between urinary retention and antipsychotic or antidepressant drugs: A systematic review. Neurourol Urodyn 2016;35(8):866-874.
15. Morandi A, Davis D, Taylor JK, et al. Consensus and variations in opinions on delirium care: a survey of European delirium specialists. Int Psychogeriatr 2013;25:2067-75.
16. Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr Soc 2008;56:1333-41.
17. Baumeister D, Ciufolini S, Mondelli V. Effects of psychotropic drugs on inflammation: consequence or mediator of therapeutic effects in psychiatric treatment?. Psychopharmacology (Berl) 2016;233:1575-89.

18. Woodford HJ, George J. Diagnosis and management of urinary tract infection in hospitalized older people. J Am Geriatr Soc 2009;57:107-14.
19. van de Sande-Bruinsma N, Grundmann H, Verloo D, et al. Antimicrobial drug use and resistance in Europe. Emerg Infect Dis 2008;14:1722-30.

3.3

Astrid M. van Strien, Patrick C. Souverein, Carolina (Karen) J.P.W. Keijsers, Eibert R. Heerdink, Hieronymus (Jeroen) J. Derijks, Rob J. van Marum

Submitted

Association between urinary tract infections and antipsychotic drug use in older patients

Abstract

Background/Objectives: Antipsychotic drugs are frequently prescribed to elderly patients, but they are associated with serious adverse effects. The objective of the current study was to investigate the association between use of antipsychotics in older patients and the risk of urinary tract infections (UTIs).

Design/Setting/Participants: Cohort study. Data were obtained from the Clinical Practice Research Datalink (CPRD) from 1 January 2000 – 29 September 2016. Participants were primary care patients ≥65 years in the United Kingdom with at least one prescription of an oral antipsychotic drug.

Measurements: Incidence of UTIs was calculated with and without exposure to antipsychotic drugs. Cox proportional hazard regression analysis with Andersen-Gill extension for recurrent events was used to calculate crude and adjusted hazard ratios (HRs) with 95% confidence interval (CI).

Results: During the study period, 191,827 patients (63.7% women, mean age 77 years) with a first prescription for an oral antipsychotic drug were identified. Current use of antipsychotics was associated with an increased risk of UTI compared with past use (adjusted HR 1.31, 95% CI 1.28-1.34). This effect was strongest in the first 14 days of antipsychotic use (adjusted HR 1.83, 95% CI 1.73-1.95) and in patients who used more than one antipsychotic drug concomitantly (adjusted HR 1.64, 95% CI 1.45-1.87). The risk was slightly higher for conventional antipsychotics (adjusted HR 1.37, 95% CI 1.33-1.41) than for atypical antipsychotics (adjusted HR 1.24, 95% CI 1.21-1.28). Stratification by sex showed that risk estimates were slightly higher in men than in women.

Conclusion: Use of antipsychotics was associated with an increased risk of UTIs in both men and women, particularly in the first weeks after the start of treatment.

Introduction

Antipsychotic drugs are frequently prescribed to older patients. A recent study in the United Kingdom reported a prevalence of antipsychotic drug use of 1% in a primary care setting.[1] However, antipsychotics may cause serious adverse effects, and treatment indications are not always rational.[1] For instance, antipsychotics are still commonly prescribed to people with a diagnosis of dementia, contrary to clinical guidelines.[1] In 2008, The Food and Drug Administration determined that the treatment of behavioral disorders with antipsychotics in elderly patients with dementia was associated with increased mortality,[2, 3] although the causes of this increased mortality are not completely understood. Potential explanations include that antipsychotic drug use is associated with an increased risk of cardiovascular events (e.g., stroke, thromboembolic events, cardiac arrhythmia) and infections (e.g., pneumonia).[4] A recent study in which the prescription of nitrofurantoin was used as proxy for uncomplicated urinary tract infections (UTIs) showed an increased risk of uncomplicated UTIs in women using antipsychotic drugs.[5] A strong temporal relationship was found, with the risk of being treated for an UTI being higher in the first week of treatment (adjusted hazard ratio 3.03, 95% confidence interval 2.63-3.50) and decreasing after 3 months (adjusted HR 1.22, 95% CI 1.17-1.28).[5] Urinary tract infections are a common problem in elderly individuals, in residents of long-term care facilities, and in hospitalized patients. Indeed, in these first two populations UTIs are the number one cause of infection.[6] It is unknown whether the observed risk of uncomplicated UTIs can be extrapolated to all UTIs and to male users of antipsychotics.

The objective of the current study was to investigate the association between use of antipsychotics in older men and women and the risk of UTIs, both complicated and uncomplicated.

Methods

Design

This study was designed as a cohort study of patients (≥65 years) in primary care with current or past use of antipsychotics.

Setting

Data were obtained from the Clinical Practice Research Datalink (CPRD, http://www.CPRD.com), an anonymized database containing computerized medical records of 674 primary care practices in the United Kingdom (UK), representing 6.9% of the population.[7,8] Data recorded in the CPRD include demographic information, prescription details, clinical events, specialist referrals, hospital admissions and major outcomes since 1987.[7] Primary care diagnoses are recorded in the CPRD, using a hierarchical clinical coding system (Read codes).[7]

The study protocol was approved by the Independent Scientific Advisory Committee of CPRD (protocol number 16_272R). Patient information is only available anonymized and de-identified in the database, and hence informed consent was not needed from patients.

Participants

Patients aged 65 years or older with at least one prescription for an antipsychotic in the period 1 January 2000 – 29 September 2016 were identified in the CPRD. Only patients with at least 1 year of valid history, before their first prescription of antipsychotic drug, were included. This was in order to verify the previous drug use and history of UTIs. The date of the first antipsychotic prescription marked the start of follow-up. Patients were followed up until the end of the study period, transfer out of the practice, last collection date for the practice, the date of a first prescription of an injectable antipsychotic, or death of the patient, whichever event occurred first.

Exposure definition

Exposure was defined as the use of antipsychotic drugs. Follow-up for each patient was classified into periods of antipsychotic use (current use, i.e. exposed) and periods of non-use (past use, i.e. non-exposed); patients could switch between periods of current and past use. We chose past antipsychotic use as reference, because the patient characteristics were then comparable in both timeframes.

Antipsychotic drug use was defined as the use of oral antipsychotics, such as tablets and solutions, because the duration of treatment episodes is not

always clear with depot (injectable) formulations. Prescriptions were retrieved from the CPRD. Information on general practitioner-prescribed medications was extracted using appropriate British National Formulary (BNF) medicine codes. For all patients, antipsychotic treatment episodes were constructed using the method of Gardarsdottir et al.[9] A treatment episode was defined as a series of successive prescriptions for antipsychotics written out by the general practitioner, taking dose changes and product changes into account. If a new prescription for the same antipsychotic was issued before the theoretical end date of the previous prescription, the number of overlapping days (units at home) was added to the end date of the subsequent antipsychotic prescription. If a different strength of the same type of antipsychotic was prescribed, the remaining days were reset to zero. We used a 14-day permissible gap between the end date of one prescription and the start of the next prescription, to allow for irregular use. If the next prescription started more than 14 days after the end of the old prescription, we considered it a new treatment episode.[9] We created separate treatment episodes for individual antipsychotics initially, and combined these episodes to allow concurrent use of multiple types of antipsychotic drugs. After each treatment episode, a washout period of 14 days was applied in which the patient was deemed not at risk of a study outcome. After the washout period, an episode of past use started (the reference period). Periods of current antipsychotic use were then further stratified according to the following:

I. **Duration** (of each treatment episode, not cumulatively over follow-up) in 1-14, 15-30, 31-90, >90 days;
II. **Standardized defined daily doses** (DDD), this is the assumed average maintenance dose/day for a drug used for its main indication in adults and is defined by the World Health Organization (WHO).[10] For example, the DDD of haloperidol is 8 mg/day for the treatment of psychosis in adults. In general, older patients receive lower doses of antipsychotics than younger patients. DDD was categorized into less than 0.125, 0.125–0.5, and more than 0.5 DDD.
III. **Type of antipsychotic:**
    1. Use of atypical antipsychotics (clozapine, olanzapine, quetiapine, amisulpiride, sulpiride, risperidone, aripiprazole),
    2. Use of conventional antipsychotics (benperidol, chlorpromazine, droperidol, flupentixol, fluphenazine, haloperidol, levomepromazine, lurasidone, pericyazine, perphenazine, pimozide, prochlorperazine, promazine, sertindole, thioridazine, trifluoperazine, zotepine, zuclopenthixol,
    3. Concomittant use of more than one antipsychotic agent.

Outcome definition

Events were defined as diagnosis of an UTI, as assessed by clinical diagnoses and referrals. As patients can experience several UTIs a year, we assessed the occurrence of UTIs during the entire follow-up period. The duration of one event was the date of the diagnosis of UTI plus 7 days. If a patient had a second diagnosis of UTI within 30 days, this was considered as one event, or cluster. UTIs were defined as Read codes for UTIs, uncomplicated UTI, cystitis, prostatitis, urosepsis, or pyelonephritis. We did not use therapy as outcome, because antibiotics for complicated UTIs are prescribed for several indications other than UTIs.

Potential confounders

We selected the following known risk factors for UTIs as potential confounders for the relationship between antipsychotic drug use and UTI: age[11], sex[12], recurrent UTIs[11], diabetes mellitus[12], immunosuppressive medication[12], stroke[11], urine incontinence[11], cognitive impairment or dementia[11], disability in activities of daily living[11], presence of a cystocele[13], catheterization[13], kidney stones or anomalies of the kidney or urinary tract[12], urinary retention[14], malignancy[14]. Radiotherapy and surgery for prostate cancer or prostatic processes[14] are additional risk factors for UTIs in men. Unfortunately, we could not adjust for disability in activities of daily living reported in the CPRD. The other potential confounders were retrieved from medical records, using Read codes and added as covariates.

Data analysis

Hazard ratios were calculated for the association between current or past use of antipsychotics (reference period) and the risk of UTI. The occurrence of an event (UTI) influences the risk of other events. This means that the analysis of recurrent events is complicated by the dependence on related events. Therefore Cox proportional hazard regression analysis with Andersen-Gill extension for recurrent events was chosen to calculate crude and adjusted HRs for the association between current use of antipsychotics and risk of UTI in comparison to past use (reference period). To allow for time-dependent updates of covariates, exposed and non-exposed periods were split into periods of maximally 182 days, if necessary. Confounders were added sequentially to the model as follows: age, sex, comorbidity, and drugs. Beside age and sex, covariates were included in the final multivariate model if they induced a change in beta coefficient of at least 10% for the individual covariates. We performed a separate

analysis in which we censored patients after their first UTI event. In this analysis we did not look at recurrent events. Further, we stratified the data for sex. Data analysis was conducted with STATA SE 14. P-values of <0.05 were considered to be statistically significant.

Results

During the study period, 191,827 patients with a first prescription of an oral antipsychotic drug were identified (63.7% women, mean age 77 years). The characteristics of the study population are shown in Table 1.

Table 1. Characteristics of study population

Characteristic	Number (n= 191,827)	Percentage (%)
Females	122,203	(63.7%)
Mean age (SD)	77.9	(SD 8.0)
History of urinary tract infection	52,466	(27.4%)
Urine incontinence	2,317	(1.2%)
Urinary retention	609	(0.3%)
Catheterization	648	(0.3%)
Cystocele or prolapse	12,442	(6.5%)
Kidney stones or anomalies of kidney or urinary tract	89	(0.1%)
Males: radiotherapy or surgery for prostate cancer	4,652	(6.7%)
Stroke	13,163	(6.9%)
Diabetes mellitus	25,236	(13.2%)
Malignancy	43,758	(22.8%)
Cognitive impairment or dementia	15,731	(8.2%)
Immune compromised: using corticosteroids or immunosuppressants or diagnosis HIV	16,858	(8.8%)

In total, 84,499 UTIs occurred in 38,887 unique patients. On Cox regression analysis, current use of antipsychotics was found to be associated with a 30% increased risk of UTI compared with past use (adjusted HR 1.31, 95% CI 1.28-1.34)

(Table 2, page 80). Adjustment for age and dementia lowered the magnitude of the effect, but it remained statistically significant. Dementia was the only confounder that changed the beta coefficient by more than 10%. We found 75,377 events of uncomplicated UTI's (89.2%), 462 events of prostatitis (0.5%), 764 events of pyelonephritis or urosepsis (0.9%) and 7891 events of recurrent UTI (9.3%) and 5 events of UTI in pregnancy (0.0%, probably misclassified).

We found a slightly higher increased risk of UTI with current use of antipsychotics compared with past use when we censored patients after the first UTI event (HR 1.94, 95% CI 1.89-2.00), (adjusted for age and sex HR 1.80, 95% CI 1.76-1.85) and (full adjusted HR 1.55, 95% CI 1.51-1.60). The UTI risk was slightly higher for current use of conventional antipsychotics (adjusted HR 1.37, 95% CI 1.33-1.41) than for current use of atypical antipsychotics (adjusted HR 1.24, 95% CI 1.21-1.28). The strongest effect was found in the first 14 days of current use (adjusted HR 1.83, 95% CI 1.73-1.95) and in patients who were current users of more than one antipsychotic drug concomitantly (adjusted HR 1.64, 95% CI 1.45-1.87).

Stratification by sex showed that risk estimates were slightly higher in men than in women. We didn't perform analysis stratified for complicated urinary tract infections, because only 0.9% of the events were classified with a Read code for urosepsis or pyelonephritis. Table 3 (page 81) shows the results with the differences between men and women.

Table 2. Hazard ratio for urinary tract infections in antipsychotic users

	Number of UTIs	Person years	Crude HR (95% CI)	Age/sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)
Past use of antipsychotic	72,350	747,267	1.00 (reference)	1.00 (reference)	1.00 (reference)
Current use of antipsychotic	12,149	79,571	1.54 (1.51-1.57)	1.43 (1.40-1.46)	1.31 (1.28-1.34)
Analysis for current antipsychotic users					
Duration of antipsychotic use (days)					
1-14	1,068	6,282	1.70 (1.60-1.81)	1.75 (1.65-1.86)	1.83 (1.73-1.95)
15-30	760	5,049	1.51 (1.41-1.62)	1.51 (1.41-1.63)	1.53 (1.42-1.64)
31-90	1,598	9,484	1.68 (1.60-1.77)	1.62 (1.54-1.70)	1.59 (1.51-1.67)
>90	8,723	58,756	1.51 (1.47-1.54)	1.36 (1.33-1.39)	1.20 (1.17-1.23)
Defined daily doses of antipsychotic drug (DDD)†					
<0.125	3,242	18,084	1.80 (1.74-1.87)	1.59 (1.54-1.65)	1.38 (1.32-1.43)
0.125-0.5	4,607	29,576	1.60 (1.55-1.64)	1.47 (1.42-1.51)	1.30 (1.26-1.34)
>0.5	4,050	31,911	1.31 (1.27-1.36)	1.27 (1.23-1.31)	1.26 (1.22-1.30)
Type of antipsychotic drug					
Atypical antipsychotics‡	5,652	42,437	1.34 (1.30-1.37)	1.27 (1.23-1.30)	1.24 (1.21-1.28)
Conventional antipsychotics§	6,247	36,032	1.76 (1.72-1.81)	1.60 (1.56-1.64)	1.37 (1.33-1.41)
Concomitant use of more than one antipsychotic	250	1,102	2.26 (1.99-2.56)	2.01 (1.78-2.28)	1.64 (1.45-1.87)

CI= Confidence interval; HR= Hazard ratio; UTI= urinary tract infection;
† DDD= defined daily dose. Defined daily dose of haloperidol for example is 8 mg for treatment of psychosis in adults. ‡ clozapine, olanzapine, quetiapine, amisulpiride, sulpiride, risperidone, aripiprazole. § benperidol, chlorpromazine, droperidol, flupentixol, fluphenazine, haloperidol, levomepromazine, lurasidone, pericyazine, perphenazine, pimozide, prochlorperazine, promazine, sertindole, thioridazine, trifluoperazine, zotepine, zuclopentixol.

Table 3. Hazard ratio for urinary tract infections in male and female antipsychotic users

	Fully adjusted HR (95% CI) men	Fully adjusted HR (95% CI) women
Past use of antipsychotic	1.00 (reference)	1.00 (reference)
Current use of antipsychotic	1.43 (1.37-1.50)	1.28 (1.25-1.31)
Current antipsychotic use		
Duration of antipsychotic use (days)		
1-14	2.06 (1.82-2.33)	1.77 (1.65-1.90)
15-30	1.70 (1.47-1.97)	1.48 (1.35-1.60)
31-90	1.80 (1.62-1.98)	1.53 (1.44-1.62)
>90	1.28 (1.21-1.34)	1.19 (1.15-1.22)
Defined daily doses of antipsychotic drug (DDD)†		
<0.125	1.50 (1.39-1.62)	1.35 (1.29-1.41)
0.125-0.5	1.43 (1.34-1.53)	1.27 (1.23-1.32)
>0.5	1.36 (1.27-1.46)	1.24 (1.20-1.28)
Type of antipsychotic drug		
Atypical antipsychotics‡	1.36 (1.28-1.45)	1.21 (1.18-1.25)
Conventional antipsychotics §	1.48 (1.28-1.45)	1.35 (1.30-1.39)
Concomitant use of more than one antipsychotic	1.92 (1.50-2.48)	1.58 (1.37-1.83)

CI= Confidence interval; HR= Hazard ratio; UTI= urinary tract infection; † DDD= defined daily dose. Defined daily dose of haloperidol for example is 8 mg for treatment of psychosis in adults. ‡ clozapine, olanzapine, quetiapine, amisulpiride, sulpiride, risperidone, aripiprazole. § benperidol, chlorpromazine, droperidol, flupentixol, fluphenazine, haloperidol, levomepromazine, lurasidone, pericyazine, perphenazine, pimozide, prochlorperazine, promazine, sertindole, thioridazine, trifluoperazine, zotepine, zuclopentixol.

Discussion

To our knowledge, this is the second study to report an increased risk of UTIs in patients currently using antipsychotics. Our previous study showed an increased risk of being treated with nitrofurantoin for an uncomplicated UTI in older female users of antipsychotics in a Dutch population.[5] This study shows an increased risk of all UTIs in male and female users. The antipsychotic-associated increased risk occurred primarily in the first 2 weeks of treatment. It is possible that patients had a delirium caused by a UTI, so that the relation is the other way around, protopathic bias. However, this is less likely for patients who were prescribed an antipsychotic first and who had a UTI >14 days after the start of the antipsychotic.
The observed association between current antipsychotic use and UTI could be related to the antipsychotic itself or to the underlying disease or psychosis. While the potential mechanisms underlying the association remain largely unknown, several mechanisms have been proposed. For instance, urinary tract problems, such as incontinence and urine retention, both of which increase susceptibility to UTIs, are reported in users of both typical and atypical antipsychotics.[15] First-generation antipsychotics that act predominantly on dopamine D2 receptors are not selective and cause a variety of side effects – D2-receptor antagonists influence the capacity and residual volume of the bladder, external urethral sphincter function, and the relaxation pressure and volume of urine at micturition via inhibition of spinobulbar reflexes.[16] The anticholinergic effects of antipsychotics may also have a role.

The association between antipsychotic drug use and different infections (pneumonia, UTIs) suggests that these drugs affect the immune system. While psychotropic medications have been shown to modulate immune activation, the effects of individual psychotropic agents on the immune system and how these effects might contribute to their efficacy remain largely unclear.[17] A recent study showed that haloperidol lowered interleukin-6 and cortisol levels in healthy volunteers,[18] and interleukin-6 and cortisol have been shown to have a role in acute or chronic stress, suppressing the immune system.[18]
We found that dementia was the only confounder in our analysis of all the comorbidities, which are known risk factor to influence the occurrence of UTI. Older patients with behavioral disturbances of dementia may be more susceptible to UTIs because of malnutrition, wrong wiping after urination, poor hygiene, or going to the toilet less often. In a group of younger patients with acute

psychosis, UTIs occurred much more often than in healthy controls and were related to the psychosis itself.[19]

The strengths of this study are its population-based nature, the substantial sample size, and the reliable collection of longitudinal data on antipsychotic prescriptions issued by general practitioners and the diagnosis of UTI. The quality of data in English general practice is enhanced by the use of the Quality and Outcomes Framework.[7,8]
However, the study also had some limitations. The presence of UTI was based on Read codes, which can lead to misclassification. Moreover, UTI may be defined differently. We expect that general practitioners in the UK follow the Scottish Intercollegiate Guidelines Network (SIGN) for diagnosing UTI.[20] According to this guideline, the diagnosis of UTI is primarily based on symptoms and signs in combination with bacteria or white cells in the urine. The diagnosis of upper UTI is based on evidence of UTI with symptoms suggestive of pyelonephritis (loin pain, flank tenderness, fever, rigor, or other manifestations of systemic inflammatory response).[20] However, older patients can present with atypical symptoms, such as confusion.[6] There was substantial misclassification of men with UTI. Of the total number of 16,055 UTI events in men, 13,932 (87%) were assigned a Read code for uncomplicated UTI, even though according to the SIGN guidelines used in the UK, all UTIs in men should be considered complicated UTIs.
Another potential limitation is underestimation of the true magnitude of the effect, because many patients may self-treat their UTI or not go to their general practitioner for their symptoms. Furthermore, the antipsychotic prescriptions were issued by general practitioners; there were no data for prescriptions issued by medical specialists.

In conclusion, the use of antipsychotics was associated with an increased risk of UTIs in both older men and women, particularly in the first weeks of treatment. This relation should be recognized by doctors prescribing for older patients, and by older patients themselves. In older patients, antipsychotic use should be restricted to those patients for whom treatment is absolutely necessary.

References

1. Marston L, Nazareth I, Petersen I, et al. Prescribing of antipsychotics in UK primary care: a cohort study. BMJ Open 2014;4:e006135,2014-006135.
2. FDA. Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances. Washington, DC, Department of Health and Human Services. 2005. Available at: http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm053171. Accessed December, 2016.
3. FDA. Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances, conventional antipsychotics. Washington, DC, Department of Health and Human Services. 2008. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm. Accessed December, 2016.
4. Knol W, van Marum RJ, Jansen PA, et al. Antipsychotic drug use and risk of pneumonia in elderly people. J Am Geriatr Soc 2008;56:661-6.
5. van Strien AM, Souverein PC, Keijsers CJPW, et al. Association of urinary tract infections with antipsychotic drug use in older females. Maturitas 2017;98:46-50.
6. Matthews SJ, Lancaster JW. Urinary tract infections in the elderly population. Am J Geriatr Pharmacother 2011;9:286-309.
7. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44:827-36.
8. Herrett E, Thomas SL, Schoonen WM, et al. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol 2010;69:4-14.
9. Gardarsdottir H, Souverein PC, Egberts TC, et al. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. J Clin Epidemiol 2010;63:422-7.
10. WHO Collaborating Center, Definition of DDD defined daily dose. Available at: http://www.whocc.no/ddd/definition_and_general_considera/. Accessed December, 2016.
11. Caljouw MA, den Elzen WP, Cools HJ, et al. Predictive factors of urinary tract infections among the oldest old in the general population. A population-based prospective follow-up study. BMC Med 2011;9:57,7015-9-57.
12. Dutch College of General Practitioners (NHG) (2013) Clinical guideline (M05): Urinary Tract Infections. Available at: https://www.nhg.org/standaarden/samenvatting/urineweginfecties. Accessed December, 2016.
13. Raz R. Urinary tract infection in postmenopausal women. Korean J Urol 2011;52:801-8.
14. Heppner HJ, Yapan F, Wiedemann A. Urosepsis in Geriatric Patients. Aktuelle Urol 2016;47:54-9.
15. Saddichha S, Kumar M. Antipsychotic-induced urinary dysfunction: anticholinergic effect or otherwise?. BMJ Case Rep 2009;2009:10.1136/bcr.02.2009.1547. Epub 2009 May 21.
16. Faure Walker N, Brinchmann K, Batura D. Linking the evidence between urinary retention and antipsychotic or antidepressant drugs: A systematic review. Neurourol Urodyn 2015.
17. Baumeister D, Ciufolini S, Mondelli V. Effects of psychotropic drugs on inflammation: consequence or mediator of therapeutic effects in psychiatric treatment?. Psychopharmacology (Berl) 2016;233:1575-89.

18. Handley R, Mondelli V, Zelaya F, et al. Effects of antipsychotics on cortisol, interleukin-6 and hippocampal perfusion in healthy volunteers. Schizophr Res 2016;174:99-105.
19. Graham KL, Carson CM, Ezeoke A, et al. Urinary tract infections in acute psychosis. J Clin Psychiatry 2014;75:379-85.
20. Healthcare Improvement Scotland: SIGN 88: Managment of suspected bacterial urinary tract infection in adults. Available at: http://www.sign.ac.uk/guidelines/fulltext/88/. Accessed December, 2016.

4.

How to recognize and measure side effects in antipsychotic users?

Astrid M. van Strien, Carolina (Karen) J.P.W. Keijsers, Hieronymus (Jeroen) J. Derijks, Rob J. van Marum

Published as
J Psychopharmacol. 2015 Aug;29(8):857-66

Rating scales to measure side effects of antipsychotic medication: a systematic review

Abstract

Introduction: Many patients experience side effects during treatment with antipsychotics. This article reviews the clinical use and psychometric characteristics of rating scales used to assess side effects in patients treated with antipsychotics.

Methods: A systematic literature search was performed using the electronic databases PubMed and Embase, with predefined search terms.

Results: In total 52 different scales were used in the 440 articles retrieved. For multiple side effects measured with one scale, the Udvalg for Kliniske Undersøgelser Side Effects Rating Scale for Clinicians (UKU-SERS-Clin) was used the most, whereas the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) had the best psychometric characteristics (Cronbach's α 0.81 and test-retest reliability 0.89). The Simpson Angus Scale (SAS) was used the most to rate extrapyramidal side effects, although the Maryland Psychiatric Research Center scale (MPRC scale) had the best characteristics (Cronbach's α 0.80, test-retest reliability 0.92 and inter-rater reliability 0.81-0.90). The Arizona Sexual Experience Scale (ASEX) was used the most to assess sexual dysfunction, but the Antipsychotics and Sexual functioning Questionnaire (ASFQ) and the Nagoya Sexual Functioning Questionnaire had the best characteristics.

Conclusion: This review will help researchers and clinicians make a purpose-oriented choice of which scale to use

Systematic review registration number: CRD42014013010.

Introduction

Antipsychotics are used worldwide for the treatment of schizophrenia, delirium, and the neuropsychiatric symptoms of dementia.[1] Unfortunately, many patients experience side effects during treatment, which may result in an impaired quality of life and early treatment discontinuation.[2,3] About half of the patients with schizophrenia experience one or more side effects.[4] The side effects of antipsychotic use for delirium have not been studied systematically,[5] but nearly half of a group of elderly patients using haloperidol, experienced parkinsonism.[6] Rating scales have been developed to evaluate the side effects of antipsychotics, such as extrapyramidal symptoms, sedation, weight gain, and sexual dysfunction.[7] However, these scales mostly evaluate a single side effect, for example parkinsonism[8] or sexual functioning,[9] and are often used for drugs other than antipsychotics alone, such as the rating scales for drug-induced parkinsonism.[8] There have been few studies of scales evaluating multiple side effects, although the use of one scale instead of several separate scales can have advantages (e.g., less time consuming) and might provide a better insight into the overall side effect profile. Lastly, rating scales can be divided into those for use in research and those for use in daily clinical practice. While psychometric characteristics are of major importance in a research setting and usability is of secondary importance, ease of use is important in a clinical setting.[7]

To date, there has been no clear review of rating scales, and their psychometric characteristics, used to assess the side effects of antipsychotics. This article reviews the clinical use and psychometric characteristics of rating scales for evaluating the side effects of antipsychotics.

Methods

This systematic review was performed using the PRISMA guidelines for systematic reviews and meta-analysis.[10] The protocol was registered under PROSPERO registration number: CRD42014013010.

Eligibility of articles

Articles describing rating scales for antipsychotic-induced side effects, written in English and Dutch, were considered eligible.

Data sources and search strategy

The databases PubMed and Embase were searched on 17 July, 2014 without limits. The search syntax used is depicted in Figure 1. All duplicate articles were excluded and the remaining articles were screened consecutively for title, abstract, and full text. If an abstract was not available, the full text of the article was screened. If the full-text article was not retrievable from the corresponding author or from national university libraries, the article was excluded. The references of the included articles were checked, in a snowball search.

Figure 1. Search syntax in Pubmed.

Pubmed [title/abstract]	Scale OR instrument
AND	
Pubmed [title/abstract]	drug induced OR adverse drug reaction OR adverse drug OR side effect OR adverse drug event OR adverse effect
AND	
Pubmed [title/abstract]	antipsychotic OR neuroleptic

Equal search strategy in Embase. No limits were used

Study selection

First, all titles were screened for relevance. The following exclusion criteria were used: (a) animal studies or non-human studies, (b) articles about children, (c) articles not about antipsychotics, (d) no rating scale discussed (if there was doubt about whether a rating scale was used, the article was not excluded) (e) articles not about adverse events or side effects, (f) side effect that was not measurable with a questionnaire or rating scale, e.g. prolonged QTc time is only measurable with an electrocardiogram (ECG), which we do not consider a rating scale. Second, the abstracts of selected articles were screened and articles were excluded with the same exclusion criteria as mentioned above and (g) a scale to measure side effects in antipsychotics was not used. Third, all possibly relevant articles were screened using the following exclusion criteria: (a) article not about adverse event scale in adults, (b) only congress abstract available, (c) full text not available, (d) language other than English or Dutch, (e) review not about side effect scales. The references of the included articles were then searched for additional articles, which were then screened as above.

The reviewers (AvS, CK) reached consensus on the eligibility of the studies after discussion based on the above eligibility and exclusion criteria.

Data extraction

Two authors (AvS and CK) independently extracted data on the number of times a rating scale was used and its psychometric characteristics. If the focus of the study was on the psychometric characteristics of the scale, the article was considered a validation study. Articles in which a rating scale was used, were considered application studies.

Strategy for data synthesis

The rating scales were classified as multidomain when multiple side effects were assessed and as single domain when only extrapyramidal symptoms or only sexual dysfunction was assessed. In the application studies, the number of times the scales were used was counted for each scale. Data from the validation studies were used to distil the psychometric characteristics of the rating scales. No additional and/or meta-analyses were performed.

Validation studies describing psychometric characteristics

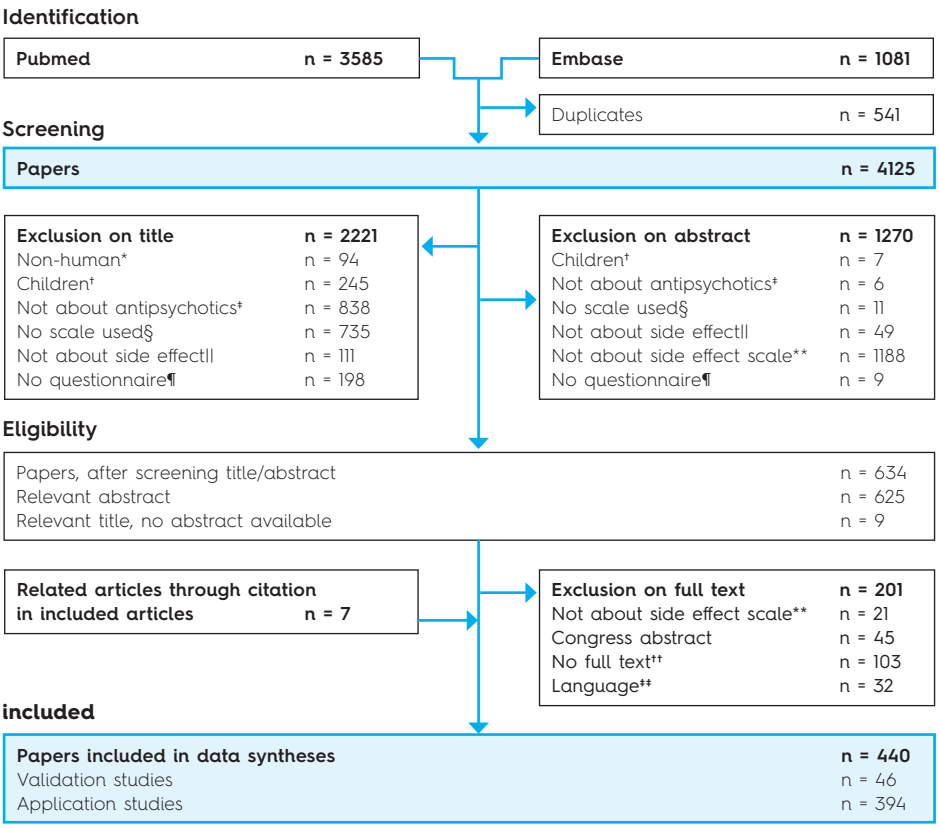
Psychometric characteristics are described in terms of reliability and validity. Reliability can be expressed in terms of internal consistency, inter-rater reliability, and test-retest reliability. Internal consistency was assessed with Cronbach's alpha, which identifies which items contribute to overall reliability, since each and every item in a rating scale has to be individually assessed for variability. Cronbach's alpha values of 0.60–0.70 were considered acceptable and values higher than 0.70 as good.[11] Inter-rater reliability and test-retest reliability or intra-rater reliability can be measured with Pearson's correlation coefficient r, Spearman's rho (ρ), intra-class correlation coefficient (ICC), or Kappa (κ). These are all correlation coefficients and a single value can be calculated to express the relationship. There is no general agreement about how to interpret the different indices of correlation and degrees of agreement. Values of 0.40–0.70 were considered to reflect a moderate correlation and values higher than 0.70 as a high correlation.[12] Validity can be expressed in terms of face validity, content validity, construct validity, convergent validity, divergent validity, and predictive validity, using correlation coefficients, as described above. Construct and convergent validity were considered sufficient if the correlation coefficient was higher than 0.70; correlation coefficients of less than 0.40 were considered to be sufficient for divergent validity.[13]

Results

Search results

Figure 2 shows the flowchart of the review. Of the 4666 articles retrieved, 440 described an antipsychotic side effects scale. Of these 440 articles, 46 articles reported the psychometric characteristics of the scale and the other 394 articles reported the use of the scale.

Figure 2. Search results with reasons for exclusion



** Exclusion criteria: *Animal studies or non-human studies †Articles about children or adolescents ‡Articles not about antipsychotics §Articles not about a rating scale ||Articles not about side effects ¶Articles about side effects not measurable with a questionnaire **Articles that report using a scale and articles report side effect, but not a scale about side effects ††No full text = not available in full text for screening, despite all efforts, and thus excluded. ‡‡Language = language other than English or Dutch*

Table 1. Frequency of application and validation of rating scales

	Rating scale	Application studies	Validation studies
Combined side effects	Udvalg for Kliniske Undersøgelser Side Effects Rating Scale for Clinicians (UKU-SERS-Clin)	65	1
	Liverpool University neuroleptic side effect rating scale (LUNSERS)	13	3
	Matson Evaluation of Drug Side effects (MEDS)	3	1
	Association for Methodology and Documentation in Psychiatry psychotropic side effect rating scale (AMDP-5)	3	0
	Antipsychotic Non-Neurological Side Effects (ANNSERS)	2	2
	Udvalg for Kliniske Undersøgelser Side Effects Rating Scale for Patients (UKU-SERS-Pat)	1	2
	Distress Scale for Adverse Symptoms	1	0
	Subjective Side Effect Scale	1	0
	Global Index of Safety (GIS)	0	2
	Approaches to Schizophrenia Communication (ASC)	0	1
	Glasgow Antipsychotic Side effect Scale (GASS)	0	1
	Subjects Response to Antipsychotics (SRA)	0	1
	Systematic monitoring of Adverse events Related to TreatmentS (SMARTS)	0	1
	Tolerability and Quality of Life (Tool questionnaire)	0	1
Extra pyramidal side effects	Simpson-Angus Scale (SAS)	128	3
	Abnormal Involuntary Movements Scale (AIMS)	117	2
	Barnes Akathisia Rating Scale (BARS)	77	3
	Extrapyramidal Symptom Rating Scale (ESRS)	62	1
	Unified Parkinson's Disease Rating Scale	28	0
	Drug Induced Extrapyramidal Symptoms Scale (DIEPSS)	27	1
	Hillside Akathisia Scale	6	0
	Rockland Simpson Dyskinesia Scale	5	0

Table 1. Continued

	Rating scale	Application studies	Validation studies
Extra pyramidal side effects	St. Hans Rating Scale for extrapyramidal syndromes	4	1
	Abnormal Kinetic Effects Scale (TAKE)	2	0
	Dyskinesia Identification System Condensed User Scale (DISCUS)	2	2
	Mindham	1	1
	Akathisia Scale	1	0
	Australian Survey of Chan for parkinsonism	1	0
	Colombia University Rating Scale	1	0
	Cornell University Rating Scale for parkinsonism	1	0
	Dimascio Extrapyramidal Symptom Scale	1	0
	KLAWANS scale for extrapyramidal symptoms	1	0
	PERG survey for parkinsonism	1	0
	Rating Scale for Extrapyramidal Side Effects (unpublished)	1	0
	Tardive Dyskinesia Rating Scale	1	0
	SADIMOD	0	3
	Akathisia Ratings of Movement Scale (ARMS)	0	1
	Consistency Across Methods of Preference Assessment (CAMPA)	0	1
	Long instrument for diagnosis of drug induced akathisia	0	1
	Maryland Psychiatric Research Center scale (MPRC scale)	0	1
	Prince Henry Hospital Akathisia Rating Scale	0	1
	Tardive Dyskinesia Videotape Rating Techique	0	1
	Yale Extrapyramidal Symptom Scale (YESS)	0	1
	Arizona Sexual Experience Scale (ASEX)	9	2
	Psychotropic Related Sexual Dysfunction Questionnaire (PRSexDQ)	2	1

Table 1. Continued

	Rating scale	Application studies	Validation studies
Sexual dysfunction	Derogatis Interview for Sexual Function (DISF-SR)	1	0
	Sexual Function Questionnaire (SFQ)	1	0
	Changes in Sexual Function Questionnaire-14	0	1
	Antipsychotics and Sexual functioning Questionnaire (ASFQ)	0	1
	Nagoya Sexual Function Questionnaire (NSFQ)	0	1
Other single side effects	Epworth Sleepiness Scale (ESS)	2	0
	International Restless Legs Scale (IRLS)	1	0
	Food Craving Inventory	1	0
	Total	600*	46

**Some studies described more than one rating scale.*

Use of rating scales

In total, 14 rating scales for multi-domain side effects, 29 for extrapyramidal side effects, 7 for sexual dysfunction, and 3 for other single-domain side effects were used (Table 1). The Udvalg for Kliniske Undersogelser Side Effects Rating Scale for Clinicians (UKU-SERS-Clin) and the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) were used the most often to assess multi-domain side effects. The Simpson-Angus Scale (SAS), the Abnormal Involuntary Movements Scale (AIMS), and the Barnes Akathisie Rating Scale (BARS) were used the most often to assess extrapyramidal side effects. The scales for sexual dysfunction and the other single domain scales were not used very often in the retrieved studies.

Psychometric characteristics

The psychometric characteristics of some of the scales were not available. For example, the UPDRS was used 28 times to measure the extrapyramidal side effects of antipsychotics, but the psychometric properties of the scale for this specific goal have not been established, and the scale has been validated in patients with Parkinson's disease only. Psychometric characteristics

were available for 11 scales that measure multi-domain side effects, 16 scales that measure extrapyramidal side effects, and 5 scales that measure sexual functioning in patients using antipsychotics (Table 2). Of the multi-domain side effect scales, the UKU-SERS-Pat, the LUNSERS the Glasgow Antipsychotic Side effect Scale (GASS), and the UKU-SERS-Clin had moderate to good reliability and acceptable validity (Cronbach's α >0.70). The UKU-SERS-Clin had an intra-class coefficient of 0.49-0.91. These scales differ in the number of items scored, the time taken to complete the scale, and the rater (clinician or patient). If the patient scores the scale, there is no inter-rater reliability. The GASS takes 5 minutes to complete and grades not only the frequency of an experienced side effect but also the distress it causes.[14] The test-retest reliability (or intra-rater reliability) of the GASS was 0.72. The LUNSERS and the UKU comprehensively assess most antipsychotic-induced side effects. The "red herring" scale of the LUNSERS identifies patients who may be over-reporting symptomatology. Although some of the red herring items are obscure, for example 'chilblains'.[15] The ANNSERS was originated for the side effects of atypical antipsychotic drugs, not the conventional variety.[16,17]

Of the scales assessing extrapyramidal side effects, the SAS, the Drug Induced Extrapyramidal Symptom Scale (DIEPSS), the Maryland Psychiatric Research Center Scale (MPRC), the St. Hans Rating Scale for extrapyramidal symptoms, and the Schedule for the Assessment of Drug-Induced Movement Disorders (SADIMOD) all had good reliability and an acceptable validity (Cronbach's α>0.70; intra-rater and inter-rater reliability >0.70). The SADIMOD has never been used in other studies.

Of the sexual dysfunction scales, the Antipsychotics and Sexual Functioning Questionnaire (ASFQ) and the Nagoya Sexual Functioning Questionnaire had the best psychometric characteristics (Cronbach's α>0.70; intra-rater and inter-rater reliability about 0.70).

Table 2. Comparison of rating scales to measure side effects of antipsychotics

	Study characteristics				
	Scale	Number of items	Time to complete (min)	Self or clinician rated	Number of participants in validation study
Combined side effects	Antipsychotic Non-Neurological Side Effects (ANNSERS)[17] (ANNSERS)[16]	39	30	Clinician and self	36 26
	Approaches to Schizophrenia Communication (ASC)[18]	17	10	Self or Clinician	-
	Glasgow Antipsychotic Side effect Scale (GASS)[14]	22	5	Self	50
	Global Index of Safety (GIS)[19] (GIS)[20]	94	60	Clinician	2987 2949
	Liverpool University neuroleptic side effect rating scale (LUNSERS)[21] (LUNSERS)[22] (LUNSERS)[15]	51	5-20	Self	50 83 29
	Matson Evaluation of Drug Side effects (MEDS)[23]*	90	60	Clinician	66
	Subjects Response to Antipsychotics (SRA)[24]	74	15-20	Self	320
	Systematic monitoring of Adverse events Related to TreatmentS (SMARTS)[7]	11	5	Self	-
	Tolerability and Quality of Life (Tool questionnaire)[25]	8	5	Self	243
	Udvalg for Kliniske Undersogelser Side Effects Rating Scale for Clinicians (UKU-SERS-Clin)[26]	48	30	Clinician	2391
	Udvalg for Kliniske Undersøgelser Side Effects Rating Scale for Patients (UKU-SERS-Pat)[27] (UKU-SERS-Pat)[28]	48	11.6	Self	93 63

	Reliability			Validity
	Internal consistency	Test retest reliability/intra-rater reliability	Inter-rater reliability	Construct validity compared to ...
	-	-	κ = 0.77 version 1 = 0.72 version 2	
	-	-	-	ρ = DISF-SR -0.273
	-	-	-	-
	α = 0.72	κ =0.72	-	ρ =LUNSERS 0.93
	- -	r= 0.99 -	- -	ρ = EUROPA vs EFESO study 0.99
	α = 0.89	r= 0.81	NA	ρ = UKU 0.82
	- -	- -		ρ = SAS 0.28; BARS 0.27 ρ = UKU 0.58
	α = 0.82	-	r = 0.99	ρ = ARMS 0.85-1.00
	α = 0.69-0.93	r= 0.39-0.83	-	ρ = DAI 0.50 ρ = SWN 0.18
	-	-	-	-
	α = 0.92	-	NA	ρ = UKU -0.35 ρ = EQ-5D 0.69
	Icc = 0.49-0.92	-	-	-
	-	ρ= 0.89 -	NA	ρ =UKU SERS Clin 0.80 ρ =UKU SERS Clin 0.46
	-		NA	

Table 2. Continued

		Study characteristics			
	Scale	Number of items	Time to complete (min)	Self or clinician rated	Number of participants in validation study
Extrapyramidal side effects	Abnormal Involuntary Movements Scale (AIMS)[29]	10	10	Clinician	16
	(AIMS)[30]				-
	Akathisia Ratings of Movement Scale (ARMS)[23]	7	10	Clinician	66
	Barnes Akathisia Rating Scale (BARS)[31]	4	10	Clinician and self	42
	(BARS)[32]				-
	(BARS)[33]				99
	Consistency Across Methods of Preference Assessment (CAMPA)[34]	3	-	Clinician	63
	Drug Induced Extrapyramidal Symptoms Scale (DIEPSS)[35]	9	-	Clinician	182
	Dyskinesia Identification System Condensed User Scale (DISCUS)[36]	34	-	Clinician	36
	(DISCUS)[37]				216
	Extrapyramidal Symptom Rating Scale (ESRS) [38]	45	15	Clinician	374
	Long instrument for diagnosis of drug induced akathisia[39]	16	-	Clinician	360
	Maryland Psychiatric Research Center scale (MPRC scale)[40]	31	-	Clinician	1107
	Mindham[41]	9	-	Clinician	-
	Prince Henry Hospital Akathisia Rating Scale[42]	10	-	Clinician	100
	SADIMOD[43]	34	30	Clinician	31
	SADIMOD[44]				31
	SADIMOD[45]				-

Reliability			Validity
Internal consistency	Test retest reliability/ intra-rater reliability	Inter-rater reliability	Construct validity compared to ...
Icc = 0.05-0.29	-	-	-
	-	-	-
α = 0.67	-	r = 0.69	ρ = 0.66-1.00
-	-	κ = 0.74-0.95	-
			ρ = DIEPSS 0.88-0.97
-	-	-	ρ = SADIMOD 0.57-0.88
-	-	-	ρ = Lower limb activity index 0.26
-	-	-	-
-	r = 0.6-0.91	icc 0.76-0.96	ρ = SAS, BARS, AIMS 0.88-0.97
-	-	-	-
α = 0.92	-	r = 0.45-0.93	-
-	-	r = 0.80-0.97	ρ = AIMS 0.96
-	-	-	-
α = 0.80	r = 0.92	r = 0.81-0.90	ρ = AIMS 0.97
-	-	-	-
α = 0.90	-	κ = 0.42-0.81	ρ = BARS 0.84
α = 0.75-0.94	r = 0.33-0.77	-	ρ =SAS, BARS, AIMS 0.57-0.88
α = 0.81-0.94	-	r = 0.46-0.71	-
-	-	-	

Table 2. Continued

		Study characteristics			
	Scale	**Number of items**	**Time to complete (min)**	**Self or clinician rated**	**Number of participants in validation study**
Extrapyramidal side effects	Simpson-Angus Scale (SAS) [46] (SAS) [47] (SAS) [48]	10	10	Clinician	14 99 15
	St. Hans Rating Scale for extrapyramidal syndromes[49]	21	-	Clinician	30
	Tardive Dyskinesia Videotape Rating Techique[50]	24	-	Clinician	94
	Yale Extrapyramidal Symptom Scale (YESS)[51]	8	-	Clinician	63
Sexual dysfunction	Antipsychotics and Sexual functioning Questionnaire (ASFQ)[52]	M 7/ F 9	5	Clinician	30
	Arizona Sexual Experience Scale (ASEX)[53] ASEX[54]	5	5	Self or clinician	247 165
	Changes in Sexual Function Questionnaire-14 [55]	14	10	Self or clinician	171
	Nagoya Sexual Function Questionnaire (NSFQ)[56]	7	5	Self	60
	Psychotropic Related Sexual Dysfunction Questionnaire (PRSexDQ)[57]	7	5	Clinician	45

*α= Cronbach's alpha, icc= intraclass correlation coefficient, ρ= Spearman's rho, r= Pearson's r, κ = Cohen's kappa, - = not described in the article NA= Not applicable, there is no inter-rater reliability in self administered scales M= male subjects, F= female subjects *In this article only the Central Nervous System Items of the MEDS were used and validated. SWN=-Subjective Wellbeing under Neuroleptics, DAI= Drug Attitude Inventory, SmPC=Summaries of Product Characteristics, CGI-SF= Clinical Global Impression - Sexual Functioning, BISF= Brief Index of sexual functioning.*

	Reliability			Validity
	Internal consistency	Test retest reliability/ intra-rater reliability	Inter-rater reliability	Construct validity compared to ...
	-	-	r = 0.71-0.96	-
	α = 0.79	-	-	-
	α = 0.83	-	r = 0.71-0.85	ρ = SADIMOD 0.66
	α = 0.82	r = 0.66-0.85	r = 0.79	ρ = AIMS 0.50
	-	r = 0.82-0.96	r = 0.83-0.99	ρ = AIMS 0.63
	-	-	κ = 0.65-0.80	ρ = Websters items 0.74-0.91
	α = M 0.84	r = 0.76	r = 0.61-0.84	ρ = SRA 0.54-0.98 ρ = ASEX 0.16-0.71
	α = 0.90	-	-	BISF "good validity"
	α = 0.90	-	-	
	α = 0.90	-	-	ρ = VAS-SFS 0.33 ρ = CGI-SDS 0.71
	α = M 0.76 α = F 0.79	r = M 0.92 r = F 0.92	NA	UKU M r = 0.69 F r = 0.85
	α = 0.68	-	-	ρ = CGI-SF 0.729

Discussion

Several rating scales are available to assess the side effects of antipsychotics, some of which assess multiple or multi-domain side effects whereas others assess single effects, such as extrapyramidal symptoms or sexual functioning. The UKU-SERS-Clin was used the most to assess multi-domain side effects, whereas the LUNSERS had the best psychometric characteristics (Cronbach's α 0.81 and test-retest reliability 0.89). The SAS was used the most to assess extrapyramidal side effects, but the MPRC had the best characteristics (Cronbach's α 0.80, test-retest reliability 0.92 and inter-rater reliability 0.81-0.90). The ASEX was used the most to assess sexual dysfunction, but the ASFQ and the Nagoya Sexual Functioning Questionnaire had the best characteristics. We found a discrepancy between the scales used and the scales validated for a particular use – most (n=21) of the scales used did not have psychometric characteristics for the population investigated. On the other hand, some validated scales have never been used (n=17).

To our knowledge, this is the first study to review rating scales that assess multi-domain side effects in one rating scale. In contrast, single-domain scales are frequently used. Suzuki et al. reported that clinical trials for schizophrenia mostly use the single-domain scales AIMS, BARS, and SAS,[58] and that the UKU side effect rating scale lacks some crucial elements, such as metabolic parameters. They also reported that multi-domain scales are difficult to score.[58] Knol et al. evaluated rating scales for drug-induced parkinsonism and concluded that the SAS, St. Hans Rating Scale for Extrapyramidal Syndromes, and DIEPSS seem to be the most valid, reliable, and easy-to-use scales for use in clinical practice.[8] We also found that the SAS, BARS, and AIMS were used the most to assess extrapyramidal symptoms and that the SAS, St. Hans Rating Scale, and DIEPSS had good psychometric characteristics. We found that the MPRC had the best characteristics. De Boer et al. described the psychometric characteristics of rating scales to assess sexual functioning in patients using antipsychotics and concluded that the ASFQ, the Changes in Sexual Functioning Questionnaire-14 (CSFQ-14), and the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) cover all aspects of sexual functioning and should preferably be used for this indication.[9] We found that the ASFQ and Nagoya Sexual Functioning Questionnaire had good psychometric characteristics. Our findings are in line with those of earlier studies and provide a clear overview of multi-domain rating scales. Side effects are frequently missed, either because clinicians do not always ask about them or do not recognize complaints as possible

side effects. A rating scale in which multi-domain side effects are combined, or the combined use of multiple rating scales, can be advantageous in patient care because many patients experience multiple side effects during treatment with antipsychotics, which may result in an impaired quality of life and early discontinuation of medication.[2, 3] There can be some discrepancies between the distress associated with certain side-effects by prescribers and consumers of neuroleptic drugs and the fact that patients are unlikely to attribute symptoms as side effects of neuroleptic medication.[59] This article provides an overview of the multi-domain and single-domain side effect scales currently available and provides clinicians and researchers with goal-oriented choices. Scales that are easy to use and which take little time to complete are most appropriate for clinical use. One option is for patients to complete a scale in the waiting room before an appointment with their physician. The UKU-SERS-Pat, the LUNSERS, and the GASS can be used as self-rating scales and can serve as a starting point for a patient–clinician discussion of drug side effects and tolerability. It should be noted that potentially life threatening side effects such as neuroleptic malignant syndrome, significant QTc prolongation are also very important, although they fail to be captured with the existing rating scales. The prescribing physician should consider to base the selection on antipsychotics in light of the differences in side effects profiles, rather than those in antipsychotic efficacy. For each patient the choice of treatment has to be made individually. In contrast, research requires the use of scales with good psychometric characteristics. The MPRC had the best psychometric properties, but this scale assesses extrapyramidal side effects only. The LUNSERS and the UKU-SERS-Clin had the best psychometric characteristics of the multi-domain side effect scales; however, it should be noted that the correlation coefficient between the patient- and clinician-rated versions of the latter scale (UKU-SERS-Pat and the UKU-SERS-Clin, respectively) varied between 0.46 and 0.80 and was not very high. Patients tended to report more, and more severe side effects than clinicians did. This is probably because clinicians tend to underestimate drug-induced discomfort experienced by patients.[28] However, it is possible that patients interpret side effects in a different manner. For example, clinicians may interpret discomfort as a mood symptom, whereas patients may consider it a side effect and overstate its severity.[27, 28] For research purposes, a clinician-administered scale might be more appropriate for monitoring the side effects of antipsychotics, because it is more objective.

Although this study provides an overview of rating scales, it had some limitations. Although the literature was searched for relevant rating scales, but it should be

appreciated that the literature does not necessarily reflect clinical practice. The frequency with which a scale is actually used in daily practice can never be determined based on the literature, and thus we can only give a global indication of how often a scale is used in clinical practice and how this figure relates to the use of other scales. However, as we also performed a snowball search of the references of included articles, we believe the search provides a fairly complete picture of the scales in use. Another potential limitation is that we assumed that relevant rating scales would be published in journals included in PubMed or Embase. Moreover, we may have missed general scales about the side effects of all psychotropic drugs, but it is unlikely that these scales would have been validated in antipsychotic users. In clinical practice, it is very difficult for acute psychotic patients to fill out self-report scales, and in this instance clinician-rated scales are probably more appropriate. However, chronic users of antipsychotic medication, such as patients with schizophrenia, are capable of filling out self-report scales, and the use of such scales to assess the side effects of medication may improve patients' medication adherence and knowledge of drug side effects, which might improve their quality of life.

In summary, given the frequency and nature of antipsychotic-induced side-effects, it is essential to assess these side effects in clinical practice. The UKU-SERS-Pat, the LUNSERS, and the GASS seem to have moderate to good reliability and acceptable validity. Because these scales can be completed by patients relatively quickly, they are the most appropriate for use in clinical practice. The UKU-SERS-Clin is a comprehensive, clinician-rated scale and can be used for research purposes, because of its good psychometric characteristics. In addition to multi-domain scales, a combination of single-domain scales can probably also be used, for example, the SAS for EPS or the ASFQ for sexual dysfunction. However, the use of a combination of single-domain scales will not cover all side effect domains and the psychometric characteristics of such combinations needs to be studied in the future.

References

1. Sarfati Y, Olivier V, Bouhassira M. New antipsychotics in the treatment of schizophrenia. A European survey. Encephale 1999; Nov-Dec;25(6):658-66.
2. de Araujo AA, de Araujo Dantas D, do Nascimento GG, Ribeiro SB, Chaves KM, de Lima Silva V, et al. Quality of life in patients with schizophrenia: the impact of socio-economic factors and adverse effects of atypical antipsychotics drugs. Psychiatr Q 2014; Sep;85(3):357-67.
3. Schouten HJ, Knol W, Egberts TC, Schobben AF, Jansen PA, van Marum RJ. Quality of life of elderly patients with antipsychotic-induced parkinsonism: a cross-sectional study. J Am Med Dir Assoc 2012; Jan;13(1):82.e1,82.e5.
4. McCann TV, Clark E, Lu S. Subjective side effects of antipsychotics and medication adherence in people with schizophrenia. J Adv Nurs 2009; Mar;65(3):534-43.
5. Seitz DP, Gill SS, van Zyl LT. Antipsychotics in the treatment of delirium: a systematic review. J Clin Psychiatry 2007; Jan;68(1):11-21.
6. Knol W, van Marum RJ, Jansen PA, Egberts TC, Schobben AF. Parkinsonism in elderly users of haloperidol: associated with dose, plasma concentration, and duration of use. J Clin Psychopharmacol 2012; Oct;32(5):688-93.
7. Haddad PM, Fleischhacker WW, Peuskens J, Cavallaro R, Lean ME, Morozova M, et al. SMARTS (Systematic Monitoring of Adverse events Related to TreatmentS): The development of a pragmatic patient-completed checklist to assess antipsychotic drug side effects. Ther Adv Psychopharmacol 2014; Feb;4(1):15-21.
8. Knol W, Keijsers CJ, Jansen PA, van Marum RJ. Systematic evaluation of rating scales for drug-induced parkinsonism and recommendations for future research. J Clin Psychopharmacol 2010; Feb;30(1):57-63.
9. de Boer MK, Castelein S, Wiersma D, Schoevers RA, Knegtering H. A systematic review of instruments to measure sexual functioning in patients using antipsychotics. J Sex Res 2014;51(4):383-9.
10. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; Jul 21;339:b2535.
11. Cicchetti DV. Multiple comparison methods: establishing guidelines for their valid application in neuropsychological research. J Clin Exp Neuropsychol 1994; Feb;16(1):155-61.
12. Sprinthall R. Basic Statistical Analysis. ninth edition ed. Boston: Allyn & Bacon; 2012.
13. Cohen J. Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit. Psychol Bull 1968; Oct;70(4):213-20.
14. Waddell L, Taylor M. A new self-rating scale for detecting atypical or second-generation antipsychotic side effects. J Psychopharmacol 2008; /;22(3):238-43.
15. Lambert TJ, Cock N, Alcock SJ, Kelly DL, Conley RR. Measurement of antipsychotic-induced side effects: support for the validity of a self-report (LUNSERS) versus structured interview (UKU) approach to measurement. Hum Psychopharmacol 2003; Jul;18(5):405-11.
16. Mahmoud A, Drake RJ, Lewis SW, Hayhurst KP, Barnes TRE. The ANNSERS (Antipsychotic Non-Neurological Side Effects Rating Scale): Validation of sexual side-effect measurement. Ther Adv

Psychopharmacol 2011; /;1(4):97-100.
17. Ohlsen RI, Williamson R, Yusufi B, Mullan J, Irving D, Mukherjee S, et al. Interrater reliability of the Antipsychotic Non-Neurological Side-Effects Rating Scale measured in patients treated with clozapine. J Psychopharmacol 2008; May;22(3):323-9.
18. Weiden PJ, Miller AL. Which side effects really matter? Screening for common and distressing side effects of antipsychotic medications. J Psychiatr Pract 2001; Jan;7(1):41-7.
19. Prieto L, Sacristan JA, Gomez JC. The validity and reliability of the global index of safety (GIS). Curr Med Res Opin 2004; Nov;20(11):1825-32.
20. Sacristan JA, Gomez JC, Badia X, Kind P. Global index of safety (GIS): a new instrument to assess drug safety. J Clin Epidemiol 2001; Nov;54(11):1120-5.
21. Day JC, Wood G, Dewey M, Bentall RP. A self-rating scale for measuring neuroleptic side-effects. Validation in a group of schizophrenic patients. Br J Psychiatry 1995; 1995/;166(MAY):650-3.
22. Jung HY, Kim JH, Ahn YM, Kim SC, Hwang SS, Kim YS. Liverpool University Neuroleptic Side-Effect Rating Scale (LUNSERS) as a subjective measure of drug-induced parkinsonism and akathisia. Hum Psychopharmacol 2005; Jan;20(1):41-5.
23. Garcia MJ, Matson JL. Akathisia in adults with severe and profound intellectual disability: a psychometric study of the MEDS and ARMS. J Intellect Dev Disabil 2008; Jun;33(2):171-6.
24. Wolters HA, Knegtering R, Wiersma D, van den Bosch RJ. Evaluation of the subjects' response to antipsychotics questionnaire. Int Clin Psychopharmacol 2006; Jan;21(1):63-9.
25. Montejo AL, Correas-Lauffer J, Maurino J, Villa G, Rebollo P, Diez T, et al. Estimation of a multiattribute utility function for the Spanish version of the TooL questionnaire. Value Health 2011; Jun;14(4):564-70.
26. Lingjaerde O, Ahlfors UG, Bech P. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand 1987; 1987/;76(1 SUPPL. 334):1-100.
27. Kim JH, Choi SW, Joe SH, Ha TH, Yoo HJ, Choi JE, et al. Reliability and validity of the Korean version of UKU-SERS-Pat in patients with bipolar disorder. Nord J Psychiatry 2008;62(6):496-502.
28. Lindstrom E, Lewander T, Malm U, Malt UF, Lublin H, Ahlfors UG. Patient-rated versus clinician-rated side effects of drug treatment in schizophrenia. Clinical validation of a self-rating version of the UKU Side Effect Rating Scale (UKU-SERS-Pat). Nord J Psychiatry 2001;55 Suppl 44:5-69.
29. Tonelli H, Tonelli D, Poiani GR, Vital MA, Andreatini R. Reliability and clinical utility of a Portuguese version of the Abnormal Involuntary Movements Scale (AIMS) for tardive dyskinesia in Brazilian patients. Braz J Med Biol Res 2003; Apr;36(4):511-4.
30. Munetz MR, Benjamin S. How to examine patients using the Abnormal Involuntary Movement Scale. Hosp Community Psychiatry 1988; Nov;39(11):1172-7.
31. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989; May;154:672-6.
32. Barnes TR. The Barnes Akathisia Rating Scale--revisited. J Psychopharmacol 2003; Dec;17(4):365-70.
33. Janno S, Holi MM, Tuisku K, Wahlbeck K. Actometry and Barnes Akathisia Rating Scale in neuroleptic-induced akathisia. Eur Neuropsychopharmacol 2005; Jan;15(1):39-41.
34. Lenert LA, Morss S, Goldstein MK, Bergen

MR, Faustman WO, Garber AM. Measurement of the validity of utility elicitations performed by computerized interview. Med Care 1997; Sep;35(9):915-20.
35. Kim JH, Jung HY, Kang UG, Jeong SH, Ahn YM, Byun HJ, et al. Metric characteristics of the drug-induced extrapyramidal symptoms scale (DIEPSS): a practical combined rating scale for drug-induced movement disorders. Mov Disord 2002; Nov;17(6):1354-9.
36. Sprague RL, Korach MS, van Emmerik RE, Newell KM. Correlations between kinematic and rating scale measures of tardive dyskinesia in a developmentally disabled population. J Nerv Ment Dis 1993; Jan;181(1):42-7.
37. Kalachnik JE, Sprague RL. The dyskinesia Identification System Condensed User Scale (DISCUS): reliability, validity, and a total score cut-off for mentally ill and mentally retarded populations. J Clin Psychol 1993; Mar;49(2):177-89.
38. Chouinard G, Margolese HC. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). Schizophr Res 2005; Jul 15;76(2-3):247-65.
39. Vinson DR. Development of a simplified instrument for the diagnosis and grading of akathisia in a cohort of patients receiving prochlorperazine. J Emerg Med 2006; Aug;31(2):139-45.
40. Cassady SL, Thaker GK, Summerfelt A, Tamminga CA. The Maryland Psychiatric Research Center scale and the characterization of involuntary movements. Psychiatry Res 1997; Apr 18;70(1):21-37.
41. Mindham RH. Assessment of drugs in schizophrenia. Asessment of drug-induced extrapyramidal reactions and of drugs given for their control. Br J Clin Pharmacol 1976; Jun;3(3 Suppl 2):395-400.
42. Sachdev P. A rating scale for acute drug-induced akathisia: development, reliability, and validity. Biol Psychiatry 1994; Feb 15;35(4):263-71.
43. Loonen AJ, Doorschot CH, van Hemert DA, Oostelbos MC, Sijben AE. The Schedule for the Assessment of Drug-Induced Movement Disorders (SADIMoD): test-retest reliability and concurrent validity. Int J Neuropsychopharmacol 2000; Dec;3(4):285-96.
44. Loonen AJ, Doorschot CH, van Hemert DA, Oostelbos MC, Sijben AE. The schedule for the assessment of drug-induced movement disorders (SADIMoD): inter-rater reliability and construct validity. Int J Neuropsychopharmacol 2001; Dec;4(4):347-60.
45. Loonen AJ, van Praag HM. Measuring movement disorders in antipsychotic drug trials: the need to define a new standard. J Clin Psychopharmacol 2007; Oct;27(5):423-30.
46. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11-9.
47. Janno S, Holi MM, Tuisku K, Wahlbeck K. Validity of Simpson-Angus Scale (SAS) in a naturalistic schizophrenia population. BMC Neurol 2005; Mar 17;5(1):5.
48. Knol W, Keijsers CJ, Jansen PA, Belitser SV, Schobben AF, Egberts AC, et al. Validity and reliability of the Simpson-Angus Scale (SAS) in drug induced parkinsonism in the elderly. Int J Geriatr Psychiatry 2009; Feb;24(2):183-9.
49. Gerlach J, Korsgaard S, Clemmesen P, Lauersen AM, Magelund G, Noring U, et al. The St. Hans Rating Scale for extrapyramidal syndromes: reliability and validity. Acta Psychiatr Scand 1993; Apr;87(4):244-52.
50. Barnes TR, Trauer T. Reliability and validity of a tardive dyskinesia videotape rating technique. Br J Psychiatry 1982; May;140:508-15.

51. Mazure CM, Cellar JS, Bowers MB,Jr, Nelson JC, Takeshita J, Zigun B. Assessment of extrapyramidal symptoms during acute neuroleptic treatment. J Clin Psychiatry 1995; Mar;56(3):94-100.
52. de Boer MK, Castelein S, Bous J, van den Heuvel ER, Wiersma D, Schoevers RA, et al. The Antipsychotics and Sexual Functioning Questionnaire (ASFQ): preliminary evidence for reliability and validity. Schizophr Res 2013; Nov;150(2-3):410-5.
53. Byerly MJ, Nakonezny PA, Fisher R, Magouirk B, Rush AJ. An empirical evaluation of the Arizona sexual experience scale and a simple one-item screening test for assessing antipsychotic-related sexual dysfunction in outpatients with schizophrenia and schizoaffective disorder. Schizophr Res 2006; 2006/01;81(2-3):311-6.
54. McGahuey CA, Gelenberg AJ, Laukes CA, Moreno FA, Delgado PL, McKnight KM, et al. The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Ther 2000; Jan-Mar;26(1):25-40.
55. Garcia-Portilla MP, Saiz PA, Fonseca E, Al-Halabi S, Bobes-Bascaran MT, Arrojo M, et al. Psychometric properties of the Spanish version of the Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) in patients with severe mental disorders. J Sex Med 2011; May;8(5):1371-82.
56. Kikuchi T, Iwamoto K, Sasada K, Aleksic B, Yoshida K, Ozaki N. Reliability and validity of a new sexual function questionnaire (Nagoya Sexual Function Questionnaire) for schizophrenic patients taking antipsychotics. Hum Psychopharmacol 2011; /;26(4-5):300-6.
57. Montejo AL, Rico-Villademoros F. Psychometric properties of the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ-SALSEX) in patients with schizophrenia and other psychotic disorders. J Sex Marital Ther 2008;34(3):227-39.
58. Suzuki T. Which rating scales are regarded as 'the standard' in clinical trials for schizophrenia? A critical review. Psychopharmacol Bull 2011;44(1):18-31.
59. Day JC, Kinderman P, Bentall R. A comparison of patients' and prescribers' beliefs about neuroleptic side-effects: prevalence, distress and causation. Acta Psychiatr Scand 1998; Jan;97(1):93-7.

5.

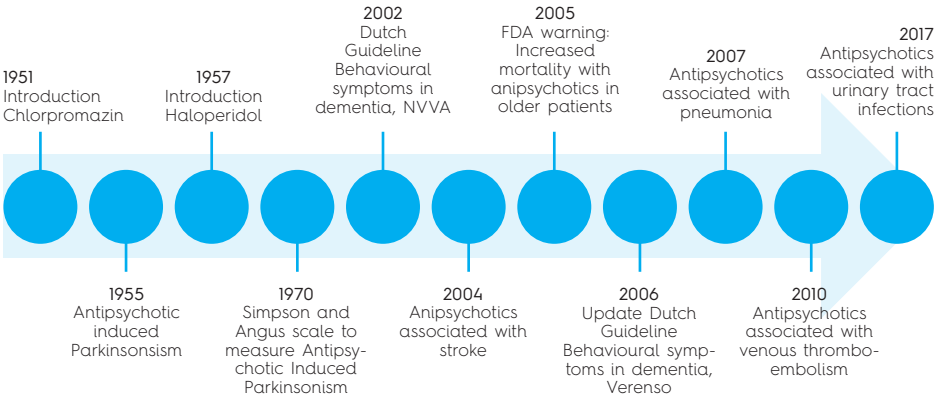
General discussion

Introduction of adverse drug reactions of antipsychotics

Antipsychotic drugs are widely used since their introduction in the 1950's to relieve psychotic symptoms for instance in patients with delirium or schizophrenia. In the Netherlands there are more than 300 000 antipsychotic users, of which more than 88 000 are older than 65 years.[1] Figure 2 shows some milestones in the history of antipsychotic drug use. Chlorpromazine was the first antipsychotic and was released in 1951. Chlorpromazine was believed to be the solution for many problems such as agitation, anxiety, depression, emotional stress with all kinds of somatic diagnoses, nausea and vomiting and menopausal complaints. Psychiatrist Seager wrote about chlorpromazine in 1955: "A related problem is the shortage of nursing staff, owing to which large wards of noisy, difficult patients have to be in the care of too few nurses, or patients have to be left at night with inadequate supervision. It is hoped to show that chlorpromazine 'largactil' may play a part in the solution of these."[2] Haloperidol was approved in 1957. A few years after the discovery of antipsychotic medication, antipsychotic induced parkinsonism (AIP) was first described to be an important adverse drug effect.[3] It was not before 1970 that the first assessment scale for AIP was published: The Simpson and Angus Scale (SAS).[3] In the years to follow, many other assessment scales were developed. Despite the development of these scales and the importance of AIP for the functioning of patients, the use of these instruments in clinical practice remained low and often instruments are used to detect AIP that are not suited for this purpose (chapter 4). In contrast to the early identification of dose related and predictable type A side effects like AIP, sedation and neurolepsia, it took almost fifty years before major, mostly type B, non predictable, adverse drug reactions like CVA, pneumonia and mortality were described in older patients. And it lasted

until 2005, before finally the Food and Drug Administration issued a warning about the increased mortality rate with atypical antipsychotics in older patients, a warning that was extended to all antipsychotics in 2008.[4] In 2002 the first Dutch guideline for antipsychotic use in dementia patients with behavioural and psychological symptoms of dementia (BPSD) in nursing homes became available,[5] with an update in 2006.[6] Because studies showed that adverse effects outweigh advantages in the efficacy of antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease, this guideline discouraged the use of antipsychotic drugs for the treatment of BPSD.[7] Despite this guideline, which will be updated to a new version in 2017, the prescription rate of antipsychotic medication has not really decreased in the past 10 years. In the Netherlands, for example, antipsychotics are still used by 37% of the nursing home patients with dementia.[8] It seems that since the introduction of antipsychotic drugs, clinicians seem to overrate efficacy of these drugs while failing to see the serious side effects associated with the use of these drugs. And even today, the balance between efficacy and harm seems to be neglected.

Figure 2. Timeline with milestones in the history of antipsychotic drug use



In this general discussion three topics will be addressed in more detail from the perspective of what is already known and what is added by this thesis. These topics are:

1. A disquisition about the reasons why it took more than 50 years before there came serious attention to adverse drug reactions of antipsychotics in older patients.
2. Implications for clinical practice.
3. Implications for future research.

Why it took more than 50 years before there came serious attention to adverse drug reactions of antipsychotics in older patients

Antipsychotic drugs are approved for the treatment of schizophrenia and bipolar disorder since the early beginning.[9] While they are frequently prescribed to older patients, antipsychotics are often used outside their approved indication, to treat behavioural disturbances in older patients with dementia.[9] The first meta-analysis that compared thioridazine or haloperidol with a placebo in agitated dementia patients, was published in 1990 and showed that only 18 of 100 dementia patients benefited from neuroleptic treatment (NNT 6).[10] A NNT of 6 may be considered acceptable if harms are negligible which clearly not the case is. In a 2005 meta-analysis of RCTs with atypical antipsychotics for dementia, the authors conclude: "Considering that many of these trials demonstrated that these medications are only modestly effective with numbers needing to treat ranging from 4 to 12 in specific meta-analyses, the likelihood for helping versus harming may be rather modest as well, such that for every 9 to 25 persons helped in these trials there possibly will be 1 death."[11]
The last two decades, more studies about the effects and side effects of antipsychotics in older patients became available, predominately being investigator initiated studies. Although some side effects, like stroke were found in RCT's, RCT's are often too small and too short of duration to find uncommon adverse drug effects. In research in older patients using antipsychotic medication, there are some difficulties we like to address: Ethics and informed consent, methodological issues in pharmaco-epidemiologic research, how side effects are measured en monitored over time and unknown causality and pathophysiologic mechanisms.

Ethics and informed consent

There are not that many randomised controlled trials of good quality studying the effect of antipsychotics on behavioural symptoms in patients with dementia. Some of the hurdles for including patients with dementia in clinical studies caused by ethical standards and informed consent related issues. The declaration of

Helsinki states: "Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection."[12] "Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research."[12] Medical ethical committees are cautious with allowing patients with dementia in clinical trials, which means that benefits and risks of interventions for this group often remain unknown and a systematic focus on ADRs is missing. For this reason it is clinically relevant to do new studies with this vulnerable group.

In research with people with dementia, it is for the physician to decide if they are mentally competent. In case a patient with dementia is not mentally competent, in the Netherlands, a legal representative needs to consent for participation in a study. Especially in intervention study's, this poses an important barrier.[13] The legal representative is not always the caregiver of the patient, so this person is not always available when you want to include a patient. This means there are two main barriers: the exclusion of vulnerable patients and the difficulties with inclusion.

The difficulties concerning problematic inclusion of older patients were also encountered in the studies described in this thesis. Despite a design in which no extra interventions were performed in the patient and only a few ml of already obtained cerebrospinal fluid (CSF) was analysed, we only found 20 patients willing to participate to our study to collect blood and CSF to investigate the relationship between serum and CSF concentration of haloperidol in an older population in a period of one year (chapter 2.1). There were some difficulties that contributed to the slow inclusion of this study. The Medical Ethical Committee judged that we were not allowed to include patients with dementia, who were not mentally competent, in this study. We could only include patients with an elevated risk of a delirium, but without a diagnosis of dementia, what made our eligible population smaller. It is difficult to generalise our results to patients with dementia, because permeability of the blood-brain-barrier can be changed in patients with Alzheimer's disease.[14] Intervention studies may give a possible benefit for the patient when participating in the study. However, this is not the case in observational studies like ours. In a study about attitudes of older adults to participation in clinical trials, 44 % answered that they would agree to participate in a trial with some personal benefit.[15] Only 21 % were

willing to participate in a trial without such gain.[15] The top two reasons for refusal to participate in a clinical trial were 'I think I am too old for this type of experiment' (24 %) and 'I am afraid for my own well-being' (21 %). The most common open-ended response was "not to be a guinea pig".[15]
These difficulties with inclusion of elderly, often demented, patients were also encountered in the multicentre randomised, stratified, double-blind, placebo-controlled HARPOON-trial ("Haloperidol prophylaxis in older emergency department patients"). In the Jeroen Bosch Hospital, 52 patients were randomised. Of these, 3 withdrew consent, 3 stopped per protocol treatment, and 12 had no blood sample drawn on day 6. For our substudy concerning the relation between haloperidol use and coagulation parameters (chapter 2.2) we could only analyze 16 haloperidol patients and 18 placebo patients. For the 3 patients who withdrew consent, a lot of time was invested in informing the patient, but the caregiver/family was probably not informed well enough. After the patient discussed the study with their family members, they decided to withdraw consent.
Of course it remains important to protect the people with dementia, but we think there is a need for a guideline on doing research with older patients. At this moment the department of Geriatric Medicine of the Radboud UMC, is working on a guideline to include older patients in medical research. This guideline aims to give researchers more guidance in including older patients in medical research. Communication and well informing of the patient and the caregivers is one of the most important issues for the researcher to deal with.

Pharmaco-epidemiology

Uncommon side effects are difficult to be found in Randomised Controlled Trials, with durations of weeks or months and a relative small group of participants. Cohort or case-control studies are better suited for this type of research. In this thesis, the studies in CPRD and PHARMO concerning the relationship between AP drug use and the occurrence of urinary tract infections are examples of this. Over the last decade serious, but relatively rare side effects, were largely found in case-control and cohort studies. Observational studies show different results than the RCTs used for registration. There are no barriers to include older patients using antipsychotics observational database-studies. But, observational studies have other methodological limitations. In a case-control design, the outcome is often formulated by using a proxy. Besides that, it is difficult to find a good control group and there is the issue of confounding. It is important to take these limitations into account. Observational studies in

large databases like Clinical Practice Research Datalink (CPRD) and PHARMO Database Network have a risk of bias and misclassification. The variability in completeness of data across patients and across time requires careful consideration. Restriction to those with complete data may result in biased analyses, and imputation may not be a straightforward approach because the patterns of missing data are complex.[16] There are no standardized definitions for diagnoses, so in CPRD, Read codes are used for the outcome of interest. If general practitioners enter information as free text, researchers will miss valuable information.[16] The disadvantage of observational studies is that causality can be difficult to made plausible, because of confounding.

Observational studies are useful to contribute to knowledge about rare side effects. These large database studies show us adverse drug effects which in clinical practice will seldom be noticed as adverse event, because they are rare or get lost in the co-morbidity of the patients in RCT's and thus can be attributed to other co-morbidities. If you want to identify these adverse events, you have to look for them in a scientific design. With the help of databases, over the last decade an association was found between antipsychotics and cerebrovascular accidents,[17] thrombo-embolism,[18] myocardial infarction,[19] and pneumonia.[20] In pharmaco-epidemiological studies it is possible to study the relation with dosage, gender and time dependency. Given the proven association of AP use with pneumonia, we wondered whether the association was just with pneumonia alone, or that there was an association between AP use and the risk of developing infections in general. Urinary tract infections as adverse drug reaction of antipsychotics were never described before and could serve as another example of infection. In this thesis we describe this adverse drug reaction in two large database studies, CPRD and PHARMO, to fill this gap in knowledge. In both studies we found an association between AP use and the risk of getting a urinary tract infection. This may serve as an example of finding an ADR which as event occurs frequently in a geriatric population and which was never thought of as being an ADR for AP use in clinical practice before. The relation between AP use and infection was never found in RCT's. We covered the disadvantages of database studies, by studying the same research question in two different databases with different outcome measures. Relevant outcomes of pharmaco-epidemiological studies can be used to further study mechanisms underlying the ADR prospectively in the right patient population.

How side effects are measured and monitored over time

As introduced before, side effects of AP use occur frequently and can be severe. The problem of side effects was addressed, by the workgroup prevention and treatment of somatic complications in antipsychotic users. They give advice for systematic monitoring over time. [21] Their advice is to take a somatic history, familial anamnesis, Mini Mental State Examination, Body Mass Index, waist circumference, blood pressure and pulse, bladder scan, check for movement disorders, perform an electrocardiogram and laboratory measures: fasted glucose, fasted lipids, liver functions and blood count, before the start of the antipsychotic in older patients.[21] After the start, they recommend to monitor patients after one month, two months, three months, six months and annual.[21] As mentioned before the most common indication of prescribing an antipsychotic in older patients are behavioural problems in dementia. Geriatricians, physicians in nursing homes and general practitioners not always perform the monitoring mentioned above.

It should be noted that the clinical judgement alone isn't enough in finding side effects. As stated earlier, side effects are frequently missed, either because clinicians do not always ask about them or do not recognize complaints as possible side effects. The use of a rating scale can add a systematic approach to the follow up of antipsychotic users. However it is not always easy to determine which scale should best be used for clinical practice or research, since psychometric characteristics of different scales on roughly the same outcome may vary. There are several rating scales available to assess the side effects of antipsychotics, some of which assess multiple or multi-domain side effects whereas others assess single effects, such as extrapyramidal symptoms or sexual functioning.

Rating scales can be either comprehensive or short. A rating scale in which multi-domain side effects are combined, or the combined use of multiple rating scales, can be advantageous in patient care because many patients experience multiple side effects during treatment with antipsychotics, which may

result in an impaired quality of life and early discontinuation of medication.[22] There can be some discrepancies between the distress associated with certain side-effects by prescribers and users of antipsychotic drugs and the fact that patients are unlikely to attribute symptoms as side effects of their antipsychotic medication.[23] Scales that are easy to use and which take little time to complete are most appropriate for clinical use. It should be noted that potentially life threatening side effects such as neuroleptic malignant syndrome, significant QTc prolongation are also very important, although they fail to be captured with the existing rating scales. Rating scales also fail to measure weight or laboratory measurements such as lipids and glucose. The prescribing physician should consider selecting an antipsychotic based on differences in side effects profiles, rather than on antipsychotic efficacy. For each patient the choice of treatment has to be made individually. In schizophrenia, patients tend to report more, and more severe side effects than clinicians do. This is probably because clinicians tend to underestimate drug-induced discomfort experienced by patients.[24] However, it is possible that patients interpret side effects in a different manner. For example, clinicians may interpret discomfort as a mood symptom, whereas patients may consider it a side effect and overstate its severity.[24] In clinical practice, it is very difficult for acute psychotic patients to fill out self-report scales, and in this instance clinician-rated scales are probably more appropriate. In frail older patients, antipsychotics are used most for behavioural problems in dementia. Patients with moderate dementia may also not be able to complete a scale about side effects.

In this thesis (chapter 4) we found that the UKU-SERS-Clin is most frequently used to assess multi-domain side effects, whereas the LUNSERS has the best psychometric characteristics (Cronbach's α 0.81 and test-retest reliability 0.89). The SAS is used the most to assess extrapyramidal side effects, but the MPRC has the best characteristics (Cronbach's α 0.80, test-retest reliability 0.92 and inter-rater reliability 0.81-0.90). The ASEX is used the most to assess sexual dysfunction, but the ASFQ and the Nagoya Sexual Functioning Questionnaire have the best characteristics. We found a discrepancy between the scales used and the scales validated for a particular use – most (n=21) of the scales used, did not have psychometric characteristics for the population investigated. On the other hand, some validated scales have never been used (n=17).

Clinical trials for schizophrenia use mostly the single-domain scales AIMS, BARS, and SAS.[25] The SAS, St. Hans Rating Scale for Extrapyramidal Syndromes and DIEPSS seem to be the most valid, reliable, and easy-to-use scales for use in clinical practice.[26]

It is important that physicians prescribing antipsychotic medication become more aware of the broad spectrum of side effects. This is important to prevent somatic complications in antipsychotic users. The UKU-SERS-Clin is a rating scale that adds a systematic approach to the follow up of antipsychotic users and should be introduced for clinical practice.

Causality and pathophysiology

Although knowledge of adverse drug effects is increasing, we still have very little understanding of causality and pathophysiology of all the different adverse drug reactions in antipsychotics. In this thesis, we tried to build upon this limited knowledge. It is unknown why some older patients develop antipsychotic induced parkinsonism at a low dosage haloperidol and others do not. In older patients there is a large, not well understood, inter-individual variation in effect and side effects, (in particular antipsychotic induced parkinsonism).[27] A previous study investigated the association between parkinsonism in elderly users of haloperidol and prescribed dose, plasma concentration, and duration of use of haloperidol in a cross-sectional design.[27] We found that the correlation of cerebral spine fluid (CSF) and serum concentration of haloperidol was significant, ($r=0.85$, $p<0.05$). The large variation in serum concentrations (with a factor 6) could not be explained by differences in drug metabolism resulting from polymorphism of CYP2D6. So, variability in transport over the blood brain barrier (BBB) is also not the explanatory factor for inter-individual variation in effects and side effects of haloperidol.

In this thesis another study investigates the possible underlying mechanism that might contribute to the known association of antipsychotics with cerebrovascular accidents,[17] thrombo-embolism[18] or myocardial infarction.[19] All these serious side effects seem to occur more frequently in the period directly after start of the antipsychotic medication. In this thesis we investigated the effect of haloperidol on thrombogenesis. We found no significant differences in laboratory markers: fibrinogen, D-dimer, P-selectin, von Willebrand factor, and osteoprotegerin in non-psychotic older patients receiving haloperidol or placebo. Thus the underlying cause of the increase in cerebrovascular events seen in haloperidol users remains to be established.

Implications for clinical practice

Although antipsychotics are frequently prescribed, guidelines state that persons with dementia who exhibit behavioural and psychological symptoms should not be given antipsychotics before trying other treatments.[28] Older people using antipsychotics have an increased risk of many possible ADRs e.g. cerebrovascular effects, parkinsonism or extrapyramidal symptoms, sedation, confusion and other cognitive adverse effects, and increased mortality.[28] As mentioned before only 18 of 100 dementia patients benefited from antipsychotic treatment.[10] The Dutch guideline from Verenso, the association of nursing home physicians, for treatment of behavioural problems in older patients with dementia, with an update in 2017, discourages prescribing antipsychotics. Despite known adverse effects and extra attention to non-pharmacologic treatment, the number of antipsychotic prescriptions had only slightly decreased over the past decade.[29] A possible explanation is that nursing home physicians and nurses expect almost half of their patients with dementia and behavioural disturbances to benefit from antipsychotic therapy and serious side effects are expect to occur only sporadically. These high expectations may contribute to the high rate of antipsychotic use among these patients.[30] Physicians should try to address symptoms including agitation, aggression, anxiety, depression, irritability, and psychosis with alternative non pharmacological treatments whenever antipsychotic use can be replaced or reduced.[31] Problem adaptation therapy is effective in reducing depression and disability in patients with cognitive impairment.[32] Cognitive behavioural therapy decreased depressive symptoms in patients with dementia ánd decreased depressive symptoms for their caregivers.[33] Music therapy has a positive effect on anxiety and depression in patients with mild to moderate Alzheimer's disease.[34] It is simple to implement and can be easily integrated in a multidisciplinary programme.[34] Aromatherapy with essential balm oil is a safe and effective treatment for clinically significant agitation in people with severe dementia.[35] Barriers for the use of non-pharmacological interventions are lack of time, emergencies (especially in night or weekend shifts), lack

of good qualified staff, and a poor nurse-to patient ratio.[30]
In patients with behavioural symptoms in dementia, the effect and side effects of treatment are often not mentioned by the patient itself, but by their professional caregivers. This raises the question whether the treatment is beneficial for the patients or for their caregivers. An improvement on a behavioural scale does not necessarily mean that the patient feels better. Side effects should be monitored and a scale like the UKU-SERS-clin can be helpful. In older patients, antipsychotic use should be restricted to those patients for which the treatment is judged to be absolutely necessary. Availability of more and better-trained nursing staff would help in the quality of non-pharmacological treatment of behavioural symptoms in dementia, therewith reducing the urgency to prescribe antipsychotic drugs. In case of dementia or if the patients is not mentally competent, the caregiver should be informed about the risk of serious adverse effects. Antipsychotic medication should be evaluated on effect and on side effects after the start and should be closely monitored. When possible physicians should try to stop antipsychotics. In a stop trial, there was no evidence that patients benefited on neuropsychiatric symptoms from continuing treatment.[36] For most patients with Alzheimer's disease, withdrawal of antipsychotics has no overall detrimental effect on functional and cognitive status.[36] The use of antipsychotic medication is not forbidden, but should be tailored to the individual patient.
A general basis for rational prescribing, regardless of patient age or sex, is the WHO guide to good prescribing, which includes the *WHO 6-step method for rational prescribing* (WHO-6-step) as shown in Figure 3 on page 124.[37]

The WHO-6-step method can be helpful to improve rational prescribing and personalised medicine. We elucidate this with an example. *The patient is a 83 year old man with dementia, who has visual hallucinations that frighten him, especially at night time. The therapeutic objective is symptomatic, to reduce fear of the hallucinations.* Figure 4 on page 125 shows the WHO-6-step for this specific case. In the treatment choice we follow the Dutch guideline of Verenso "behavioural symptoms in dementia". A relative contra-indication is that this patient falls once a week. We chose haloperidol, although the evidence is scarce for patients with dementia. We prescribe him haloperidol 1mg once daily ante noctem. We give the patient instruction that the aim is to reduce the hallucinations and the fear, but that he should know that there is an increase in falls risk. After a week evaluation, the patient has fallen twice and says that he still has the frightening hallucinations. We stop the haloperidol.

Figure 3. WHO-6-step of rational prescribing from the Guide to Good Prescribing

Who-6-step of rational prescribing

1 Patient's problem	Symptoms Diagnosis Patient characteristics
2 Therapeutic objective	With parameters - curative - symptomatic - preventive - palliative
3 Treatment choice	A Standard treatment based on available evidence
	B Verify suitability for patient - contra-indications - interactions - co-medications
4 Start treatment	Writing prescription Starting treatment
5 Give patient information, instruction	Patient information Instructions Warnings
6 Monitor treatment	Monitor treatment based on effect - continue - adjust - or stop

Figure 4. WHO-6-step of rational prescribing in a case of a 83 year old man

Who-6-step of rational prescribing

1 Patient's problem	83 year old man with dementia experiencing frightening visual hallucinations
2 Therapeutic objective	- Symptomatic - Reduction of fear and hallucinations
3 Treatment choice	A Dutch guideline Verenso 2017
	B Haloperidol: - Contraindications, patient falls once a week - Because all antipsychotics increase risk of falls, no safer alternative is available
4 Start treatment	Haloperidol 1mg once daily ante noctem
5 Give patient information, instruction	Take one tablet before going to sleep, beware of elevated risk of falls
6 Monitor treatment	Monitor treatment for one week: - No effect - Increase in falls - Stop medication

This makes clear that prescribing in frail older patients is trial and error and that it is important to closely monitor your patient. Randomised Controlled Trials are not always helpful. A drug that doesn't work in 90% of the patients, can work in the other 10%. The model of n=1, personalized care for the individual patient should be used more. Patient behaviour is not as black or white with reference values as a glucose level or a blood pressure.

Given the results of this thesis and the current knowledge regarding serious adverse events, doctors should be very reserved in prescribing antipsychotic drugs for problematic behaviour. In the Netherlands, antipsychotics are used by 37% of the nursing home patients with dementia.[8] This number of prescriptions, can never be explained and defended on current evidence. The results from this thesis contribute to knowledge that can be used for the clinician in balancing between limited effectiveness of antipsychotics and serious adverse effects in older patients.

Implications for future research

What is necessary to reduce lack of knowledge and decrease clinical uncertainty? This thesis adds some elements of evidence. However, there is still a lot unknown about the pathophysiology of side effects associated with antipsychotic use. We didn't find an explanation for inter-individual variation of extrapyramidal side effects in haloperidol users. An age related decline of endogenous dopamine in the brain has been a consistent finding in post-mortem studies.[38] They suggest a decline in dopamine level of 5-15% per decade.[38] Position emission tomography imaging now allows for the endogenous dopamine level in vivo by using paradigms involving competitive binding of endogenous dopamine and dopaminergic radiotracers to dopamine receptors in response to the administration of an antipsychotic[38]. The hypothesis can be tested in a study by measuring plasma concentration of an antipsychotic, dopamine D2 receptor occupancy for a given dose and relating these findings to clinical outcomes in elderly (measuring extrapyramidal symptoms).

We didn't find an association between AP use and changes in coagulation parameters. The underlying cause and pathophysiology for the increase in cardio- and cerebrovascular events remains to be established. The diagnoses of schizophrenia as well as hospitalization increases sympathic activation and catecholamine blood levels are prothrombogenic factors.[39] Prospective studies are needed to elucidate the biological mechanisms involved in the relationship between cerebrovascular accidents, venous thrombo-embolism and antipsychotic medication versus the mental disorder itself.

We were the first to find an increased risk in urinary tract infections in older antipsychotic users. There were no earlier studies that showed this association before. The association was the strongest in the first week after start of the antipsychotic. It is unknown what the mechanism is that causes this increased risk. Besides urinary tract infection, others found an association of antipsychotics and pneumonia.[20] The association of antipsychotic drug use and different infections suggests that there is a possible effect of antipsychotic drugs on the

immune system. Antipsychotic drugs influence the production of cytokines.[40] Psychotropic medications have been shown to modulate immune activation. However, the effects of individual psychotropic agents on the immune system and how these might contribute to their efficacy remain largely unclear.[41] Haloperidol, Clozapine, Risperidon and Quetiapine showed inconclusive patterns of immunomodulation.[41] Many antipsychotics induce metabolic syndrome, a condition associated with increased inflammation. It is difficult to disentangle whether these increases in inflammatory markers are a direct consequence of the treatment rather than of their metabolic effects.[41] More research is necessary to investigate how antipsychotics modulate immune modulation.

Besides the need for future research to unravel pathophysiological mechanisms in antipsychotics users, there is also a need to monitor serious adverse events. In the Netherlands, information should be collected about monitoring after the start of an antipsychotic. A Dutch version of the UKU-SERS-Clin should be validated in an older population. This study can be performed in nursing home residents, geriatric or psychiatric wards in the Netherlands.
Physicians, nurses and patients should be stimulated to report adverse drug effects for all drugs, not only antipsychotic drugs. In the Netherlands, reporting serious adverse events is mandatory. An initiative to stimulate adverse drug effects reporting has started in the Jeroen Bosch Hospital, 's-Hertogenbosch. This hospital is a model for reporting adverse drug effects in collaboration with LAREB, the Dutch pharmacovigilance center. All health care workers in this hospital can report a case of an adverse drug reaction by email. Clinical pharmacologists study these cases sent by email. Aim of this collaboration is how reporting of adverse drug effects in hospital can be stimulated and to improve patient safety.

A guideline for participation of older patients in medical research can help in including more frail older patients and thereby improve evidence based medicine in this vulnerable group.

Final thoughts and overall conclusion

For better implementation of the Dutch guideline from Verenso, for treatment of behavioural problems in older patients with dementia, with an update in 2017, a change in the system is necessary. Seager wrote in 1955: "A problem is the shortage of nursing staff."[2] This hasn't changed in 62 years. Hugo Borst en Carin Gaemers presented in the "Algemeen Dagblad" from October 2016 "the manifest sharp on care for older patients".[42] To carry out this manifest, 70.000 extra health care professionals and two billion euro is necessary.[43] One tablet of haloperidol costs 3 euro cents, a nurse is a lot more expensive.

This thesis shows that given the broad spectrum of serious side effects, anti-psychotic use should be restricted to those patients for whom the treatment is judged to be absolutely necessary. Health care workers should improve their knowledge about the effect and adverse effects of antipsychotic medication. Antipsychotic medication should be evaluated on effect and on side effects after the start and should be monitored closely, especially in the first week after the start.

References

1. GIPdatabank Nederland. Available at: https://www.gipdatabank.nl/databank.asp?tabel=01-basis&geg=gebr&item=N05. Accessed January, 2017.
2. Seager CP. Chlorpromazine in treatment of elderly psychotic women. Br Med J 1955;1:882-5.
3. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11-9.
4. FDA. Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances. Washington, DC, Department of Health and Human Services. 2005. Available at: http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm053171. Accessed January, 2017.
5. Nederlandse richtlijn voor antipsychoticagebruik bij ouderen 2002. Available at: http://www.zzpclientagenda.nl/ECD%20files/M32/Doc/RICHTLIJN%20PROBEELGEDRAG.doc. Accessed January, 2017.
6. Richtlijn Probleemgedrag Verenso 2006. Available at: http://www.verenso.nl/assets/Uploads/Downloads/Richtlijnen/VER00316Probleemgedragherzien02.pdf. Accessed January, 2017.
7. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 2006;355:1525-38.
8. Nijk RM, Zuidema SU, Koopmans RT. Prevalence and correlates of psychotropic drug use in Dutch nursing-home patients with dementia. Int Psychogeriatr 2009;21:485-93.
9. Hollingworth SA, Siskind DJ, Nissen LM, et al. Patterns of antipsychotic medication use in Australia 2002-2007. Aust N Z J Psychiatry 2010;44:372-7.
10. Schneider LS, Pollock VE, Lyness SA. A metaanalysis of controlled trials of neuroleptic treatment in dementia. J Am Geriatr Soc 1990;38:553-63.
11. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934-43.
12. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 2013. Available at: http://www.wma.net/en/30publications/10policies/b3/. Accessed January, 2017.
13. Kim SY. The ethics of informed consent in Alzheimer disease research. Nat Rev Neurol 2011;7:410-4.
14. van Assema DM, Lubberink M, Bauer M, et al. Blood-brain barrier P-glycoprotein function in Alzheimer's disease. Brain 2012;135:181-9.
15. Bloch F, Charasz N. Attitudes of older adults to their participation in clinical trials: a pilot study. Drugs Aging 2014;31:373-7.
16. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44:827-36.
17. Kleijer BC, van Marum RJ, Egberts AC, et al. Risk of cerebrovascular events in elderly users of antipsychotics. J Psychopharmacol 2009;23:909-14.
18. Parker C, Coupland C, Hippisley-Cox J. Antipsychotic drugs and risk of venous thromboembolism: nested case-control study. BMJ 2010;341:c4245.
19. Yu ZH, Jiang HY, Shao L, et al. Use of antipsychotics and risk of myocardial infarction: a systematic review and meta-analysis. Br J Clin Pharmacol 2016;82:624-32.
20. Knol W, van Marum RJ, Jansen PA, et al. Antipsychotic drug use and risk of pneu-

monia in elderly people. J Am Geriatr Soc 2008;56:661-6.
21. Cahn W, Ramlal D, Bruggeman R, et al. Preventie en behandeling van somatische complicaties bij antipsychoticagebruik. Tijdschrift voor Psychiatrie 2008:579-91.
22. de Araujo AA, de Araujo Dantas D, do Nascimento GG, et al. Quality of life in patients with schizophrenia: the impact of socio-economic factors and adverse effects of atypical antipsychotics drugs. Psychiatr Q 2014;85:357-67.
23. Day JC, Kinderman P, Bentall R. A comparison of patients' and prescribers' beliefs about neuroleptic side-effects: prevalence, distress and causation. Acta Psychiatr Scand 1998;97:93-7.
24. Lindstrom E, Lewander T, Malm U, et al. Patient-rated versus clinician-rated side effects of drug treatment in schizophrenia. Clinical validation of a self-rating version of the UKU Side Effect Rating Scale (UKU-SERS-Pat). Nord J Psychiatry 2001;55 Suppl 44:5-69.
25. Suzuki T. Which rating scales are regarded as 'the standard' in clinical trials for schizophrenia? A critical review. Psychopharmacol Bull 2011;44:18-31.
26. Knol W, Keijsers CJ, Jansen PA, et al. Systematic evaluation of rating scales for drug-induced parkinsonism and recommendations for future research. J Clin Psychopharmacol 2010;30:57-63.
27. Knol W, van Marum RJ, Jansen PA, et al. Parkinsonism in elderly users of haloperidol: associated with dose, plasma concentration, and duration of use. J Clin Psychopharmacol 2012;32:688-93.
28. Richter T, Meyer G, Mohler R, et al. Psychosocial interventions for reducing antipsychotic medication in care home residents. Cochrane Database Syst Rev 2012;12:CD008634.
29. Zuidema SU, Koopmans RTCM, Schols JMGA, et al. Trends in psychofarmaca gebruik bij patienten met dementie. Tijdschrift voor Ouderengeneeskunde 2015;april.
30. Cornege-Blokland E, Kleijer BC, Hertogh CM, et al. Reasons to prescribe antipsychotics for the behavioral symptoms of dementia: a survey in Dutch nursing homes among physicians, nurses, and family caregivers. J Am Med Dir Assoc 2012;13:80.e1,80.e6.
31. Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. JAMA 2012;308:2020-9.
32. Kiosses DN, Ravdin LD, Gross JJ, et al. Problem adaptation therapy for older adults with major depression and cognitive impairment: a randomized clinical trial. JAMA Psychiatry 2015;72:22-30.
33. Teri L, Logsdon RG, Uomoto J, et al. Behavioral treatment of depression in dementia patients: a controlled clinical trial. J Gerontol B Psychol Sci Soc Sci 1997;52:P159-66.
34. Guetin S, Portet F, Picot MC, et al. Effect of music therapy on anxiety and depression in patients with Alzheimer's type dementia: randomised, controlled study. Dement Geriatr Cogn Disord 2009;28:36-46.
35. Ballard CG, O'Brien JT, Reichelt K, et al. Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with Melissa. J Clin Psychiatry 2002;63:553-8.
36. Ballard C, Lana MM, Theodoulou M, et al. A randomised, blinded, placebo-controlled trial in dementia patients continuing or stopping neuroleptics (the DART-AD trial). PLoS Med 2008;5:e76.
37. de Vries, TPGM, Henning RH, Hogerzeil HV,

et al. Guide to good prescribing - A practical manual. Geneva: World Health Organisation; 1994. Available at: http://apps.who.int/medicinedocs/pdf/whozip23e/whozip23e.pdf. Accessed January, 2017.
38. Uchida H, Mamo DC, Mulsant BH, et al. Increased antipsychotic sensitivity in elderly patients: evidence and mechanisms. J Clin Psychiatry 2009;70:397-405.
39. Masopust J, Maly R, Andrys C, et al. Markers of thrombogenesis are activated in unmedicated patients with acute psychosis: a matched case control study. BMC Psychiatry 2011;11:2.
40. Pollmacher T, Haack M, Schuld A, et al. Effects of antipsychotic drugs on cytokine networks. J Psychiatr Res 2000;34:369-82.
41. Baumeister D, Ciufolini S, Mondelli V. Effects of psychotropic drugs on inflammation: consequence or mediator of therapeutic effects in psychiatric treatment?. Psychopharmacology (Berl) 2016; 233:1575-89.
42. Scherp op ouderenzorg manifest. Available at: http://www.ad.nl/gezond/het-manifest-kunt-u-hier-lezen-en-ondertekenen~a0c31272/. Accessed January, 2017.
43. Manifest ouderenzorg Hugo Borst. Available at: http://www.nu.nl/politiek/4381584/manifest-ouderenzorg-hugo-borst-zou-2-miljard-euro-kosten.html. Accessed January, 2017.

6.

Summary and Summary in Dutch / Nederlandse samenvatting

Summary

Antipsychotics are frequently prescribed to older patients for treatment of delirium and behavioural problems in dementia. In the Netherlands there are more than 300.000 antipsychotic users, of which more than 88.000 older than 65 years. However, antipsychotics can have serious adverse effects.

From a pharmacokinetic and pharmacodynamic perspective side effects can be better understood. Most side effects seem to be a group effect and are not limited to a single drug. In **chapter 2.1** we investigated a large, not well understood, inter-individual variation in effect and side effects (in particular antipsychotic induced parkinsonism) in older patients. This was studied in haloperidol, the first choice antipsychotic in treatment of delirium. We investigated two possible explanations in pharmacokinetics. First we investigated polymorphisms of the cytochrome P450 CYP2D6, because this contributes to the biotransformation of haloperidol. Second, we investigated variation in transport over the blood-brain barrier (BBB). We included 20 patients >64 years with an elevated risk to develop delirium who were prescribed haloperidol 1mg/day during five days before an elective surgery performed under spinal anaesthesia. Introductory the surgery, cerebrospinal fluid (CSF) (2ml) and a blood sample (2ml) were taken. We found a large inter-individual variation in haloperidol serum concentrations (factor 6). Serum and CSF concentrations of haloperidol averaged 0.52 µg/litre (range 0.17-0.99µg/litre) and 0.04 (range <0.01-0.09µg/litre) respectively (ratio averaged 11.45%). The correlation of CSF and serum concentration was significant ($r=0.85$, $p<0.05$). Variation in serum levels haloperidol could not be explained by differences in drug metabolism resulting from polymorphisms of CYPD2D6. Variability in transport over the BBB is not the explanatory factor for inter-individual variation in response. An alternative explanation is the number of remaining dopamine-2 receptors in the brain.
In **chapter 2.2** we investigated whether factors of thrombogenesis are activated in older, non-psychotic hospitalised patients treated with haloperidol.

We wanted to reveal the underlying mechanism of the increase in (cerebro) vascular events in older antipsychotic users. With a subset of patients included in a randomised, stratified, double-blind, placebo-controlled trial "Haloperidol prophylaxis in older emergency department patients" HARPOON study we studied this research question. This subset of patients consisted of all the patients that were included in the Jeroen Bosch Hospital between June 2014 and March 2015. Patients >70 years with an increased risk of developing delirium, according to the "VMS criteria", were randomised to haloperidol 1mg twice a day or placebo. Before the start of haloperidol and at day 6, after 10 gifts of haloperidol, blood was collected. In the Jeroen Bosch Hospital we analysed 16 patients that received haloperidol in comparison to 18 patients that received placebo. There were no significant changes in levels of markers of thrombogenesis fibrinogen and D-dimer, p-selectin as marker of platelet activation, and von Willebrand factor and osteoprotegerin as markers of endothelial activation between the haloperidol and the placebo group. We did find a significant difference in both groups over time, between day 1 and day 6, in which haloperidol is not the direct cause of changes in trombogenic factors. Fibrinogen increased significant during the hospital stay and P-selectin decreased significant in both groups over time. Possibly there are indirect factors that are related to the disease or hospital admission that could be the explanation.Thus the underlying cause of the increase in cerebrovascular events seen in haloperidol users remains to be established.

In **chapter 3** we investigated different side effects in frail older patients in clinical practice. Falls in the elderly are common and often serious. The general message that psychotropic drugs increase falls is already well accepted. However, the contribution of specific psychotropic drugs to fall frequency in elderly has not been quantified precisely until now. We describe this in **chapter 3.1**. Between 1st January 2011 and 1st April 2012 416 patients visited the day clinic of the department of geriatric medicine of the University Medical Centre Utrecht. Psychotropic medication use was present in one third (34%) of the patients. Patients who used psychotropic medications had a significant lower gait speed on the 4 meter walk test (0.8 versus 0.9m/second, p-value 0.041) and lower isometric grip strength (29.3 versus 37.9kg, p-value 0.001) compared to non users. Frequent falling, at least more than two time in the past year, was after correction for confounders a risk factor in antipsychotic users (OR 3.62, 95% CI 1.27-10.33). Hypnotic and anxiolytic medication use was significantly associated with frequent falls (OR 1.81; 95% CI 1.05-3.11) as well as short-acting

benzodiazepines or Z-drugs use (OR 1.94; 95% CI 1.10-3.42) and antidepressant use (OR 2.35; 95% CI 1.33-4.16). The use of different groups of psychotropic medication was strongly associated with falls. This relation should be explicitly recognised by doctors prescribing for older people, and by older people themselves. If possible such medication should be avoided for elderly patients especially with other risk factors for falling.

Over the last decade new side effects in antipsychotic medication are still found. In previous studies it is suggested that treatment with antipsychotics increases the risk of mortality in older patients. Although the cause of this increased mortality is not completely understood, antipsychotic drug use is associated with an increased risk of cardiovascular events, such as stroke, thrombo-embolic events, and cardiac arrhythmia, and infections, such as pneumonia. In **chapter 3.2** we investigated the association between urinary tract infections (UTIs) and antipsychotic drug use in older women. In a cohort study between 1998 and 2008 we looked at recurrent prescriptions of nitrofurantoin, as representation for uncomplicated UTI in women >65 years. Person time for current use of antipsychotic was compared to past use of an antipsychotic. For this study we used data from the PHARMO Database Network. The PHARMO database network includes the pharmacy dispensing records of community dwelling residents in the Netherlands. In total 18,541 women were followed from their first prescription of an antipsychotic till the end of their registration in the database or the end of the study period. Current use of antipsychotics was associated with a 33% increased risk of UTIs compared with past use (adjusted for age and history of urinary tract infections HR 1.33, 95% CI 1.27-1.39). The risk of getting a UTI was higher in the first week after start of the antipsychotic medication (adjusted HR 3.03, 95% CI 2.63-3.50). Conventional antipsychotics showed a slightly higher point estimator (HR 1.36, 95% CI 1.30-1.43) than atypical antipsychotics (HR 1.22, 95% CI 1.13-1.30). As we did not have access to clinical data, the presence of a urinary tract infection was based on the prescription of nitrofurantoin, which could have led to misclassification. In general, Dutch physicians are reluctant to prescribe antimicrobial drugs because of the risk of resistance, and treat only those patients with a proven or very high suspicion of infection. Complicated UTIs are treated with antibiotics that reach urine and tissue, such as fluorochinolones, and so we cannot generalize our findings to complicated urinary tract infections. The association between uncomplicated UTIs and antipsychotic use is probably an underestimation, because antibiotics other than nitrofurantoin are also prescribed for uncomplicated urinary tract infections. If these findings were also generalisable to men and to complicated

urinary tract infections we studied this research question in **chapter 3.3**. For this study we used the Clinical Practice Research Datalink (CPRD). This is an anonymised database containing approximately 12 million complete electronic medical records from over 600 participation general practices across the United Kingdom. Primary care diagnoses, prescriptions, laboratory test results, referrals and patient demographics are recorded in the CPRD using a hierarchical clinical coding system (Read codes). In this cohort study we also looked at recurrent urinary tract infections in older antipsychotic users. During the study period, 191,827 patients (63.7% women, mean age 77 years) with a first prescription of an oral antipsychotic drug were identified. Current use of antipsychotics was associated with an increased risk of UTI compared with past use (adjusted HR 1.31, 95% CI 1.28-1.34). The strongest effect was found within the first 14 days after the start of the antipsychotic (adjusted HR 1.83, 95% CI 1.73-1.95) and for patients with more than one antipsychotic drug concomitantly (adjusted HR 1.64, 95% CI 1.45-1.87). The risk was slightly higher for conventional antipsychotics (adjusted HR 1.37, 95% CI 1.33-1.41) compared to atypical antipsychotics (adjusted HR 1.24, 95% CI 1.21-1.28). Stratification by sex showed that risk estimates were slightly higher in men than in women.

The mechanism how antipsychotics cause urinary tract infections is unknown. D2-receptor antagonists have been suggested to influence the capacity and residual volume of the bladder. Anticholinergic side effects of antipsychotic medication are another cause of urine retention. The retention of urine, which can lead to bacterial growth, possibly underlies the increase in uncomplicated UTI. Doctors should be alert to the occurrence of UTIs in both men and women after the start of an antipsychotic drug, especially in the first two weeks.

In **chapter 4** we focus on the recognition and measurement of side effects in antipsychotics. As described before in this thesis, unfortunately, many patients experience side effects during treatment, which may result in an impaired quality of life and early treatment discontinuation. Adverse drug reactions are frequently missed, either because clinicians do not always ask about them or do not recognize complaints as possible side effects. There can be some discrepancies between the distress associated with certain side-effects by prescribers and consumers of antipsychotic drugs and the fact that patients are unlikely to attribute symptoms as side effects of antipsychotic medication. In this chapter we give an overview of all available scales to measure side effects in antipsychotics. Psychometric characteristics are described in terms of reliability and validity. Reliability is the extend in which results are influenced by accidental conditions. Validity is the extend that the test measures what it should

measure and what you really want to know. Some scales are used frequently, but psychometric characteristics are not always well described. Other scales are reliable and valid, but are almost never used in clinical practice. In total, we found 52 different scales that measure side effects of antipsychotics. To measure multi-domain side effects the Udvalg for Kliniske Undersøgelser Side Effects Rating Scale for Clinicians (UKU-SERS-Clin) was used the most. The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) had de best psychometric characteristics (Cronbach's α 0.81 and test-retest reliability 0.89). The Glasgow Antipsychotic Side effect Scale (GASS) is the fastest and takes 5 minutes to complete. The scales differ in number of items that are scored, the time to complete the scale and if the scale is filled out by the patient self or by the clinician. The Simpson Angus Scale (SAS), followed by the Abnormal Involuntary Movements Scale (AIMS) and the Barnes Akathisie Rating Scale (BARS) were used the most to assess extrapyramidal side effects, however the Maryland Psychiatric Research Center scale (MPRC scale) had the best characteristics (Cronbach's α 0.80, test-retest reliability 0.92 and inter-rater reliability 0.81-0.90). The Arizona Sexual Experience Scale (ASEX) was used the most to measure sexual dysfunction, but the Antipsychotics and Sexual functioning Questionnaire (ASFQ) and the Nagoya Sexual Functioning Questionnaire had the best characteristics. It should be noted that potentially life threatening side effects such as neuroleptic malignant syndrome, significant QTc prolongation are also very important, although they fail to be captured with the existing rating scales. The prescribing physician should consider basing the selection of antipsychotics in light of the differences in side effects profiles, rather than those in antipsychotic efficacy. The prescribing physician should monitor adverse drug reactions and can use one of the scales above.

Finally **chapter 5** describes a general discussion where the individual studies of this thesis are placed in a broader perspective.

Nederlandse samenvatting

Antipsychotica worden frequent voorgeschreven aan oudere patiënten voor de behandeling van een delier of gedragsproblemen bij dementie. In Nederland zijn er meer dan 300.000 antipsychotica gebruikers, onder wie er meer dan 88.000 ouder zijn dan 65 jaar. Antipsychotica kunnen echter ernstige bijwerkingen hebben.

Bijwerkingen kunnen beter begrepen worden door verdieping in de farmacokinetiek (wat doet het lichaam met het geneesmiddel) en farmacodynamiek (wat doet het geneesmiddel met het lichaam) van deze middelen. De meeste bijwerkingen lijken tot nu toe een groepseffect te zijn en zijn niet gelimiteerd tot een afzonderlijk middel. In **hoofdstuk 2.1** onderzochten we een grote, onbegrepen, inter-individuele variatie in effect en bijwerkingen bij ouderen (met name antipsychotica geïnduceerd parkinsonisme). Dit werd bestudeerd bij haloperidol, het eerste keus medicament bij de behandeling van een delier. We onderzochten twee mogelijke verklaringen hiervoor in de farmacokinetiek. Allereerst het verschil in polymorfismen van het cytochroom P450 CYP2D6, want deze enzymen dragen bij aan de biotransformatie van haloperidol. Ten tweede verschil in variatie in transport over de bloed-hersen-barrière. We includeerden 20 patiënten vanaf 65 jaar met een verhoogd risico op een delier, die gedurende 5 dagen haloperidol 1 maal daags 1 mg als profylaxe kregen voorgeschreven voor een electieve operatie. Voorafgaand aan de operatie werd bloed afgenomen en tijdens de spinaal anesthesie werd liquor van deze patienten afgenomen. Er bleek een grote spreiding in serum haloperidol concentraties (factor 6). Daarnaast bleek er een zeer hoge correlatie tussen liquor- en serumspiegels ($r=0,85$, $p<0,05$, bij een gemiddelde serumconcentratie van 0,52 µg/liter (spreiding 0,17-0,99µg/liter) en gemiddelde liquorconcentratie van 0,04 (spreiding <0,01-0,09µg/liter) (ratio gemiddeld 11,45%). De spreiding in serum spiegels haloperidol kon niet verklaard kon worden door verschillen in metabolisme als gevolg van polymorfismen van CYP2D6. Ook variabiliteit in transport over de bloed-hersen-barrière lijkt niet de verklaring te zijn voor inter-individuele

variatie in respons. Een alternatieve verklaring zou de variatie in het aantal overgebleven dopamine-2 receptoren in de hersenen kunnen zijn.
In **hoofdstuk 2.2** onderzochten we farmacodynamische effecten, namelijk of trombogenese factoren worden geactiveerd bij niet psychotische, oudere haloperidol gebruikers, om het onderliggende mechanisme van de toename in (cerebro)vasculaire events te kunnen verklaren. In een substudie van de gerandomiseerde, gestratificeerde, dubbel-blinde, placebo-gecontroleerde studie "HAlopeRidol Profylaxe bij Oudere patiënten die via de spoedeisende hulp worden OpgenomeN", de zogenaamde HARPOON studie hebben we deze vraag onderzocht. Deze subset van patiënten bestond uit alle patiënten die in het Jeroen Bosch ziekenhuis werden geïncludeerd tussen juni 2014 en maart 2015. Patiënten boven de 70 jaar met een verhoogd risico op een delier volgens de VMS (veiligheidsmanagmentsysteem) criteria, werden gerandomiseerd om haloperidol 1 mg twee maal daags of placebo te krijgen. Voor het starten van haloperidol en op dag 6, na 10 giften haloperidol werd bloed afgenomen. In het Jeroen Bosch Ziekenhuis analyseerden we 16 patiënten die haloperidol hadden gekregen in vergelijking met 18 patiënten die placebo hadden ontvangen. Er waren geen significante verschillen tussen de haloperidol en placebo groep in de stollingsmarkers: fibrinogeen en D-Dimeer, plaatjes activatie marker: P-selectine en endotheelcelactivatie markers: von Willebrand factor en osteoprotegerine. Er was wel een significant verschil in beide groepen over de tijd (dag 1 versus dag 6), dus haloperidol lijkt niet een rechtstreekse veroorzaker van veranderde stolling. Fibrinogeen steeg significant tijdens de ziekenhuisopname en P-selectine daalde significant in beide groepen. Wellicht zijn er indirecte factoren, die ziekte- of ziekenhuis gebonden zijn die verklarend zouden kunnen zijn. Het mechanisme van het verhoogde risico op trombose en CVA bij antipsychoticagebruikers blijft hiermee onverklaard.

In **hoofdstuk 3** onderzochten we verschillende bijwerkingen bij kwetsbare ouderen in de klinische praktijk. Vallen komt bij ouderen regelmatig voor en kan ernstige gevolgen hebben. Dat gebruik van psychofarmaca een oorzaak kan zijn voor vallen, is al langer bekend. Welke bijdrage specifieke groepen van psychofarmaca hieraan leveren hebben we nader onderzocht in **hoofdstuk 3.1**. Tussen 1 januari 2011 en 1 april 2012 bezochten 416 patiënten de dagkliniek van de afdeling geriatrie van het Universitair Medisch Centrum in Utrecht. Ongeveer een derde van deze patiënten gebruikten psychofarmaca. Patiënten die psychofarmaca gebruikten hadden een significant lagere snelheid op de 4 meter looptest (0,8 versus 0,9 m/seconde; p-waarde 0,041) en een lagere handknijpkracht

(29,3 versus 37,9kg; p-waarde 0,001), in vergelijking met niet gebruikers. Frequent vallen, dat wil zeggen meer dan twee keer een val in het afgelopen jaar, kwam na correctie van confounders, vaker voor bij antipsychoticagebruikers (Odds Ratio (OR) 3,62; 95% BI 1,27-10,33). Bij gebruik van langwerkende benzodiazepines, maar ook bij gebruik van kortwerkende benzodiazepines en Z-drugs kwam frequenter vallen voor (OR 1,81; 95% BI 1,05-3,11). Antidepressiva hadden een (gecorrigeerde OR van 2,35; 95% BI 1,33-4,16). Samenvattend betekent dat, dat het gebruik van verschillende groepen psychofarmaca sterk geassocieerd was met vallen. Dokters zouden zich bewust moeten zijn van deze bijwerking, wanneer ze deze medicatie voorschrijven aan kwetsbare ouderen. Waarschijnlijk is het zinvol om deze medicatie te proberen te staken. Bij patiënten met andere risicofactoren voor vallen, is het advies om terughoudend te zijn met voorschrijven van de verschillende psychofarmaca.

In de laatste decennia worden nog steeds nieuwe bijwerkingen aangetoond van antipsychotica. In eerdere studies wordt gesuggereerd dat behandeling met antipsychotica het risico op sterfte verhoogd bij ouderen. Cerebrovasculaire en cardiovasculaire ziekten worden als mogelijke oorzaken van deze verhoogde sterfte beschouwd. Eerder werd ook al aangetoond dat patiënten die antipsychotica gebruiken, in de eerste week na starten een verhoogde kans hebben op het ontwikkelen van een pneumonie. In **hoofdstuk 3.2** onderzochten we de associatie tussen urineweginfecties en het gebruik van antipsychotica bij oudere vrouwen. In een cohort studie tussen 1998 en 2008 keken we naar het herhaaldelijk voorkomen van voorschriften nitrofurantoïne, als representatie voor het voorkomen van ongecompliceerde urineweginfecties bij vrouwen boven de 65 jaar. Persoonstijd tijdens gebruik van een antipsychoticum werd vergeleken met persoonstijd van mensen die in het verleden een antipsychoticum hadden gebruikt. Voor deze studie hebben we gebruik gemaakt van een grote database met daarin afleverdata van verschillende apotheken van een groot aantal inwoners van Nederland (PHARMO). In totaal werden 18.541 vrouwen vanaf hun eerste voorschrift van een antipsychoticum gevolgd tot aan het einde van hun registratie in de database of het einde van de studieperiode. Huidig gebruik van een antipsychoticum bleek significant geassocieerd te zijn met het krijgen van ongecompliceerde urineweginfecties, in vergelijking met gebruik van een antipsychoticum in het verleden. Gecorrigeerd voor leeftijd en voorgeschiedenis van urineweginfecties gaf dit een (Hazard Ratio (HR) van 1,33; 95%BI 1,27-1,39). Het risico op een urineweginfectie was het hoogst in de eerste week van gebruik van een antipsychoticum (HR 3,03; 95% BI 2,63-3,50). Klassieke antipsychotica hadden een licht hoger risico (HR 1,36; 95% BI

1,30-1,43) dan atypische antipsychotica (HR 1,22; 95% BI 1,13-1,30). We hadden alleen data van medicatie voorschriften in deze studie en niet van diagnoses. Nederlandse artsen staan er om bekend dat ze terughoudend zijn met het voorschrijven van antibiotica en dit alleen doen bij een bewezen infectie of een zeer hoge verdenking hierop. Urineweginfecties worden niet slechts behandeld met nitrofurantoïne, hoewel dit de eerste keus is volgens de Nederlandse Huisartsen Genootschap standaard, maar ook met andere soorten antibiotica. Dit kan tot misclassificatie hebben geleid en daarmee waarschijnlijk een onderschatting van het effect. Om te onderzoeken of deze bevindingen ook voor mannen golden en voor gecompliceerde urineweginfecties onderzochten we deze vraag in **hoofdstuk 3.3**. Voor deze studie werd gebruik gemaakt van de Clinical Practice Research Datalink (CPRD). Dit is een ge-anonimiseerde database die elektronische gegevens bevat van 12 miljoen patiënten, vanuit 600 participerende huisartspraktijken in Groot Brittannië. Medische diagnoses, medicatievoorschriften, verwijzingen, laboratoriumuitslagen en demografische gegevens worden bijgehouden volgens een codeersysteem. Ook in deze cohort studie werd gekeken naar het terugkerend voorkomen van urineweginfecties tijdens het gebruik van antipsychotica. Gedurende de studieperiode werden er 191.827 patiënten (63.7% vrouwen, gemiddelde leeftijd 77 jaar) met een eerste voorschrift van een oraal antipsychoticum geïdentificeerd. Huidig gebruik van een antipsychoticum was geassocieerd met een verhoogd risico op een urineweginfectie in vergelijking met gebruik van een antipsychoticum in het verleden (gecorrigeerde HR 1,31; 95% BI 1,28-1,34). Het sterkste effect werd gevonden in de eerste 14 dagen na de start van het antipsychoticum (gecorrigeerde HR 1,83; 95% BI 1,73-1,95) en bij patiënten met gelijktijdig gebruik van meer dan één antipsychoticum (gecorrigeerde HR 1,64; 95%CI 1,45-1,87). Het risico was iets hoger voor gebruik van klassieke antipsychotica (gecorrigeerde HR 1,37; 95% BI 1,33-1,41) in vergelijking met atypische antipsychotica (gecorrigeerde HR 1,24; 95% BI 1,21-1,28). Stratificatie voor geslacht liet een licht hoger risico zien voor mannen in vergelijking met vrouwen.

Het onderliggende mechanisme hoe antipsychotica urineweginfecties veroorzaken is onbekend. Van D2 receptor antagonisten wordt gesuggereerd dat deze invloed hebben op de capaciteit en het residu volume in de blaas. Daarnaast kunnen anticholinerge bijwerkingen zorgen voor blaasretentie. Residu in de blaas kan leiden tot groei van bacteriën, wat weer kan leiden tot een infectie. Voorschrijvers van antipsychotica zouden alert moeten zijn op het ontstaan van urineweginfecties bij mannen en vrouwen, voornamelijk in de eerste twee weken na voorschrijven van het antipsychoticum.

In **hoofdstuk 4** focussen we op de herkenning en het meten van bijwerkingen van antipsychotica. Zoals eerder beschreven in dit proefschrift hebben antipsychotica veel verschillende soorten bijwerkingen. Bijwerkingen kunnen resulteren in een verminderde kwaliteit van leven en het vroegtijdig staken van de behandeling. Bijwerkingen worden frequent gemist, omdat de arts er niet altijd naar vraagt, of de klachten van de patiënt niet als mogelijke bijwerking worden herkend. Er kan een discrepantie zijn in de last geassocieerd met bijwerkingen door voorschrijvers en gebruikers van antipsychotica. Patiënten herleiden klachten niet altijd als bijwerking van het antipsychoticum. We geven in dit hoofdstuk een overzicht van de beschikbare schalen om bijwerkingen van antipsychotica te meten. Hoewel bepaalde schalen veel worden gebruikt, is de betrouwbaarheid (de mate waarin de uitkomsten op een schaal beïnvloed worden door toevallige omstandigheden) en validiteit (de mate waarin daadwerkelijk gemeten wordt wat men wil weten) niet altijd goed onderzocht. Andersom zijn sommige schalen betrouwbaar en goed gevalideerd, maar worden in de klinische praktijk weinig gebruikt. In totaal werden 52 verschillende schalen gevonden die bijwerkingen van antipsychotica meten. Om meerdere bijwerkingen met één schaal te meten werd de Udvalg for Kliniske Undersøgelser Side Effects Rating Scale for Clinicians (UKU-SERS-Clin) het meest gebruikt. De Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) had de beste psychometrische karakteristieken (Cronbach's α 0.81 en test-hertest betrouwbaarheid 0.89). De Glasgow Antipsychotic Side effect Scale (GASS) is het snelst en in 5 minuten af te nemen. De schalen verschillen van elkaar in het aantal items dat gescoord wordt, de tijd om de schaal af te nemen en de rater (arts of patiënt zelf). De Simpson Angus Scale (SAS), gevolgd door de Abnormal Involuntary Movements Scale (AIMS) en de Barnes Akathisie Rating Scale (BARS) werden het meest gebruikt om extrapyramidale bijwerkingen te meten, hoewel de Maryland Psychiatric Research Center scale (MPRC scale) de beste karakteristieken had (Cronbach's α 0.80, test-hertest betrouwbaarheid 0.92 en inter-rater betrouwbaarheid 0.81-0.90). De Arizona Sexual Experience Scale (ASEX) werd het meest gebruikt om sexuele dysfunctie te meten, maar de Antipsychotics and Sexual functioning Questionnaire (ASFQ) en de Nagoya Sexual Functioning Questionnaire hadden de beste karakteristieken. Mogelijk levensbedreigende bijwerkingen zoals het maligne neurolepticasyndroom of QTc verlenging kunnen worden gemist bij het gebruik van de schalen. De voorschrijvende arts zou de keus van het antipsychoticum moeten richten op het bijwerkingenprofiel van het middel, meer dan op de effectiviteit. De voorschrijvende arts zou bijwerkingen moeten monitoren en zou bovengenoemde schalen hiervoor kunnen gebruiken.

Tenslotte omvat **hoofdstuk 5** een algemene discussie waarbij de resultaten van de individuele onderzoeken in dit proefschrift in een breder perspectief worden geplaatst.

7.

Appendices

List of Co-authors

Co-authors of manuscripts presented in this thesis and their affiliations during conductance of the research

Manuela di Biase	Department of Anaesthesiology, Jeroen Bosch Hospital, 's-Hertogenbosch
Adriaan J.C. Van den Brule	Laboratory for Molecular Diagnostics, Jeroen Bosch Hospital, 's-Hertogenbosch
Hieronymus J. (Jeroen) Derijks	Hospital Pharmacy ZANOB, 's-Hertogenbosch Utrecht Institute for Pharmaceutical Sciences (UIPS). Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht
Mariëlle H. Emmelot-Vonk	Department of Geriatric Medicine, University Medical Center, Utrecht
Eibert R. (Rob) Heerdink	Utrecht Institute for Pharmaceutical Sciences (UIPS). Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht

Carolina J.P.W. (Karen) Keijsers	Department of Geriatric Medicine, Jeroen Bosch Hospital, 's-Hertogenbosch
Huiberdina L. (Dineke) Koek	Department of Geriatric Medicine, University Medical Center, Utrecht
Petra M. (Marije) Leliveld - van den Heuvel	Department of Geriatric Medicine, Rijnland Hospital, Leiderdorp
Rob J. Van Marum	Department of Geriatric Medicine, Jeroen Bosch Hospital, Department of General Practice and Elderly Care Medicine VU University Medical Center, Amsterdam
Prabath W.B. Nanayakkara	Department of Internal Medicine, VU University Medical Center, Amsterdam
Nathalie C. Péquériaux	Thrombosis Service and Department of Clinical Chemistry and Haematology, Jeroen Bosch Hospital, 's-Hertogenbosch
Edmée J.M. Schrijver	Department of Internal Medicine, VU University Medical Center, Amsterdam
Patrick C. Souverein	Utrecht Institute for Pharmaceutical Sciences (UIPS). Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht
Annemieke Vermeulen Windsant - Van den Tweel	Hospital Pharmacy ZANOB, 's-Hertogenbosch

List of publications

Publications related to this thesis

van Strien AM, Schrijver EJM, Keijsers CJPW, Péquériaux NC, Nanayakkara PWB, Derijks HJ, van Marum RJ. Haloperidol does not activate thrombogenic factors in older, nonpsychotic, hospitalized patients. *J Clin Psychopharmacol.* 2017 May, 5.

van Strien AM, Souverein PC, Keijsers CJ, Heerdink ER, Derijks HJ, van Marum RJ. Antipsychotic drug use associated with urinary tract infections in older women. *Maturitas.* 2017 Apr;98:46-50.

van Strien AM, Keijsers CJ, Derijks HJ, van Marum RJ. Rating scales to measure side effects of antipsychotic medication: A systematic review.
J Psychopharmacol. 2015 Aug;29(8):857-66.

van Strien AM, Vermeulen Windsant-van den Tweel A, Leliveld-van den Heuvel M, di Biase M, van den Brule AJ, van Marum RJ. Correlation of haloperidol concentration in blood and cerebrospinal fluid: a pharmacokinetic study.
J Clin Psychopharmacol. 2014 Aug;34(4):516-7.

van Strien AM, Koek HL, van Marum RJ, Emmelot-Vonk MH. Psychotropic medications, including short acting benzodiazepines, strongly increase the frequency of falls in elderly.
Maturitas. 2013 Apr;74(4):357-62.

Other publications

Golüke NM, van Strien AM, Dautzenberg PJ, Jessurun N, Keijsers CJ. Skin lesions after oral acetylcholinesterase inhibitor therapy: a case report.
J Am Geriatr Soc. 2014 Oct;62(10):2012-3.

Schrijver EJ, de Vries OJ, Verburg A, de Graaf K, Bet PM, van de Ven PM, Kamper AM, Diepeveen SH, Anten S, Siegel A, Kuipéri E, Lagaay AM, van Marum RJ, van Strien AM, Boelaarts L, Pons D, Kramer MH, Nanayakkara PW. Efficacy and safety of haloperidol prophylaxis for delirium prevention in older medical and surgical at-risk patients acutely admitted to hospital through the emergency department: study protocol of a multicenter, randomised, double-blind, placebo-controlled clinical trial.
BMC Geriatr. 2014 Aug 28;14:96.

van Strien AM, Keijsers CJPW, Schouten HJ, BrouwersJRBJ; Factor Xa remmers en directe trombine remmers, nieuwe orale anticoagulantia (NOAC) bij kwetsbare ouderen.
Ins & Ouds, tijdschrift voor Geriatrie, December 2013, eerste jaargang; 16-23.

Van den Dool C, van Strien AM, den Akker IL, Bonten MJ, Sanders EA, Hak E. Attitude of Dutch hospital personnel towards influenza vaccination.
Vaccine. 2008 Mar 4;26(10):1297-302.

Curriculum Vitae

Astrid Maria van Strien was born on 18 oktober 1983 in Alphen aan den Rijn and grew up in Bunnik. In 2001 she graduated from her secondary school Utrechts Stedelijk Gymnasium. From 2001 till 2007 she studied medicine in Utrecht. After a year at the department of geriatric medicine at the Jeroen Bosch Hospital, 's-Hertogenbosch, she started her residency geriatric medicine. During her residency she worked two years at the internal medicine department of the Meander Medisch Centrum, Amersfoort, 9 months old age psychiatry at Pro Persona, Ede and 3 months at the neurology department at the Antonius hospital, Nieuwegein. For her residency geriatric medicine she worked at the Jeroen Bosch Hospital and the University Medical Center Utrecht. During her residency, she started a fellowship program in clinical pharmacology and the Basic University Teaching Qualicifation was obtained. During both her training programs, a start was made with her PhD. Since june 2013 she works as a geriatrician at the Jeroen Bosch hospital, 's-Hertogenbosch. In september 2013 she obtained her registration as a clinical pharmacologist. At the Jeroen Bosch Hospital, research and patient care activities were combined from that time on. Astrid lives in Vught with Lex Kurvink, together they have a daughter Veerle.

Dankwoord

Allereerst wil ik de deelnemers bedanken die vrijwillig en belangeloos wilden meewerken aan mijn onderzoek. Met mijn promotieteam bestaande uit Rob van Marum als promotor en Karen Keijsers en Jeroen Derijks als copromotoren had ik het niet beter kunnen treffen. Ik wil de Raad van Bestuur van het Jeroen Bosch ziekenhuis heel hartelijk bedanken dat zij mijn promotietraject hebben gefaciliteerd en mede mogelijk hebben gemaakt. Als promovendus van de VU ben ik maar al te blij dat ik een "Jeroen Bosch Ziekenhuis" team had. Een promotietraject gaat denk ik altijd met ups en downs, maar wat kan ik nu trots en tevreden zijn met het eindresultaat.

Beste Rob, ik wil je bedanken voor je optimisme en je vertrouwen. Vanaf het eerste moment was jij er van overtuigd dat ik dit promotietraject tot een goed einde zou brengen. Met je humor en relativeringsvermogen ben je een geliefde collega voor mij. Ik heb mogen profiteren van jouw grote netwerk en dankzij jou dit mooie proefschrift volbracht. Ik hoop dat ik nog lang op de kamer naast je zal zitten en dat ik bij je binnen kan blijven lopen.

Beste Karen, ik leerde je pas kennen in 2011 in het UMC Utrecht. Wie had ooit gedacht dat we zo goede vriendinnen zouden worden. In juni 2013 begonnen we gelijktijdig aan onze baan als klinisch geriater in het Jeroen Bosch Ziekenhuis. Zoals je toen tegen mij zei: "As, je hebt echt een vrouw nodig in je promotieteam!" Wat was ik blij dat je ook echt mijn co-promotor werd, dank voor al je positieve commentaren en lieve woorden. Samen gingen we op statistiek cursus, wat heb ik veel van je geleerd op dat gebied. Mede dank aan je tweelingzus Loes voor "controle" van "onze" statistiek. Ik heb bewondering voor je enorme energie en drijfkracht.

Beste Jeroen, ik wil je bedanken voor je methodologische kennis, die je als epidemioloog inbracht tijdens mijn promotieoverleg. Dankzij jouw prettige feedback,

werden mijn artikelen steeds beter. Ondanks je drukke werkzaamheden vanuit de apotheek reageerde je altijd snel en maakte je altijd tijd voor mijn stukken.

Ik wil mijn collega geriaters uit het Jeroen Bosch Ziekenhuis bedanken voor de tijd die ik kreeg om te werken aan mijn onderzoek. Janet Bootsma, Esther Cornegé, Paul Dautzenberg, Truuke Kamminga, Karen Keijsers, Angele Kerckhoffs en Rob van Marum, dankzij jullie collegialiteit, gezelligheid en humor ga ik iedere dag met veel plezier naar mijn werk.
Beste A(N)IOS, ik geniet er niet alleen van om jullie dingen te leren, door jullie blijf ik zelf ook iedere dag leren. Verpleegkundige, paramedici, secretaresses en andere medewerkers op de afdeling geriatrie, ik ben trots op dit fijne team.

Mijn speciale dank gaat ook uit naar Patrick Souverein. Beste Patrick, dank voor alle tijd die je vrij hebt gemaakt om samen met mij te werken aan de PHARMO en CPRD database. Ik keek met plezier uit naar de gezellige middagen in het David de Wied, waar we meestal begonnen met een kopje koffie en een verhaal over de vakantie. Op het gebied van methodologie en statistiek heb ik veel van je geleerd. Ook Rob Heerdink wil ik bedanken voor zijn bijdrage aan deze twee studies.

Ik wil Peter de Crom en Renate Paanakker, consultverpleegkundigen van de geriatrie in het JBZ speciaal bedanken voor al het extra werk dat ze voor mijn studies verricht hebben. Terwijl ik bij de ouderenpsychiatrie werkte in 2012, renden jullie soms zelfs mee naar de operatiekamer met een patiënt om maar te zorgen dat de buisjes met liquor correct werden afgenomen. In 2014 werd jullie team versterkt door Desiree Dudink. Met hulp van jullie drieën wisten we in ruim een half jaar tijd 52 patiënten te includeren voor de HARPOON studie, dank daarvoor!

Ik dank ook Edmée Schrijver, mijn collega promovendus aan de VU voor de samenwerking op de HARPOON studie, evenals Prabath Nanayakkara. Edmée, bedankt voor de gezelligheid en de discussies over het wel of niet geven van haloperidol.

Ik wil Eugenie Gemen bedanken voor de samenwerking hier met het laboratorium. Van jou punctualiteit kan ik nog wat leren. Mede dank aan Nathalie Péqueriaux voor de samenwerking.

Ik wil Adriaan van den Brule, Manuela di Biase, Erik van Maarseveen, Marije Leliveld – van den Heuvel en Annemieke Vermeulen Windsant – van den Tweel bedanken voor hun hulp en samenwerking bij de farmacokinetiek van haloperidol studie.

Dineke Koek en Mariëlle Emmelot-Vonk dank voor jullie begeleiding bij de cardiovasculaire database studie in het UMC Utrecht. Dineke, wat heb ik een bewondering voor jou als wetenschapper, met jouw nauwkeurige en kritische commentaar hebben we een mooi klinisch relevant artikel geschreven.

Henrike Schouten en Clara Drenth, oud-onderzoekers van de geriatrie, jullie waren voor mij een voorbeeld hoe je promotie onderzoek kan combineren met patiëntenzorg.

De leden van de leescommissie: prof. dr. M.L. Stek, prof. dr. F.G. Schellevis, prof. dr. A.C.G. Egberts, prof. dr. S.U. Zuidema, dr. W. Knol, wil ik hartelijk bedanken voor de beoordeling van mijn manuscript.

Lieve vriendinnen, wat ben ik blij dat ik jullie nog steeds met enige regelmaat zie. Saskia, Lizet, jullie ken ik al zo lang! Lieve Maaike, Wendy, Lotte, Fleur en Marlene, ook al ben ik weg uit Utrecht, ik ben blij dat ik jullie nog steeds regelmatig zie. Geneeskundevriendinnetjes vanaf het begin en hopelijk ook nog voor lang.
Lieve meiden van de "rollators, men & kids", Karen, Ilse-Sigrid, Marije, Esther, Marloes, we delen onze passie voor de geriatrie, maar daarnaast delen we ook lief&leed. Jullie vriendschap is heel waardevol voor mij. Een van jullie mijn co-promotor, twee van jullie zullen mijn paranimfen zijn.

Lieve Ilse-Sigrid en Marloes, mijn paranimfen, we begonnen in de zomer van 2010 samen in het Jeroen Bosch Ziekenhuis. Wat was het soms hard werken, maar we hadden altijd steun aan elkaar. Ilse-Sigrid, wat is jouw vriendschap waardevol voor mij. Je hebt het niet altijd even makkelijk gehad, met name ook het laatste jaar, toch was je altijd geïnteresseerd en stond je altijd voor me klaar. Marloes, wat ben je altijd vrolijk en lief.

Lieve opa en oma van Strien, dank dat jullie toestemming gaven om jullie schitterende foto op de kaft van mijn proefschrift af te laten drukken. Dank voor de interesse die jullie altijd tonen. Jullie zijn voor mij een voorbeeld hoe je gelukkig

samen oud kan worden. Mede door jullie heb ik gekozen voor het prachtige beroep klinisch geriater en daar heb ik nog altijd geen spijt van.

Lieve familie, Ferdinand, Jolinde, Niels, Mien, Chris en in het bijzonder lieve papa en mama, ik ben jullie dankbaar dat jullie er altijd voor me zijn. Papa en mama, van jullie heb ik mijn doorzettingsvermogen, wat ik goed heb kunnen gebruiken tijdens dit promotietraject. Ook al begreep niemand precies wat ik deed, jullie zagen mijn harde werken.

Lieve Lex, jij bent mijn maatje, wat hebben wij het goed samen op het Mariaplein in Vught. Dank dat je voor mij wilde verhuizen naar Brabant. Na een lange, drukke dag werken, kom ik blij weer thuis bij jou en Veerle. Wat hebben we samen een prachtig dochtertje. Ik hou heel veel van jullie!

This thesis shows that given the broad spectrum of serious side effects, antipsychotic use should be restricted to those patients for whom the treatment is judged to be absolutely necessary. Health care workers should improve their knowledge about the effect and adverse effects of antipsychotic medication. Antipsychotic medication should be evaluated on effect and on side effects after the start and should be monitored closely.

Astrid van Strien

Astrid van Strien is a geriatrician and clinical pharmacologist at the Jeroen Bosch Hospital, Den Bosch. Her grandfather and grandmother (cover) have been a great source of inspiration for her and one of the reasons she has chosen for geriatric medicine. This thesis is therefore dedicated to them. They are an example of how to grow old happily together.

ISBN: 978-94-92303-13-4