BALANCING THE BENEFITS AND RISKS OF ANTIPSYCHOTIC USE IN ELDERLY PATIENTS

Bart Kleijer

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BALANCING THE BENEFITS AND RISKS OF ANTIPSYCHOTIC USE IN ELDERLY PATIENTS

Een afweging van de baten en risico's van antipsychoticagebruik bij oudere patiënten
(met een samenvatting in het Nederlands)

Proefschrift

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Bart Christiaan Kleijer

geboren op 18 december 1965 te
Waddinxveen

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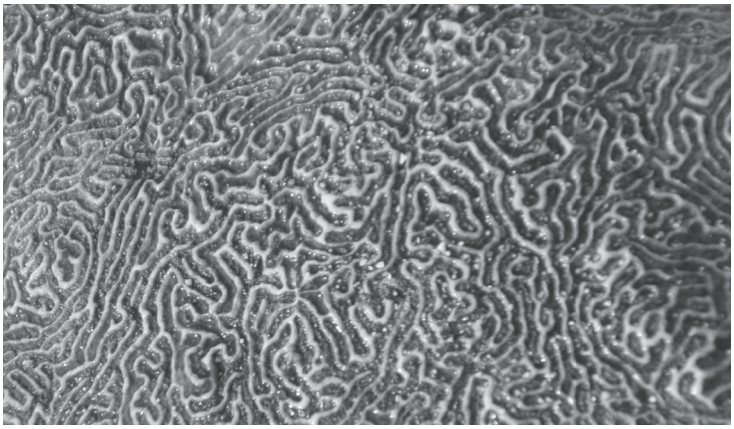
GENERAL INTRODUCTION



GENERAL INTRODUCTION

A variety of psychiatric behavioural symptoms commonly occur in patients of advanced age. Sometimes these are caused by delirium, more often these are related to neurodegenerative disease, of which the most common is dementia. The incidence of Alzheimer's disease doubles every five years of age reaching a prevalence of about 30 percent at the age of 85.[1] Most patients with dementia develop behavioural symptoms at some point during the course of the disease[2]. The prevalence of behavioural symptoms in nursing homes even raises above 80%[3-5]. Patients with behavioural symptoms cause considerable distress, both to themselves and to their informal and professional caregivers[6]. As the population of western Europe and the US is aging steadily, the burden of these problems increases as well[7]. To alleviate the behavioural symptoms of these patients, as well as the burden for the caregivers, antipsychotics were first introduced for patients with dementia in 1955. Ever since their introduction, their use has been criticised. In the first article published about this subject, Seager wrote "One of the difficult nursing problems in a mental hospital concerns the group of elderly long-stay patients (with dementia) who suffer from periods of restlessness, confusion, and disorientation or who are continually in a state of agitation, with stereotyped speech and activity. 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 problems." After reporting positive results in 60% of 29 elderly women with dementia, he concludes that "the drug has been effective in improving the general behaviour (…) though this improvement was not uniformly good. Most of them became more manageable, with few noisy outbursts or demonstrations of violence". Finally he states "that this drug may prove of much value for those patients who are still at home but tend to wander round the house at night and keep the rest of the family awake, or who are somewhat preoccupied with hypochondriacal symptoms. If this is so, it will go some way towards solving the problem of shortage of bed-space and of nursing staff in mental hospitals"[8]. Since then, the use of antipsychotics steadily increased, but little research was done to proof their efficacy. In 1966 there was little evidence of a positive effect, as only two randomised controlled trials (RCTs) were published since 1955, both having negative results. However, the use of chlorpromazine and other antipsychotics in the long-term treatment of elderly patients with dementia in psychiatric hospitals was already widespread. The first double-blind withdrawal study was carried out in 1966 by Burton, who found no deterioration after withdrawal in 85% of patients, leading to his conclusion that "our trial suggests that about 80 percent of elderly demented patients are receiving tranquillizers unnecessarily"[9]. Despite these scientific results, the use of

antipsychotics continued to increase in the US. By 1973, the use of promazine, thioridazine and haloperidol was advised in the management of behavioural symptoms, as "a tranquillizing regimen can be an important part of the management"[10]. In a letter to the British Medical Journal in 1977 Silverman stressed the importance of prescribing haloperidol to the agitated patient with dementia, as "it is most important to prove to the family that the difficult behaviour can be controlled rapidly and effectively, as the demand for admission to a non-existent psychogeriatric bed is intense and angry from the family"[11]. The first published epidemiologic studies reported that more than 20% of nursing home residents used antipsychotics, often without documented diagnosis[12].

This high volume of use led to federal regulations designed to reduce inappropriate use (the Omnibus Budget Reconciliation Act of 1987 [OBRA-87]). The implementation of OBRA-87 resulted in a small decrease in its use in US nursing homes[13]. The first meta-analysis of RCTs of antipsychotics in dementia was published in 1990 by Schneider, who concluded that a modest effect can be expected in about 20% of patients[14]. The atypical antipsychotic risperidone, introduced in 1997, was promoted to be more efficacious and to have less adverse effects (especially less extrapyramidal symptoms) than the conventional antipsychotics. From 1999 to 2004, the pharmaceutical company Johnson & Johnson aggressively promoted its antipsychotic risperidone in United States nursing homes. Olanzapine was promoted by the company Lilly in nursing homes with a 'five at five' slogan, claiming that 5 mg's of olanzapine at five o'clock would guarantee a quiet residential ward at night.

By the year of 2000, a record of 24% of all nursing home residents in the United States received at least one prescription of atypical antipsychotics[15], which raised to 30% in 2004[16]. Similar figures were found in other countries[17]. However, in another meta-analysis in 2005 Schneider stated that although small statistical effect sizes on symptom rating scales support the evidence for the efficacy of aripiprazole and risperidone, incomplete reporting restricts estimates of response rates and clinical significance, and adverse events further limit effectiveness[18]. In a review in 2010, Ballard concluded that studies have demonstrated either none or modest benefits for short-term (up to 12 weeks) treatment of aggression and psychosis in Alzheimer's disease[19]. Despite this repeated proof of limited evidence of efficacy, the prevalence of antipsychotic use in Dutch nursing homes remains high at an estimated 35-37% [20-21]. These figures are in line with those from other Western countries[22]. The reasons for this high prescription rates are not clear. There is evidence that antipsychotic use varies greatly between nursing homes, even when adjusted for differences in patient characteristics[23-25]. This high variability in prescription behaviour among physicians indicates potential inappropriate use and room for improvement. Off-label use of antipsychotics is also common in other patient groups such as in patients with an intellectual disability[26-27] and in psychiatric patients with aggressive behaviour[28].

Risks

Several adverse effects of antipsychotics often occur in elderly patients. Drug-induced parkinsonism influences the quality of live[29] and antipsychotics may induce gait disturbances, falls and fractures[30-31]. It is speculated that some adverse effects of antipsychotics are more harmful and sometimes even lethal in elderly patients with dementia. On April 11, 2005, the FDA issued a health advisory for increased all-cause risk of death with atypical antipsychotics in people with dementia[32]. These warnings were based on a post-hoc analysis of RCTs. During a typical 10-week RCT for the effect of atypical antipsychotics on the behavioural symptoms of dementia, the incidence of death in patients using antipsychotics was about 4.5%, compared to 2.6% in the placebo group.

The causes of death varied, with most of the deaths appeared to be either cardiovascular (heart failure, sudden death) or infectious (pneumonia). The start of antipsychotic therapy is associated with an increased risk of pneumonia[33]. Observational studies suggest that treatment with conventional antipsychotic drugs may also increase mortality[34-35]. In 2008, the FDA therefore extended its warning to all antipsychotics. In a meta-analysis of RCTs for patients with dementia, Schneider found a risk of 1.9% of cerebrovascular adverse events, compared to 0.9% with placebo. Olanzapine is associated with a threefold, but not significant increase in risk[36]. In contrast, several epidemiological studies did not find an increase in risk[37-39]. The increase in risk of venous thrombosis and consequent pulmonary embolism is also controversial[40-41]. It has been suggested that massive pulmonary embolism may be an underrecognized cause of sudden death[42]. The mechanism of increased thrombosis is unclear, as platelet serotonin blockade theoretically decreases platelet aggregation[43-44]. Recently, it has been shown that atypical antipsychotics may indeed increase the risk of gastro-intestinal bleeding[45]. Antipsychotic use is associated with metabolic syndrome[46], diabetes[47] and hyperlipidemia[48]. In rare occurrences, antipsychotic induced prolongation of the QT interval can cause sudden death[49-50]. Finally, antipsychotic drug use is generally considered to increase the risk of cardiovascular disease in the elderly, but the available literature on this subject is scarce and studies found opposite effects[51-52].

Objective of this thesis

In the pharmacotherapy of the behavioural symptoms of dementia a big gap exists between the available scientific evidence and the reality of daily clinical practice. While evidence-based medicine emphasises the limited success of antipsychotic treatment and the serious adverse effects, and asks for limited use of this medication, antipsychotic medication is still widely used in elderly patients with dementia. This thesis aims to reduce this gap. We aim to elucidate the reasons for the high antipsychotic prescription rates among institutionalised patients with dementia. Furthermore, we investigate the course of the behavioural symptoms of these patients when

treated with antipsychotics. Finally, we aim to extend our knowledge of the adverse effects of this treatment in elderly patients, focussing on thromboembolic events.

Outline of this thesis

To elucidate the reasons for prescribing antipsychotics for elderly nursing home residents with dementia, we looked at differences in antipsychotic prescribing rates among nursing homes *(chapter 2.1)*. The attitudes of nursing home physicians and nurses towards the use of antipsychotic medication for the behavioural symptoms of dementia are investigated in *chapter 2.2*. The effect of antipsychotics on the course of behavioural symptoms in elderly nursing home patients with dementia is described in *chapter 2.3*. In *chapter* 3, we focus on a number of potential adverse effects of antipsychotic therapy in the elderly which may explain the raised mortality found in randomised clinical trials. First, we look at the risk of cerebrovascular events in elderly users of antipsychotics *(chapter 3.2)*. Then, we investigate the risk of venous thromboembolism and subsequent pulmonary embolism *(chapter 3.3)* and we aim to investigate the controversial relationship between antipsychotic use and the occurrence of acute myocardial infarction in the elderly *(chapter 3.4)*. Finally, the findings of this thesis are discussed within a broader perspective.

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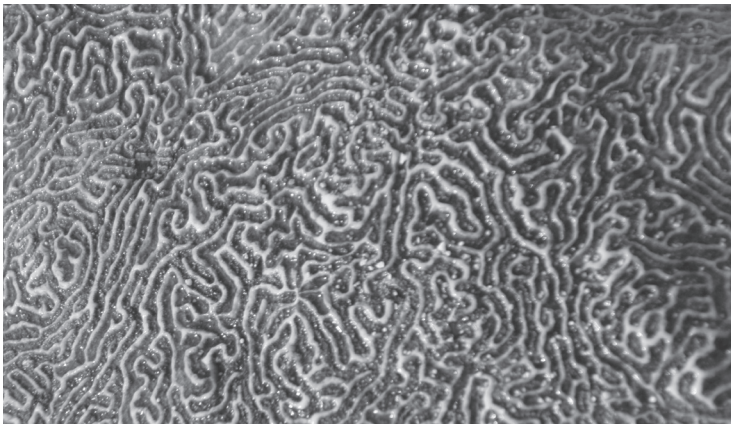
2

ANTIPSYCHOTIC USE IN PATIENTS WITH DEMENTIA IN LONG TERM CARE FACILITIES

2.1

VARIABILITY BETWEEN NURSING HOMES IN PREVALENCE OF ANTIPSYCHOTIC USE IN PATIENTS WITH DEMENTIA



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ABSTRACT

Background

Antipsychotic drugs (APD) are widely prescribed for people with dementia residing in long term care facilities (LTCFs). Concern has been expressed that such prescribing is largely inappropriate.

Objectives

To examine differences in facility-level prevalence of APD use in a sample of LTCFs for patients with dementia and to investigate if these differences can be explained by patient and facility related characteristics.

Methods

A point prevalence study was conducted using data (2008-2010) from the VU University Resident Assessment Instrument (VURAI) database from nursing homes and residential care facilities in the Netherlands. Patients were selected who had a diagnosis of dementia and not a diagnosis of schizophrenia. LTCFs were classified into homes with high, medium and low prevalence of APD use. LTCF and patient characteristics were extracted from the VURAI; facility-level resident satisfaction surveys were provided by the National Institute for Public Health and the Environment.

Results

In total, 20 LTCFs providing care for 1090 patients with dementia were investigated. Overall, 31% (range 5 - 52%) of patients used an APD. In the six facilities with the highest prevalence of APD use (mean 41%, range 29 - 52%), at least one behavioural symptom was present in 62% (range 47 - 85%) of their patients. In the seven facilities with medium APD use, APDs were used by 23% (range 19-28%) of patients, while behavioural problems remained frequent (57%, range 29 - 73%), and in the seven facilities with the lowest prevalence of APD use (mean 13%, range 5 - 18%) still 54% (range 28 - 73%) of the patients were recorded to exhibit at least one of the behavioural symptoms. Facilities with a high prevalence of APD use were often large, more often situated in urban communities and more often showed a below average satisfaction on staffing, personal care and recreational activities.

Conclusion

There was considerable variation between the participating LTCFs in the prevalence of APD use. These differences could only partly be explained by differences in patient characteristics such as presence of behavioural symptoms. Variability was more related to LTCF setting characteristics and consumer satisfaction. This indicates potential inappropriate prescribing because of differences in institutional prescribing culture.

INTRODUCTION

Patients with dementia are often treated with antipsychotic drugs (APD) to alleviate behavioural symptoms, even though there is little evidence of their efficacy for this indication and it has never been shown that long-term APD therapy in patients with dementia positively influences quality of life[1-3]. Furthermore, the use of APDs in patients with dementia is associated with serious adverse effects, with reported increased mortality[4-5]. Despite uncertainties about the benefits and risks of APDs in the elderly, the prevalence of APD use in the elderly population remains high, especially in long term care facilities (LTCF) with an estimated 25% in the United States[6], 18 - 22% in the United Kingdom[7-8], 33% in Belgium[9-10], 28% in Germany[11] and 37% in a large sample of nursing homes the Netherlands[12]. However, the variability in use of APDs is high between nursing homes within a country[8,13-17], indicating that the decision to prescribe APDs is not only driven by the clinical need of the resident, but is also strongly influenced by physicians' attitudes and believes, and the organisational culture of the long-term care environment[18]. Although several studies showed the existence of large variation in the extent of APD prescribing between nursing homes, little research has been done into factors associated with this variability. In this study, we investigate the variability in prevalence of APD use in a sample of Dutch nursing homes, and we examine the differences by relating these to LTCF and patient related characteristics.

METHODS

Setting and LTCF selection

A point prevalence study was conducted in the Netherlands using LTCF and resident characteristics collected with the Resident Assessment Instrument (RAI/MDS) 2.0, and information on organizational resources and facility-level resident satisfaction surveys from the National Institute for Public Health and the Environment (RIVM), an independent government funded institute.

The VU University Resident Assessment Instrument Database (VURAI) is a database, which at the end of 2010 contained over 60,000 Minimum Data Set (MDS) assessments of 9,387 residents of 48 LTCFs, collected from 1997 onwards[19-22]. These assessments contain over 400 items (demographic, diagnostic, clinical, and treatments), including the use of APDs, the diagnosis of dementia and items from which rating scales can be derived to adjust for severity of dementia, behavioural disturbances and concurrent delirium. LTCF nurses are required to complete assessments for all residents. Residents are generally assessed upon admission and every

three months thereafter. Extra assessments are performed in case of a significant change in a resident's condition. Staff performing the MDS assessments on each of the wards had received standardized training.

Additional data on the various characteristics of LTCFs in the Netherlands were collected from the RIVM. These data include information on organizational resources and results from a validated questionnaire on the quality of care to be completed by residents or their legal representatives of LTCFs. This survey is conducted by independent research institutes under supervision of the Centre of Consumer Experiences in Health Care (CKZ), using the Consumer Quality index for Long-term Care (CQ-index). The CQ-index is based on the American Consumer Assessment of Healthcare Providers and Systems (CAHPS) nursing home survey[23] and enables a nationwide comparison of the quality of long-term care[24]. Surveys were held every two years from February 2008 onwards. In each LTCF the residents were interviewed or, in psychogeriatric wards, legal representatives of residents were sent a mail questionnaire. If a legal representative survey was not conducted or not available (e.g. because of small or mixed patient groups) the resident interview survey was used as a proxy. All LTCFs were included who had at least ten patients with a diagnosis of dementia but not a diagnosis of schizophrenia, residing at the facility at the time of the CQ-index survey.

Prevalence of LTCF facility-level antipsychotic use

For each resident within the selected LTCFs having a diagnosis of dementia (but not schizophrenia), the resident assessment closest to the date of the latest CQ-index survey of the LTCF was taken, allowing a maximum gap of three months. Nursing home staff recorded the frequency of use of antipsychotic drugs taken by the resident in the seven days before the assessment. Exposure to antipsychotics was considered to be present if any use was recorded.

Determinants of antipsychotic drug use

Facility characteristics were drawn from both the MDS assessment and the CQ-index survey. These included mean age and sex of the population, setting and size of the LTCF, and satisfaction of the residents or their legal representatives with the LTCF. Population characteristics were drawn from the MDS assessments and included use of psychotropics, prevalence of behavioural symptoms, cognitive performance and ADL (activities of daily living) performance. From the MDS medication section, the concomitant use of anxiolytics, antidepressants and hypnotics was analysed. To assess behaviour the following items from the RAI 2.0 section on anxiety/mood were analyzed: resisting care (ADL assistance, eating, or medication), anxiousness or restlessness, verbally abusive behaviour, physically abusive behaviour, conflict with caregiver, socially inappropriate/disruptive behaviour, wandering,

hallucinations, delusions, and the worsening or new onset of indicators of delirium (i.e. being easily distracted, showing disorganised speech and having a fluctuating consciousness). These items were dichotomized into 'observed' or 'not observed' in the last three days before measurement. The used MDS items have been validated in three studies[22,25-27]. Cognitive function was dichotomized, using the validated MDS Cognitive Performance Scale (CPS)[28]. A score from 0-3 on this scale equals a normal to moderate impairment, a score above 3 equals severe to very severe impairment. The CPS has been validated against the Mini-Mental State Examination[29]. ADL dependency was also dichotomized, using a validated MDS ADL self-performance hierarchy scale, which ranges from 0 to 6[30]. A score between 0 and 3 was recorded as relatively independent, a score from 4 to 6 was recorded as dependent. Depression was measured with the Depression Rating Scale (DRS), a summative measure of seven symptoms of depression, which has been found to perform well against several gold-standard depression scales (such as the Geriatric, Hamilton and Cornell depression scales)[31]. Scores of 3 or higher on the DRS have been shown to be indicative of depression[32].

The CQ-index questionnaire contained 65 questions, of which results on 17 items have been published. Of these, three questions best reflecting the perceived quality of care were pre-selected by consensus procedure by the authors: (1) do you feel there are enough nurses and aides; (2) do the nurses and aides pay enough personal attention to your family member; and (3) does the nursing home provide enough recreational and social activities. For each of these questions, the average score of the respondents of the LTCF was compared with the average score of all LTCFs and categorized into three categories: below average, average, and above average.

Data analysis

The LTCFs were classified into tertiles (high, medium and low prevalence of APD use), based on the proportion of patients with dementia exposed to APDs at the time (+/- 3 months) of the resident satisfaction survey. The Chi squared test for trend was used to compare frequencies between LTCFs with high, medium and low APD use, weighted by the number of patients. Analyses were performed with SPSS (SPSS Inc. Chicago, Illinois, USA) for Windows, version 16.0.

RESULTS

MDS data were available for 48 LTCFs from January 1st 2006 to January 1st 2010. CQ-index surveys were measured from 2008 onwards for 36 of these facilities. After exclusion of 16 facilities because of an insufficient number of patients with dementia, 20 facilities remained available for analysis (Table 1). Alzheimer's dementia was

Table 1 LTCF characteristics with a low , medium and high antipsychotic prescription prevalence.

		Tertiles			
	Overall	**lowest tertile**	**middle tertile**	**highest tertile**	**p for trend*****
Use of antipsychotics, mean % (range)	**31 (5 - 52)**	**13 (5 - 18)**	**23 (19 - 28)**	**41 (29 – 52)**	**<0.01**
Number of facilities	20	7	7	6	
Number of patients with dementia, mean (range) *	55 (11 - 202)	17 (11 - 22)	59 (23 - 129)	93 (15 - 202)	
Setting , no. of facilities					
rural	5	4	1	0	**<0.01**
urban	15	3	6	6	
Facility size, no. of facilities					
Small facility (< 80 beds)	7	4	2	1	**<0.01**
Medium size facility (80 - 140 beds)	7	3	2	2	
Large facility (> 140 beds)	6	0	3	3	
Male, mean % (range) **	25 (9 - 34)	22 (9 - 33)	23 (9 - 31)	27 (13 - 34)	0.14
Agegroup, mean % (range)					
60-74 years	9 (0 - 19)	2 (0 - 5)	9 (4 - 13)	11 (7 - 19)	**<0.01**
74-85 years	38 (13 - 57)	34 (13 - 55)	35 (28 - 57)	40 (13 - 52)	
>85 years	53 (36 - 80)	64 (41 - 72)	56 (36 - 65)	49 (29 - 80)	
Facility offering acute admissions, respite care, n					
No	5	2	3	0	**<0.01**
Yes	15	5	4	6	
Availability of qualified personnel, n					
Above average	3	2	1	0	**<0.01**
Average	7	3	3	1	
Below average	10	2	3	5	
Personal attention and care, n					
Above average	2	1	1	0	**<0.01**
Average	14	6	4	4	
Below average	4	0	2	2	
Provided recreational and social activities, n					
Above average	3	2	1	0	**0.02**
Average	11	4	2	5	
Below average	6	1	4	1	
Use of other psychotropics					
Use of anxiolytics, mean % (range)	17 (0 - 41)	16 (0 - 41)	18 (4 - 28)	16 (0 - 32)	0.82
Use of antidepressants, mean % (range)	23 (0 - 45)	18 (0 - 36)	25 (7 - 44)	24 (13 - 45)	0.39
Use of hypnotics, mean % (range)	16 (5 - 38)	19 (5 - 38)	18 (7 - 23)	14 (11 - 31)	0.11
High ADL dependency, mean % (range)	45 (0 - 68)	31 (6 - 68)	38 (0 -55)	53 (27 - 57)	**<0.01**

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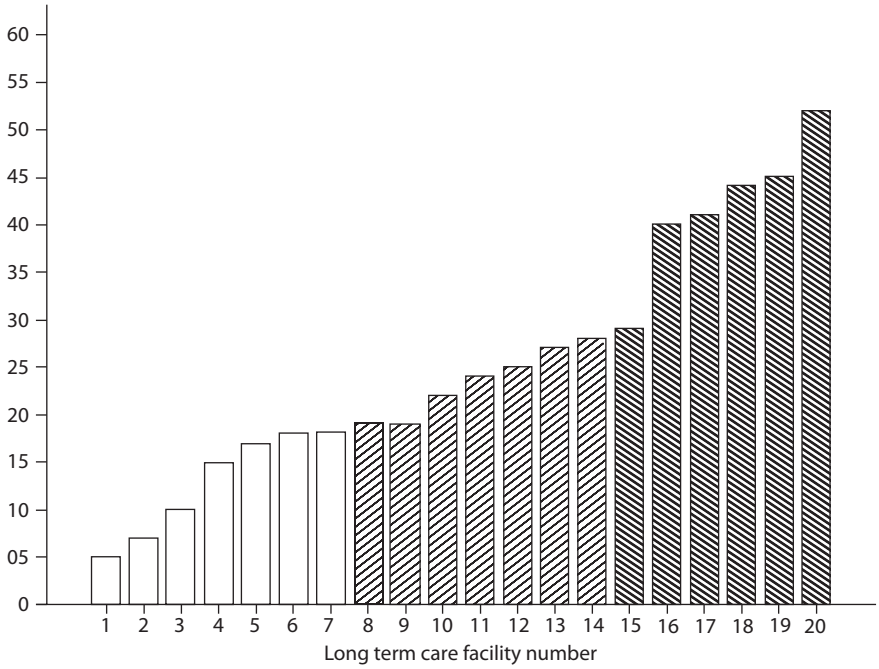
Table 1 (Continued)

		Tertiles			
	Overall	**lowest tertile**	**middle tertile**	**highest tertile**	**p for trend*** **
Use of antipsychotics, mean % (range)	**31 (5 - 52)**	**13 (5 - 18)**	**23 (19 - 28)**	**41 (29 – 52)**	**<0.01**
Moderate to severe impaired cognition, mean % (range)	48 (0 - 68)	32 (0 - 68)	42 (11 - 52)	56 (27 - 63)	**<0.01**
Depressive symptoms present, mean % (range)	34 (0 - 50)	19 (0 - 50)	31 (11 - 47)	40 (13 - 50)	**<0.01**
Behavioural symptoms present, mean % (range)					
Resisting care (ADL assistance, medication)	21 (0 - 45)	21 (0 -45)	21 (7 - 36)	21 (7 - 30)	0.97
Anxiousness or restlessness	24 (7 - 50)	26 (8 - 50)	21 (7 - 46)	25 (9 - 45)	0.77
Exhibited verbally abusive behaviour	15 (0 - 23)	8 (0 - 20)	12 (0 - 21)	19 (7 - 23)	**<0.01**
Physically abusive behaviour	15 (0 - 27)	8 (0 - 18)	15 (0 - 26)	16 (0 - 27)	0.05
Conflict with caregiver	17 (0 -38)	13 (0 - 27)	18 (5 - 38)	18 (9 - 32)	0.41
Socially inappropriate/ disruptive behaviour	22 (0 - 32)	12 (0 - 32)	17 (4 - 29)	27 (9 - 32)	**<0.01**
Wandering	15 (0 -31)	12 (0 - 20)	18 (0 - 31)	13 (7 - 22)	0.46
Hallucinations	12 (0 -34)	12 (5 -20)	14 (4 - 21)	11 (0 - 34)	0.46
Delusions	12 (0 - 47	13 (0 - 47)	15 (0 - 31)	9 (1 - 34)	**0.02**
Any of the target symptoms mentioned above	59 (28 - 85)	54 (28 - 73)	57 (29 - 73)	62 (47 - 85)	0.06
Delirium signs of recent onset, mean % (range)					
Being easily distracted	13 (0 -38)	18 (0 - 33)	16 (6 - 38)	10 (3 - 32)	**<0.01**
Speech is disorganised	9 (0 - 25)	13 (0 - 24)	11 (0 - 25)	7 (0 - 21)	0.66
Consciousness fluctuates during the day	14 (0 - 50)	22 (9 - 36)	18 (0 - 50)	9 (3 -26)	**0.02**

*included in this study.
** mean percentage of patients and range between facilities.
*** Chi square test for trend, p-values <0.05 are marked in bold.
****Consumer Quality survey items reflecting perceived quality of care by the residents or their legal representatives: above average: % of LTCF with scores comparable to the 30% LTCFs best performing; average: % of LTCF with scores within the range of 30% - 70% of all LTCFs; below average: % of LTCFs with scores comparable to the 30% worst performing LTCFs.
Abbreviations LTCF: long term care facility, APD; antipsychotic drug, T1; first tertile, T2; second tertile, T3; third tertile, ADL; activities of daily living.

diagnosed in 48% of patients, and mixed or other forms of dementia in 52%. The prevalence of APD use varied between LTCFs from 5% to 52%; the overall prevalence was 31%. The seven facilities in the lowest tertile of APD use had a mean prevalence of 13% (range 5 -18%, Figure 1). The seven facilities with medium APD

Figure 1 Mean prevalence of antipsychotic therapy per participating LTCF.



The facilities are shown in increasing order of prevalence (%). White bars represent the lowest tertile (range of APD use 5% - 18%), grey bars the next tertile (range 19% – 28%), and black bars the highest tertile (range 29% – 52%).

use had a prevalence of 23% (range 19 -28%), and the six facilities in the highest tertile for APD use recorded a prevalence of 41% (range 29 -52%). There was no significant difference between prevalence of anxiolytic, antidepressant and hypnotic use between these groups. There was an almost significant trend toward more behavioural symptoms in facilities with a higher prevalence of APD use ($p = 0.06$): in the six LTCFs with a high prevalence of APD use, at least one of the behavioural symptoms was present in 62% of the patients. In the next seven facilities behavioural problems remained frequent (57%), and in the seven facilities with the lowest APD use still 54% was recorded to exhibit at least one of the behavioural symptoms. The facilities with the highest prevalence of APD use reported significantly ($p < 0.05$) higher levels of verbally abusive behaviour and socially inappropriate/disruptive behaviour, but showed lower levels of indicators of delirium (being easily distracted, showing a fluctuating consciousness, and delusions). Facilities with a high prevalence of APD use generally had more severely ADL-dependent and

cognitively impaired patients. Facilities in the highest tertile of APD use had a mean percentage of 40% of patients with a DRS indicative of depression, while the lowest tertile reported 20%. Compared with facilities in the lowest tertile, facilities with a high prevalence of APD use are more often large (3 vs 0) and more often situated in urban communities (6 vs 3). CQ-index surveys were available for all facilities; 12 facilities reported results from legal representatives mail questionnaires and 8 facilities reported results from resident interviews. Facilities in the highest tertile of APD use have more often below average satisfaction on staffing (5 vs 2) and personal care (2 vs 0).

DISCUSSION

In this study, we investigated the variability of APD use in a sample of Dutch LTCFs, and we related this APD use to the prevalence of behavioural symptoms. Our study showed a high variability between LTCFs in APD use. Although facilities with a high prevalence of APD use reported more patients with certain behavioural problems, we found a discrepancy between the difference in prevalence of APD use among the facilities in the lowest and highest tertile of APD use (13 vs 41%), and the difference in prevalence of behavioural symptoms among these facilities (i.e., at least one symptom present; 54 vs 62%). The remarkable large variability in APD use found in our study (5 - 52%) thus cannot be explained fully by differences in the prevalence of behavioral symptoms across facilities. We also examined the variability in APD use by relating it to resident (or resident representative's) satisfaction, as measured with the CQ-index. A high prevalence of APD use was associated with average to below average satisfaction on staffing, personal care and activities.

The large variability in APD use is comparable with results from other studies. The first report dates from 1980, showing that APD use in US nursing homes varied from 0 to 46%, with the larger nursing homes accounting for most of the prescriptions[15]. In Norway a wide variation in APD use (0 to 61%) was found, which could not be explained by size or nursing staff/resident ratio[17]. In the United Kingdom, Guthrie found an unexplained variation in prescribing, showing a threefold use of APDs in the highest prescribing practices[8].

The finding that this variability in APD use in LTCFs cannot fully be explained by resident characteristics is in line with international studies. Rochon also found that differences in prescribing rates between nursing homes in Canada could not be explained by the variation in clinical condition of their patients[33]. Chen concluded the same from a similar study in United States nursing homes[14]. In Belgium, APD use was significantly lower in nursing homes where patients received treatment from a general practitioner with additional training in gerontology[10]. This suggests the presence of a

prescribing culture where in some settings physicians prescribe APDs, while in other settings physicians would have prescribed nonpharmacological interventions. This might be explained by a lack of possibilities for nonpharmacological treatment of the behavioural problems of dementia in some facilities. The use of recreational activity programs can improve quality of live, and decrease the demand for APD therapy[34-35]. We found a strong association between low satisfaction on provided recreational activities, and facility-level APD use. Small-sized, non-urban LTCFs with high resident or resident legal representatives satisfaction reported the lowest prevalence of APD use. Rural LTCFs have been associated with high caregiver satisfaction, possibly because of closer relationships between professional and family caregivers within the community[36]. Our results correspond to those of Testad et al., who compared nursing homes in the UK, Austria and Norway, and found significantly lower prevalence of APD use in LTCFs with smaller units of care, and a better care staff - resident ratio[37].

In the study presented here, a high prevalence of APD use is associated with low satisfaction on staffing levels. In a survey exploring the reasons to prescribe APDs, elderly care physicians often named the lack of good qualified nurses as a barrier to the success of nonpharmacological interventions, thereby increasing the demand for APDs[38]. Increased nurse staffing levels have shown to improve the quality of care in U.S. nursing homes[39]. This suggestion is supported by the study of Fossey et al. that showed that training programmes for nursing home staff resulted in a decrease of the proportion of patients using APDs by 54% without a change in behavioural scores[40]. Small homelike care environments are believed to improve the quality of live of elderly people with dementia, possibly leading to less behavioural problems and consequently less APD use, but this assumption awaits further confirmation[41-45]. Analyses of the care programmes of facilities with a high and low prevalence of APD use may result in best practice models that can help to reduce APD use. In Finland, benchmarking care outcomes between LTCFs, including the publication of prevalence of APD use, has led to a remarkable decrease in the use of APDs and various improvements in nursing care patterns[46].

Nevertheless, we found more patients with certain behavioural problems (verbally abusive behaviour and socially inappropriate/disruptive behaviour) in facilities with a high prevalence of APD use. In addition, patients were more ADL dependent, showed more cognitive decline and showed more signs of depression. These higher patient care needs may cause a relative shortage of care in these facilities. Although this can explain part of the variation in APD use, other explanations can not be ruled out. Although the items in the RAI database are descriptive, the scoring of behavioural problems can be subjective and depending upon the tolerance of nursing staff for specific behavioural patterns. Also, the presence of more residents with severe behavioural problems, often already treated with APDs at admission, may facilitate the prescription of APDs to residents with moderate problems. Bronskill

found an unexplained higher mortality in nursing homes with a high prevalence of APD use[47]. The use of APDs in patients with dementia has not only been shown to increase the risk of death,[4,48-49], stroke[50], and cardiac arrhythmias[51], but several adverse effects such as APD induced parkinsonism[52], gait disturbances[2], and daytime sedation[2], have been shown to negatively influence quality of live. As these adverse effects are common, a facility with a high prevalence of APD use is likely to have a large proportion of patients in which these adverse effects outweigh the benefits of their treatment. Therefore, a high prevalence of APD use signals potentially inappropriate prescribing.

This study has several limitations. First, the 20 LTCFs for which detailed information was available are not necessarily representative of all 1700 LTCFs in the Netherlands, as the LTCFs decision to work with RAI is voluntary. The small sample size also limits the generalizability of the results. As we used a cross sectional design, the associations between prevalence of APD use and facility characteristics cannot be used to infer causation.

The results of the CQ-index survey should be interpreted cautiously, as, for the purpose of this study, we restricted us to three pre-selected questions, not necessarily reflecting the global impression of the quality of care. We used results of direct interviews with the residents (8 facilities) and mail questionnaires to legal representatives (12 facilities). Both types of surveys have their limitations. Patients with dementia are likely to be underrepresented in the sample of residents interviewed for the survey. The legal representative's opinion does not necessarily reflect the quality of the provided care itself, and has been found to depend on the quality of the caregiver-resident relationship[53]. Verbeek compared small-scale facilities with wards within large facilities, and found an association of small-scale facilities and caregiver satisfaction with nursing staff, but did not find differences in quality of life for the patients themselves between these settings[54]. However, legal representatives' reports have been shown to correlate well with self-rated quality of live in patients with dementia[55].

We do not know the reasons to prescribe APDs, and do not know to what extent the behavioural symptoms are influenced by the use of APDs. If APDs are effective in reducing behavioural symptoms, this might partly explain the small variation in behavioural symptoms between the APD prevalence tertiles. However, in a previous study, we have shown that the effect of APDs on behavioural symptoms, as measured with the RAI assessment instrument, is limited, with most patients showing equal or even higher symptom scores after the start of therapy[56].

Strengths of our study included the availability of both detailed resident assessments and satisfaction surveys, enabling to associate APD use with perceived quality of care at facility level.

In conclusion, in a sample of 20 nursing homes in the Netherlands we found a large variability of APD use. The large variability in APD use could only partly

be explained by the patients' characteristics, and was clearly correlated to facility characteristics, such as facility size, and the perceived quality of care. The association between a high prevalence of APD use, and low quality of care as perceived by the residents and their legal representatives is worrisome and warrants further investigation.

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2.2

REASONS TO PRESCRIBE ANTIPSYCHOTICS FOR THE BEHAVIORAL SYMPTOMS OF DEMENTIA: A SURVEY IN DUTCH NURSING HOMES AMONG PHYSICIANS, NURSES, AND FAMILY CAREGIVERS

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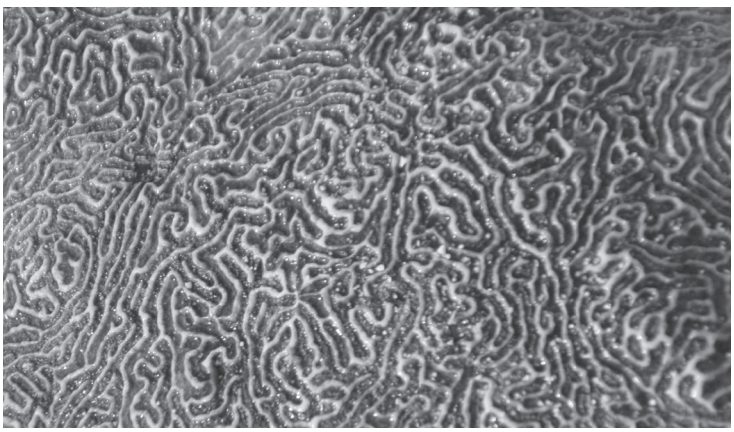

J Am Med Dir Assoc (in press)

ABSTRACT

Objectives

Despite serious safety concerns, prescription rates of antipsychotics for the treatment of the behavioral and psychological symptoms of dementia (BPSD) remain high, especially in nursing homes. This high prevalence of antipsychotic use cannot be explained by the modest success rate reported in the literature. In this study, we aim at clarifying the reasons for prescribing an antipsychotic drug (APD) in BPSD and look at the role of nurses and family caregivers in the decision making process that precedes the prescription of an APD.

Design

Questionnaire used in a one-on-one interview with elderly care physicians, nurses and family caregivers.

Method

We conducted a survey in 23 nursing homes in the Netherlands. On each dementia ward, the physician selected one or two patients who started antipsychotics most recently. An interviewer then held a structured questionnaire with the physician, the nurse, and the first relative of the patient. The first part of the interview consisted of questions about the general ideas of the physicians and the second part consisted of case-related questions to physicians, nurses and family caregivers.

Results

Physicians, nurses and family caregivers generally consider the possible benefits of antipsychotics to outweigh the risk of side effects. The main reasons to start therapy are agitation and aggression. Physicians felt pressured by nurses to prescribe in 17% of cases. Physicians felt supported by the guideline of the Dutch Association of Elderly Care Physicians. The estimated average success rate in the discussed cases (the patient is expected to improve on the target behavior) among physicians was 50%, nurses reported 53% and relatives 55%. The most frequently expected adverse reactions were increased fall risk, sedation and parkinsonism. Nurses expected cognitive decline. The family felt insufficiently informed about the side effects in 44% of the cases.

Conclusions

The interviewed nursing home physicians and nurses expect almost half of their patients with dementia and behavioral disturbances to benefit from antipsychotic therapy. Serious side effects were expected to occur only sporadically. These expectations may contribute to the high rate of antipsychotic use among these patients.

INTRODUCTION

Behavioral and psychological symptoms of dementia (BPSD) are major contributors to the burden of dementia for both patients and caregivers, affecting 50-80% of the patients.[1-4] The prevalence in nursing homes even rises above 80%.[5-7] Antipsychotic drugs (APDs) are the most frequently prescribed pharmacological treatment for BPSD.[8-9] According to Dutch guidelines, haloperidol is the first-choice APD for the treatment of delirium and agitation or aggression, but atypical APDs are increasingly used.[10-11] The efficacy of APDs in the treatment of BPSD is limited, with estimates ranging between one of five and one of three patients showing improvement.[12-18] Schneider et al found a strong placebo effect of 21%.[15] The use of APDs is not without risks. In 2008, the US Food and Drug Administration issued a warning concerning the risk of increased mortality in patients with dementia using APDs (odds ratio [OR] 1.7) .[19] Other studies confirmed this increased risk.[20-23] The use of APDs has also been associated with an increased risk of cerebrovascular accidents[24-25], hip fractures[26-27] and pneumonia.[28-29] The prevalence of APD use in Dutch nursing homes remains high at an estimated 35 to 37%.[7,30] These figures are in line with those from other Western countries.[31-32] The problem of APD overprescription in nursing homes is documented in various countries including the Netherlands.[9,33-37] This may seem surprising because the guideline on BPSD of the Dutch association of elderly care physicians advocates nonpharmacological interventions, and advises pharmacological therapy only in selected situations.[10] Given the importance of the problem, it is surprising that only a few articles have been published concerning the reasons for prescribing APDs in BPSD.[38-44] In an interview with 8 geriatric psychiatrists, it was concluded that the psychiatrist felt pressured to prescribe, largely because of resource issues and lack of viable alternative treatments.[40] In a survey based on responses to a Web-based questionnaire to 110 elderly care physicians, nursing staff request for medication, insufficient resources and insufficient knowledge of staff are named by physicians as barriers to the use of nonpharmacological methods.[41-43] In a study describing factors associated with psychotropic drug use in nursing homes, fewer registered nurse staffing hours were associated with more use of psychotropic drugs in nursing homes.[45] Nurses and family caregivers may have a large influence on the decision to prescribe APDs for BPSD. In this study, we aim at clarifying the reasons for prescribing an APD in BPSD and look at the role of nurses and family caregivers in the decision-making process that precedes the prescription of an APD.

METHODS

Setting and Design

We performed structured interviews with elderly care physicians, nursing home nurses, and primary care givers of nursing home patients who recently were prescribed

an APD for BPSD. We aimed at interviewing 30 physicians. Selection of elderly care physicians for an interview took place in the following order: first, we contacted elderly care physicians in the broad region of Utrecht. Second, we contacted elderly care physicians at a national educational course. Eligible physicians were required to have at least three years of experience as an elderly care physician to ensure they had enough experience in treating patients with BPSD. The nursing homes are situated all throughout the Netherlands in both rural and urban areas. To avoid the risk of interviewing too many physicians using the same treatment protocols, we allowed a maximum of two physicians per institution. The physicians were all interviewed face-to-face by one of the authors (E.C.) at the nursing home. We subdivided the questions presented by the interviewer to the physicians into 2 categories. First, we asked for their general ideas concerning the prescription of APDs for BPSD. Secondly, we presented a set of questions concerning the last patient for whom the elderly care physician had actually prescribed an antipsychotic drug for BPSD. This case had to fulfil the following requirements: the patient was aged 65 years or older, had a diagnosis of dementia, the physician him- or herself had started the APD for BPSD, and the patient did not have a delirium. For each selected patient, the interviewer also contacted the primary responsible nurse and primary family caregiver. Because the interview aimed to clarify the opinions of the interviewed and their role in the decision-making process, personal information about the patient used in the cases was not known by the interviewer and other authors of this study. The interviews with the nurses were either face-to-face or by telephone. The nurse had to be the primary caregiver of the patient involved and all questions were related to this particular patient. We interviewed the family caregivers by telephone. They were asked questions concerning the prescription of the APD in their relative (the case) and their role in the decision-making process to prescribe antipsychotics. After answering the questions from the questionnaire, we asked physicians, nurses and family caregivers to give their opinion of the use of an APD for BPSD in the discussed case. To categorize the behavioral problems, we used the items from the guideline of the Dutch association of elderly care physicians for behavioral problems in patients with dementia.[8] This guideline describes 12 neuropsychiatric disturbances common in dementia: agitation, aggression, negativism, night-time behavior disturbances, constant requests for attention, irritability, disinhibition, aberrant motor behavior, hoarding behavior, socially inappropriate behavior, apathy and excessive unexplained crying or laughing.

Informed consent

The nursing home management boards gave permission for the interviews. Upon approval of the management board, the elderly care physicians contacted the primary responsible nurses and primary family caregivers for informed consent. Only after nurses and caregivers gave informed consent was the interviewer given the

information necessary for contacting them. In case of refusal of family caregivers to be contacted, only the physician and nurse were interviewed.

RESULTS

The interviews were conducted between April and August 2009. From the elderly care physicians contacted, 27 from 23 different nursing homes could be interviewed (mean age [Standard deviation {SD}]: 47[10]; mean years [SD] of nursing home experience 12 [9] years; 48% female). They discussed 37 cases in which they had recently prescribed an antipsychotic drug for BPSD. For each case, the primary responsible nurse could also be interviewed (86% female, mean age [SD]: 35[9], mean years [SD] of nursing home experience 9 [7] years). Most family caregivers (32/37) consented in being interviewed. In most cases, the family caregiver was a child (62%) or spouse (16%) of the patient.

Non-case-related Opinions

In general, physicians estimate APDs to be effective for BPSD in 48% of the cases. They consider them most effective for hallucinations, delusions and agitation/aggression (Table 1). However, when BPSD symptoms improve during APD therapy, physicians expect this to be a placebo effect (not directly related to the pharmacological effects) in 38% of the cases. "You often treat the environment and not the patient him/herself," was a comment frequently added to this question. They estimate the effect of APDs to be comparable with the effect of other psychotropic drugs (eg, antidepressants and anxiolytics) on BPSD. There is a high awareness of possible side effects: an increased risk of falls, sedation, and drug-induced parkinsonism are expected to occur in more than half of the patients. In most cases, elderly care physicians fully supported their decision to prescribe an APD. Only in a minority (1 of 6) of cases do physicians feel strongly pressured by the nursing staff or (less frequently) by the family of the patient to prescribe APDs. Physicians feel supported in decision making by the guideline of the Dutch association of elderly care physicians[10] although 50% feel that scientific evidence on the subject is limited. As one respondent commented, "the published articles on the subject are not pragmatic. In daily practice you try different APDs and different doses, and often one of these APDs eventually works". According to the physicians, nonpharmacological interventions were insufficiently pursued in 28% of the cases. Barriers for the use of nonpharmacological interventions are lack of time, emergencies (especially in night or weekend shifts), lack of good qualified staff, and a poor nurse-to-patient ratio. One physician added, "when the patient is really suffering from the behavioral symptoms, there is often no alternative to prescribing antipsychotics." Physicians

Table 1 General Opinion of Elderly Care Physicians on APD therapy for Patients with Dementia and BPSD

Patients with BPSD in own patient group, mean % (SD)	37 (24)
Estimated effect of antipsychotics on BPSD in own patient group, mean % (SD)	48 (25)
A priori expected effect on symptoms, mean % (SD)	
Delusions	68 (24)
Hallucinations	72 (21)
Agitation/ aggression/ irritability	43 (20)
Disinhibition	26 (18)
Negativism/ refusal of care	19 (17)
Apathy	5 (13)
Night-time behaviour disturbances	33 (26)
Aberrant motor behavior / wandering	16 (16)
Constant requests for attention	20 (17)
A priori expected side effects, mean % (SD)	
Increased fall risk	60 (26)
Sedation	54 (26)
Parkinsonism	51 (21)
Dysphagia	28 (22)
Cognitive decline	23 (18)
Pneumonia	10 (14)
Stroke	3 (4)
Increased risk of death <3 months	10 (9)
Expected placebo effect, mean % (SD)	38 (21)
No of cases in which the physician felt pressured to prescribe, mean % (SD)	
Total	17 (19)
Who pressures to prescribe, mean % (SD)	
Nurses	86 (23)
Family	17 (27)
Feeling supported by protocol or available evidence in prescribing APD, mean % (SD)	
Protocol	79 (16)
Available evidence	52 (32)
Sufficient use of non-pharmacological interventions, mean % (SD)	72 (23)
Barriers to non-pharmacological interventions, no. of times mentioned by physicians	
Lack of time	13
Urgencies (night/weekend shifts)	12
Lack of good qualified staff (nurses)	11
Few staff members (nurses)	8
Situation is already escalated	5
Changes needed for sufficient nonpharmacological interventions, no. of times mentioned by physicians	
More qualified staff/ education	18
More nursing staff	10
More resources/money	4
More activity therapy	4
More psychologists	3
More volunteers	3
Smaller groups in living room	3
Expected effectiveness of other medications for BPSD, mean % (SD)	
Antidepressants	43 (22)
Anxiolytics	54 (22)
Anticonvulsives	27 (24)
NMDA-antagonists	20 (23)
Cholinesterase inhibitors	39 (24)

APD, antipsychotic drug; BPSD, behavioral and psychological symptoms of dementia; NMDA, N-methyl-D-aspartate; SD, standard deviation.

Table 2 Case- related results

Question (Answered by)	Percentage (n)
Who took the initiative to propose prescription of an APD (Physicians)	
Nurse	67.6 (25)
Physician	13.5 (5)
Caregiver	10.8 (4)
Colleague physician	8.1 (3)
How long did the symptoms exist before the prescription date (Physicians)	
< 1 week	5.4 (2)
1 week – 1 month	21.6 (8)
1 month – 3 months	16.2 (6)
> 3 months	56.8 (21)
Frequency of symptoms (Physicians)	
3 times a week to < once a day	13.5 (5)
Once a day – 3 times a day	27 (10)
> 3 times a day	59.5 (22)
Were psychosocial interventions tried before prescribing an APD (Physician)	
Yes	94.6 (35)
No	5.4 (2)
Prescribed antipsychotics (Physicians)	
Haloperidol	37.8 (14)
Risperidon	21.6 (8)
Pipamperon	16.2 (6)
Clozapine	5.4 (2)
Quetiapine	5.4 (2)
Olanzapine	5.4 (2)
Penfluridol	5.4 (2)
Cisordinol	2.7 (1)
Which opinion counted most in the decision to prescribe (Physicians)	
Physician	67.6 (25)
Nurse	16.2 (6)
Family	5.4 (2)
Colleague physician	5.4 (2)
Psychologist	2.7 (1)
Psychiatrist	2.7 (1)
Which non-pharmacological interventions were tried (Physicians)	
Consult psychologist	27 times
Consult psychiatrist	5 times
Consult physiotherapist	5 times
Consult psychiatric nurse	1 times
Music therapy	5 times
Daily program	5 times
Other therapies (8 different types)	8 times
Informed consent caregivers (Caregivers)	
Yes	84 (31)
No	16 (6)
Caregivers informed about side effects (Caregivers)	
Sufficient	44 (14)
Not completely sufficient	16 (5)
Insufficient	40 (13)
Caregivers' opinion was weighted enough in the decision to prescribe an APD (Caregivers)	
Sufficient	84 (27)
Not completely sufficient	3 (1)
Insufficient	13 (4)

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Table 2 (Continued)

Question (Answered by)	Percentage (n)	
Main symptom causing prescription of APD		
Physicians	Agitation:	40.5
	Agression:	27.0
Nurses	Agitation:	51.4
	Agression:	27.0
Caregivers	Agitation:	65.6
	Agression:	21.9
What is the probability of the antipsychotic to be effective in this particular case		
Physicians		50.3
Nurses		52.8
Caregivers		55.3
Which side effect is expected	**Physicians**	**Nurses**
Increased fall risk	54 (31)	46 (31)
Sedation	52 (27)	40 (28)
Parkinsonism	45 (30)	34 (26)
(increase of) dysphagia	22 (22)	21 (25)
Cognitive decline	16 (18)	37 (28)
Pneumonia	7 (13)	5 (11)
Stroke	3 (6)	6 (17)
Increased risk of death	5 (7)	9 (22)
Opinion concerning start APD		
Supporting	*Physicians:*	81 (30)
	Nurses:	89 (33)
	Caregivers:	62 (23)
Against	*Physicians:*	8 (3)
	Nurses:	8 (3)
	Caregivers:	19 (7)
Neutral	*Physicians:*	11 (4)
	Nurses:	3 (1)
	Caregivers:	19 (7)

APD, antipsychotic drug

believe better education and more nursing staff would help to make nonpharmacological interventions more successful, and would reduce the use of antipsychotics.

Case-related Opinions

In the 37 cases presented, the main reasons for prescribing APDs were agitation and aggression (Table 2). According to the physicians, these symptoms were present for more than three months in 57% of the cases and for more than 3 times daily in 60% of the cases. The initiative to consider prescription of antipsychotic drugs was taken by the nursing staff in 67% of the cases, by a physician in 21% and by the family caregiver in 11%. Physicians stated that in 67% of the cases their opinion was decisive in the prescription of the antipsychotic. In 16% of the prescriptions, the opinion of the nursing staff bore the largest weight. Physicians and nurses supported the prescription in most cases. In 8% of the cases, the physician prescribed

the APD without supporting this therapy. Reasons given here were being pressured and running out of other options. Before prescribing APDs, nonpharmacological interventions were used in 95% of the patients. In most cases (73%), a psychologist was consulted so as to improve the effects of nonpharmacological interventions before starting pharmacological therapy. The *a priori* estimated success rate (patient is expected to improve on the target behavior) in the discussed cases was comparable among physicians, nursing staff, and family caregivers (50%, 53% and 55%). In the presented cases, nurses expected in general the same side effects as physicians. Mostly mentioned were an increased risk of falls, sedation, and parkinsonism. Nurses more often expect antipsychotic drug use to result in cognitive decline. Most caregivers (62%) consented in the prescription of an APD to relieve BPSD in their relative, and 84% of caregivers find their opinion sufficiently weighted by the physician in the decision to prescribe an APD. However, 16% of the caregivers were not consulted about the prescription of an APD. In 19% of cases the caregivers felt opposed to the prescription of the APD. Most caregivers (56%) considered themselves to be not sufficiently informed on the possible side effects and risks of APDs. Some of them said they did not need to know about all of the side effects, as the physician would have weighted this in the decision to prescribe an APD. On the other hand, other family caregivers were afraid of the many side effects APDs have and thought that physicians would not notice the severity of these side effects. Some told the interviewer that they got scared when they found information about it on the Internet.

DISCUSSION

This study was conducted within the setting of Dutch nursing homes. In Dutch nursing homes, medical care is provided by specially trained elderly care physicians who have their main practice within the nursing homes and have all received a 2-year training in psychogeriatric medicine. This study shows that Dutch elderly care physicians are expecting a good response to treatment in 48% of patients in their population. If a physician expects a 50-50 chance of effectiveness (which means a number needed to treat of 2), it will often be justified to start an APD for BPSD. This expected effectiveness, however, is more than studies justify.[12-18] Although not studied, a possible explanation for this is that physicians tend to value their own subjective experience more than evidence coming from literature. This is not surprising given the fact that studies on the effect of APDs for BPSD are seldom performed in populations comparable with those in the Dutch nursing homes. In addition, because we are not capable of identifying those patients most likely to react positively on APD therapy, the burden that BPSD can be for the patient, caregiver or

other patients may justify a short trial with APDs. The elderly care physicians often stated that, even though nonpharmacological treatments are usually given, they feel that understaffing and lack of time are important barriers for more success of these nonpharmacological therapies.

Although the initiative for the prescription of an APD mostly comes from the nursing staff, physicians feel that they make the final decision and in almost all cases in which an APD was prescribed they felt that is was the right decision. It is however surprising that in 3 cases (8%) an APD was prescribed although the physician was not supportive of this. There is a high awareness among physicians of potential side effects. More severe side effects as stroke, pneumonia or death were seldom mentioned as a potential problem. A possible explanation for this unawareness is that, as all patients in this frail population have a risk of pneumonia, stroke, and death, these events are not necessarily attributed to the start of an APD. Also, the absolute increase in risk is small compared with the high mortality rates in nursing homes, which is often an estimated 30 % or more per year. Finally, the focus of therapy in this last phase of life will be more on quality than on quantity of the remaining months or years.

In general, there is a high level of agreement among opinions of physicians, nurses, and caregivers. In most of the presented cases, they feel that APD therapy was justified. However, this study suggests that communication with caregivers can be improved. In the Netherlands, it is regulated by law that the primary caregiver is provided with sufficient information to form a reasoned decision on behalf of his or her relative. In the interviews, most of the caregivers felt that they did not get enough information on possible side effects. It is also remarkable that only 84% of the caregivers gave informed consent to the start of APD therapy, and 19% of the caregivers said that they were actually opposed to this. This implies that legal directives concerning informed consent are not always followed and that communication between physician and caregivers should be improved.

Limitations

One-on-one interviewing is a good way to gather results with a good quality. However, it is very time-consuming. This results in a relatively low number of interviewed physicians, nurses and family caregivers. Interviews with a small group of participants are always susceptible to bias. Selection bias may be possible, since physicians interested in the subject are more prone to participate. However, because it can be expected that these physicians are better informed than colleagues, this would result in lower estimated success rates and higher awareness of serious side-effects than in the general population of elderly care physicians. Although we ask explicitly to recall the last patient who started an APD, recall and selection bias with the selected cases remains possible, as physicians could have chosen the cases

in which antipsychotics were effective or in which they felt that communication with caregivers was good. We documented which nonpharmacological interventions were tried, but for reasons of time we did not go into detail and did not ask which of these interventions were found useful in the specific cases.

Strengths of this Study

The strengths of this study included the ability to interview experienced elderly care physicians and nurses from a representative sample of Dutch nursing homes. In all nursing homes, psychologists were available. For nearly each patient, we interviewed his or her primary caregiver. We were therefore able to compare the opinions of physicians, nurses, and the primary caregivers on the start of antipsychotic treatment for each patient. To our best knowledge, this is the first study to do so.

CONCLUSIONS

It is possible to draw some conclusions from this study. First, it seems that it is not so much pressure from nursing staff or family that makes physicians prescribe an APD for BPSD. Also, physicians, nurses, and caregivers seem to overestimate the effectiveness of APD therapy in BPSD. Existing evidence-based guidelines for elderly care physicians are available in the Netherlands and better implementation of these guidelines in clinical practice may reduce inappropriate APD prescription. But not only more appropriate prescribing can help. It is also believed that the availability of more and better-trained nursing staff would help in the quality of nonpharmacological treatment of BPSD, therewith reducing the urgency to prescribe APDs. Last, the position of the caregivers should get more attention. In view of the risks associated with APDs, the provision of information needed to give informed consent must be improved.

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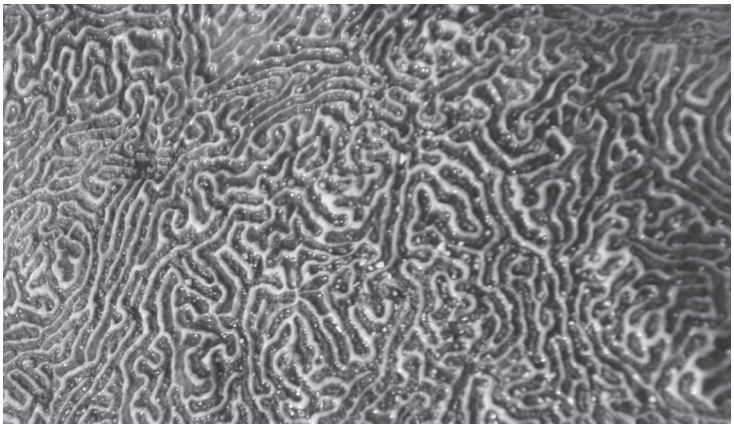
2.3

THE COURSE OF BEHAVIORAL PROBLEMS IN ELDERLY NURSING HOME PATIENTS WITH DEMENTIA WHEN TREATED WITH ANTIPSYCHOTICS



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ABSTRACT

Background

Although antipsychotic treatment of behavioral problems in dementia is common, studies investigating the course of these symptoms in nursing homes are scarce. Our primary objective is therefore to describe the course of behavioral problems during antipsychotic treatment in a large sample of elderly nursing home patients with dementia.

Methods

The course of behavioral problems during antipsychotic treatment was studied by comparing the characteristics of patients before, during and after antipsychotic treatment. The study was conducted using the VURAI, a database with over 40,000 assessments of over 10,000 nursing home residents in the Netherlands. We used the Challenging Behavior Profile (CBP) to measure an overall behavior score.

Results

In total, 556 patients starting with antipsychotics were studied. Of these, 101 (18.2%) improved and 260 (46.8%) deteriorated at three months on the behavior score, compared with their scores before therapy ($z=-7.955$; $P<0.0001$). Patients with severe challenging behavior showed improvement more often than patients with mild disturbances. The course of behavioral symptoms after withdrawal was evaluated in 520 patients. Of these patients, 352 (68%) remained stable or improved at 3 months compared with their scores before withdrawal ($z=-0.697$; $p= 0.486$), this figure was 58% at 6 months after withdrawal ($z = -2.77$; $p = 0.006$).

Conclusions

During treatment of nursing home residents with dementia with antipsychotics the severity of most behavioral problems continues to increase in most patients, with only one out of six patients showing improvement. After withdrawal of antipsychotics, behavioral problems remained stable or improved in 58% of patients.

INTRODUCTION

Antipsychotic drugs are frequently used in nursing home patients for the treatment of behavioral problems in dementia. The prevalence of antipsychotic drug use in Dutch nursing homes has been estimated at approximately 35 % (van Dijk et al., 2000; Zuidema et al., 2007) High levels of antipsychotic drug use have also been reported from other countries such as Canada (24%) (Bronskill et al., 2004), Switzerland (36%) (Gobert and D'hoore, 2005) and Finland (39%) (Alanen, et al., 2006). In the U.S.A. antipsychotic use remains high (27%) (Briesacher et al., 2005), despite the development of special legislation (OBRA) in 1987 in witch specific indications for the use of antipsychotic medications were established to decrease their inappropriate use as chemical restraints. (Shorr et al., 1994). This high prevalence has raised concerns given the high risk of antipsychotic drug related adverse events and the documented limited efficacy of these drugs in the treatment of behavioral problems in dementia (Schneider et al., 1990; Carson et al., 2006). More recently, new concerns have attracted attention. In 2005 the U.S. Food and Drug Administration (FDA) stated that the use of atypical antipsychotic drugs in elderly patients with dementia led to an approximately 1.6-1.7 fold increase in mortality (Kuehn, 2005). In 2008, this warning was extended to all antipsychotic drugs (Kuehn, 2008). Despite these concerns, there is no evidence of any substantial change in prescription behavior (Valiyeva et al., 2008). The lack of alternative care options, pressure from family and nursing staff "to do something", and concerns regarding deterioration of behavior after stopping may explain why nursing home physicians continue to prescribe antipsychotic drugs. Marked clinical improvements in some patients may influence the physicians perceived success rate. Studies investigating the course of behavioral symptoms in nursing homes are scarce. To our knowledge, there are no large long-term longitudinal studies assessing the course of behavioral symptoms of nursing home patients before, during, and after treatment with antipsychotic drugs. Our primary objective was to describe the course of behavioral problems in a large sample of nursing home patients with dementia treated with antipsychotic drugs.

METHODS

Setting

In this observational study, the effect of antipsychotic drug treatment on behavioral symptoms in nursing home patients with dementia was studied by comparing these symptoms before and after the first start of antipsychotic drug treatment using the Dutch Vrije Universiteit Resident Assessment Instrument Database (VURAI). The Resident Assessment Instrument (RAI) Database contains more than 400 Minimum

Data Set (MDS) items covering 13 domains, including functional, cognitive and behavioral items. It includes a dichotomous registration of antipsychotic drug use in the last week before the assessment. Data are collected with the RAI version 2.0 (Hawes et al., 1997). The VURAI contains over 40,000 anonymous RAI assessments of more than 10,000 residents of 10 nursing homes in the Netherlands. Data were collected from 2002 to march 2008. Nursing home nurses are required to complete assessments for all residents. Residents were generally assessed upon admission and quarterly thereafter. Extra assessments were performed in case of a significant change in a resident's condition. The personnel performing the MDS assessments on each of the wards had received standardized training.

Study population

The source population comprised all nursing home patients aged 55 years and older who were admitted to a dementia ward or had a diagnosis of dementia. At least two MDS assessments had to be available.

Antipsychotic exposure

Nursing home staff recorded the frequency of use of antipsychotic drugs taken by the patient in the 7 days before the assessment. New antipsychotic drug use was identified by the first MDS that reports any use of antipsychotic drugs in the last week. If multiple starts occurred, only the initial episode was used for analysis.

Outcome measures

To assess behavior we used the Challenging Behavior Profile (CBP) (Gerritsen et al., 2008). The CBP includes 9 items from the RAI 2.0 anxiety/mood section. A score of 0 on these items indicates no occurrence, a score of 1 indicates that the assessed problem was exhibited up to 5 days a week over the previous 30 days, and a score of 2 indicates that the problem was exhibited at least 6 days a week or daily over the previous 30 days. In addition, five items were included from the RAI 2.0 behavior section. For these items, a score of 1 indicates that the problem was exhibited up to three days over the previous week; a score of 2 indicates that the problem occurred almost daily (4-6 days) over the previous week; a score of 3 indicates that the problem occurred daily. For an optimally balanced contribution of each item to this scale score, categories 1 and 2 of the items with four response categories are taken together. The items are grouped in four subscales: conflict, agitation, withdrawal and attention seeking. The CBP score is the sum of the four subscales and ranges from 0 to 30. It is defined as being "extreme" if the total score is greater or equal than 15. A score of 10-15 was defined as "severe", 5-10 as "moderate" and 1-5 as "mild". A detailed description of the CBP items is given in Table 1. The used MDS items have been validated in three studies comparing these items with (among others) the Psychogeriatric Dependency

Table 1 Construction of the CBP score	
Challenging behavior profile score: theoretical maximum score	30
Conflict subscale	9
E1d Repetitive persistent anger with self or others	2
E4ba Verbally abusive behavior	2
E4ca Physically abusive behavior	2
E4ea Resisting care	2
F2a Conflict with or repeated criticism of staff	1
Withdrawal subscale	4
E1o Withdrawal from activities of interest	2
E1p Reduced social interaction	2
Agitation subscale	7
B5d Periods of restlessness	1
E1n Repetitive physical movements	2
E4aa Wandering (more than 3 days a week)	2
E4da Socially inappropriate behavior	2
Attention seeking subscale	10
E1a Negative statements	2
E1b Repetitive questions	2
E1c Repetitive verbalizations	2
E1h Repetitive health complaints	2
E1i Repetitive anxious complaints / concerns	2

Abbreviations: CBP = Challenging Behavior Profile; RAI = Resident Assessment Instrument

Rating Scale, the Brief Psychiatric Rating Scale and the Physician Behavior Checklist Score. These studies demonstrated good interrater reliability coefficients (0.63) and concurrent validity correlations of 0.51 to 0.58 (Hawes et al., 1995; Frederiksen et al., 1996; Snowden et al., 1999; 2003). For the CBP internal consistency, inter-rater reliability and validity against the Behavior Rating Scale for Psychogeriatric Inpatients (GIP) have been established (Gerritsen et al., 2008). Since the CBP does not cover all individual items describing behavior or neuropsychiatric functioning, we also assessed outcomes on the following MDS items: unrealistic fear, unpleasant mood in the morning, attention deficit, incoherent speech, delusions and hallucinations.

Data analysis

We calculated the CBP scores for all assessments during the entire follow-up. For each patient the assessment closest before the first assessment mentioning antipsychotic drug use was used to calculate the CBP before start. The first assessment mentioning antipsychotic drug use was used to estimate the scores during treatment.

The first assessment without antipsychotic drug use was used to calculate the scores after withdrawal of therapy. Any increase in the CBP score is considered a deterioration, and any decrease an improvement of symptoms. A withdrawal was considered successful if the patient remained stable or improved at the first and next assessment after withdrawal.

Statistical analysis was performed with SPSS, version 15.0. Wilcoxon matched pairs signed ranks test was used to evaluate the difference in symptom and overall scores before, during and after treatment for each individual. As we expect the number of missing values to be low and at random, we used pair-wise deletion of missing data resulting in variable numbers of patients for the assessed items.

RESULTS

Of 10,318 nursing home residents included in the VURAI database, 9852 patients were aged 55 years or older. After excluding 5831 patients without diagnosis of dementia, our study population consisted of 4021 patients. From these, antipsychotic drug use was recorded for 1904 patients at any time during follow-up (47%). After excluding 243 patients for lack of follow-up, 1661 patients remained for analysis. The mean age was 83 years, 68% were women and 82% suffered from moderate to severe cognitive problems, defined as a score >2 on the Cognitive Performance Scale which ranges from 0 - 6 (Hartmaier et al., 1994). The patients' characteristics are shown in Table 2. Almost half of these patients used an antipsychotic drug during the entire follow-up (820 patients) so effects of starting or stopping an antipsychotic drug could not be measured. We identified 319 patients with a first start of antipsychotic drug treatment during follow-up, 285 patients who stopped using antipsychotic drug during follow-up and 237 patients with both a start and stop of an antipsychotic drug. While most of the data were complete, missing information in 3% of patients resulted in variable numbers of patients eligible for analysis. Patients were followed until death (44%), discharge (7%) or the end of the study period (49%). The average time-interval between the assessments was 105 days (median 91 days). During treatment, mean scores for all evaluation points on the CBP and individual subscales were worse than the last recorded scores (Figure 1). Of the 556 patients starting on a antipsychotic drug, 101 (18%) improved and 260 (47%) deteriorated on the CBP score compared to their scores before therapy (Wilcoxon test, $z = -7.955$; $p<0.001$) - see Table 3. After at least three months of use, 134 (24%) improved and 296 (53%) deteriorated compared to baseline (Wilcoxon test, $z = -7.531$; $p<0.001$). The mean CBP increased from 6.1 at admittance to 7.6 before therapy. It increased to 8.9 directly after start and was 9.4 after at least 3 months of use. Patients with severe behavioral problems prior to antipsychotic drug

Table 2 Characteristics of the study population	
Total number of antipsychotic users	1661
Mean age at admission (year +/- standard deviation, range)	83 +/- 8 (55-103)
Mean duration of follow-up (year +/- standard deviation)	1.5 +/- 1.4
Male gender	32%
Mean cognitive performance scale (0-6)	3.7
Percentage of patients with moderate to severe cognitive problems	82%
Challenging behavior profile score at admission	
-none	7%
-mild	33%
-moderate	31%
-severe	19%
-extreme	10%
Functional impairment (ADL hierarchy scale)*	
-Independent	4%
-Supervision	7%
-Extensive assistance 1 (no extensive assistance in locomotion)	15%
-Extensive assistance 2 (no total dependence in eating and / or locomotion)	32%
-Dependent	25%
-Total dependence	8%
History of stroke	18%
Use of hypnotics	19%
Use of anxiolytics	16%
Use of antidepressants	20%

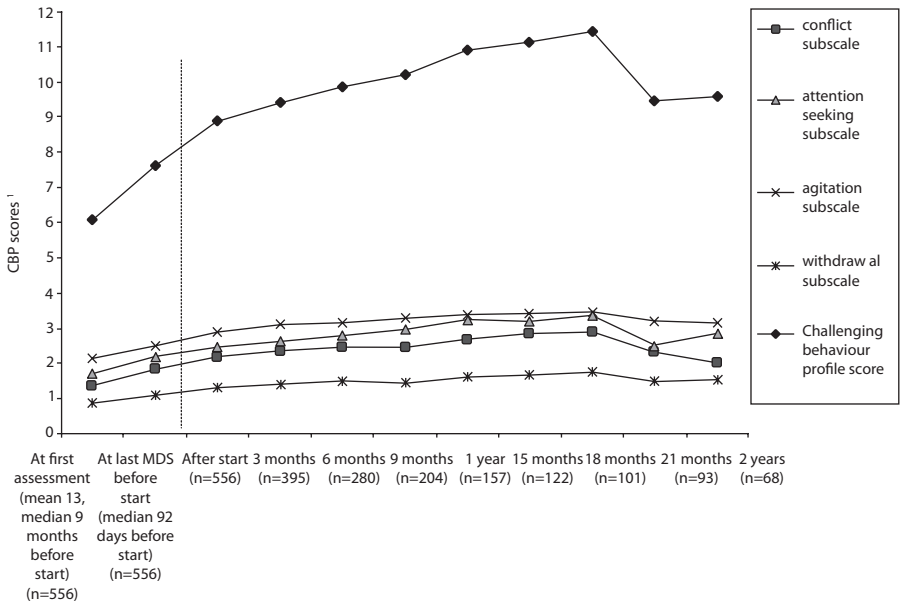
Abbreviations: ADL = Activities of Daily Living
*The hierarchical ADL scale ranges from minor oversight to highly dependent (Morris et al., 1999).

use showed improvement more often than patients with mild problems (Table 4). The course of challenging behavior after withdrawal of therapy was evaluated in 520 patients (data missing in 3 patients, 0.6%) (Table 5 and Figure 2). The challenging behavior profile improved in 155 patients (30%), worsened in 168 (32%), and remained stable in 197 patients (38%) (Wilcoxon test, z=-0.697; p = 0.486). At next assessment, these figures are 27% improvement, 42% worsening and 31% unchanged, (z=-2.77; p=0.006).

DISCUSSION

We examined the course of behavioral symptoms in nursing home patients with dementia who started antipsychotic treatment during their stay. We found an

Figure 1 Course of Challenging behaviour for starters



[1] higher score means deterioration of behavior.
Abbreviations: CBP= challenging behavior profile; MDS= Minimum Data Set

estimated prevalence of antipsychotic drug use of 47% in our population during the study period from 2002 to 2008, which is comparable to the prevalence found by van Dijk (two-year prevalence 56%) in 1995 and by Zuidema (point prevalence 37%) in 2003 (van Dijk, 2000; Zuidema, 2007). Short-time antipsychotic use may have been missed in our study, resulting in an underestimation of the prevalence. At group level, we observed an improvement of behavioral symptoms in one-fifth to a quarter of the patients while half of the patients showed a worsening of behavioral symptoms. These results are in line with results from other studies: Schneider's meta-analyses on the effects of treatment with conventional antipsychotic drugs on agitation showed improvement in 18% of treated patients compared to controls (Schneider et al., 2006a). For the atypical antipsychotic drugs, Schneider reported benefit in 26 -32% of patients randomly assigned to olanzapine, risperidone and quetiapine compared to 21% with placebo (Schneider et al., 2006b). After 3 months, no difference in functioning, care needs, or quality of life was found (Sultzer et al., 2008). In a 12-week randomized controlled trial (RCT) among 345 patients with Alzheimer's disease, de Deyn et al. found no significant

Table 3 **Wilcoxon matched signs paired ranks test for changes in challenging behavior profile before and at first assessment after start of antipsychotic drug use (n = 556)**

	number of patients improved[1]	number of patients worsened[2]	number of patients unchanged	p	z
Challenging behavior profile overall score	101 (18%)	260 (47%)	195 (35%)	<0.001	-8.0
Conflict subscale score	68 (12%)	159 (28%)	333 (59%)	<0.001	-5.9
Persistent anger with self or others	31 (6%)	72 (15%)	381 (79%)	<0.001	-3.8
Verbally abusive behaviors	22 (5%)	66 (14%)	396 (82%)	<0.001	-4.5
Physically abusive behaviors	17 (4%)	35 (7%)	432 (89%)	<0.008	-2.6
Resisting care	26 (5%)	59 (12%)	399 (82%)	<0.001	-3.4
Conflict with or repeated criticism of staff	14 (3%)	27 (6%)	442 (92%)	0.042	-2.0
Withdrawal subscale score	34 (6%)	87 (15%)	443 (79%)	<0.001	-4.7
Withdrawal from activities of interest	22 (5%)	58 (12%)	403 (83%)	0.001	-3.3
Reduced social interaction	18 (4%)	57 (12%)	408 (84%)	<0.001	-4.1
Agitation subscale score	58 (10%)	160 (28%)	344 (61%))	<0.001	-6.9
Periods of restlessness	10 (2%)	50 (10%)	427 (88%)	<0.001	-5.1
Repetitive physical movements	14 (3%)	51 (11%)	418 (87%)	<0.001	-4.6
Wandering	22 (5%)	41 (8%)	421 (87%)	<0.02	-2.4
Socially inappropriate/disruptive behavior	21 (4%)	89 (18%)	374 (77%)	<0.001	-6.6
Attention seeking subscale score	64 (11%)	146 (26%)	357 (63%)	<0.001	-4.8
Negative statements	33 (7%)	61 (13%)	391 (81%)	0.005	-2.8
Repetitive questions	29 (6%)	51 (11%)	405 (84%)	0.145	-1.5
Repetitive verbalizations	23 (5%)	52 (11%)	410 (85%)	0.03	-3.0
Repetitive health complaints	18 (4%)	38 (8%)	429 (88%)	0.002	-3.1
Repetitive anxious complaints/concerns	15 (3%)	37 (8%)	433 (89%)	0.021	-2.3
Other items (not included in CBP)					
Expressions of unrealistic fear	20 (4%)	57 (12%)	408 (84%)	<0.001	-3.7
Fear that something terrible is about to happen	8 (2%)	22 (5%)	455 (94%)	0.03	-2.1
Unpleasant mood in the morning	14 (3%)	50 (10%)	420 (87%)	<0.001	-4.2
Reduced ability to focus, sustain, or shift attention	26 (5%)	77 (16%)	383 (79%)	<0.001	-5.2
Incoherent speech	11 (2%)	62 (13%)	413 (85%)	<0.001	-5.2
Delusions	10 (2%)	11 (2%)	448 (96%)	0.827	-0.2
Hallucinations	9 (2%)	15 (3%)	445 (95%)	0.221	-1.2

Abbreviations: CBP = challenging behavior profile
[1] The actual number of patients showing any improvement on these symptoms after start of antipsychotics.
[2] The actual number of patients showing any worsening on these symptoms after start of antipsychotics.

Table 4 **Linear-by-linear association of severity of behavior and response to therapy (p<0.001)**

CBP score before start of antipsychotic drug	No challenging behavior	Mild challenging behavior	Moderate challenging behavior	Severe challenging behavior	Extreme challenging behavior	Total
Patients without improvement on CBP after start of antipsychotic drug	51 (100%)	156 (88%)	144 (81%)	71 (75%)	33 (61%)	455 (82%)
Patients with improvement on CBP after start of antipsychotic drug	0 (0%)	22 (12%)	34 (19%)	24 (25%)	21 (39%)	101 (18%)

Abbreviations: CBP = challenging behavior profile

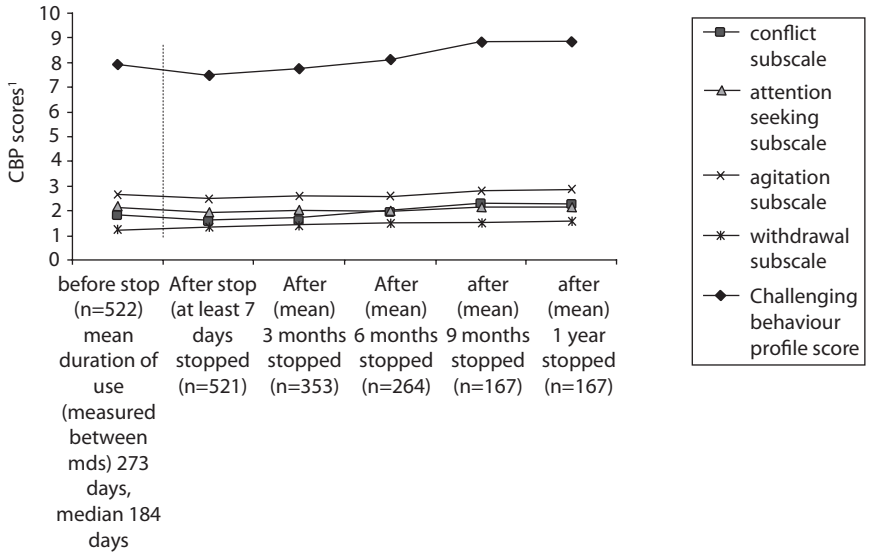
Table 5 **Wilcoxon matched signs paired ranks test for changes in challenging behavior profile before and at first assessment after withdrawal of antipsychotic drug use (n =520)**

	number of patients improved	number of patients worsened	number of patients unchanged	p	z
Challenging behavior profile overall score	155 (30%)	168(32%)	197 (38%)	0.5	-0.7
Conflict subscale score					
Persistent anger with self or others	61 (12%)	47 (9%)	412 (79%)	<0.1	-1.6
Verbally abusive behaviors	66 (13%)	41 (8%)	413 (79%)	<0.005	-3.1
Physically abusive behaviors	36 (7%)	29 (6%)	455 (88%)	0.2	-1.3
Resisting care	58 (11%)	40 (8%)	422 (81%)	<0.05	-2.0
Conflict with or repeated criticism of staff	28 (5%)	14 (3%)	480 (92%)	<0.05	-2.1
Withdrawal subscale score	38 (7%)	65 (13%)	417 (80%)	<0.05	-2.0
Withdrawal from activities of interest	42 (8%)	62 (12%)	416 (80%)	0.45	-0.7
Reduced social interaction					
Agitation subscale score	55 (11%)	30 (6%)	435 (84%)	<0.01	-2.7
Periods of restlessness	40 (8%)	47 (9%)	433 (83%)	0.45	-0.8
Repetitive physical movements	45 (9%)	23 (4%)	452 (87%)	<0.01	-2.6
Wandering	68 (13%)	46 (9%)	406 (78%)	<0.05	-2.1
Socially inappropriate/disruptive behavior					
Attention seeking subscale score					
Negative statements	57 (11%)	50 (10%)	413 (79%)	0.08	-1.8
Repetitive questions	58 (11%)	49 (9%)	413 (79%)	0.27	-1.1
Repetitive verbalizations	49 (9%)	32 (6%)	439 (84%)	0.03	-2.1
Repetitive health complaints	40 (8%)	25 (5%)	455 (88%)	0.05	-2.0
Repetitive anxious complaints/concerns	45 (9%)	34 (7%)	441 (85%)	0.1	-1.6
Other items (not included in CBP)					
Expressions of unrealistic fear	35 (7%)	42 (8%)	443 (85%)	0.85	-0.2
Fear that something terrible is about to happen	25 (5%)	14 (3%)	481 (93%)	<0.05	-2.0
Unpleasant mood in the morning	39 (8%)	44 (8%)	437 (84%)	0.2	-1.2
Reduced ability to focus, sustain, or shift attention	49 (9%)	50 (10%)	420 (81%)	0.77	-0.3
Incoherent speech	51 (10%)	52 (10%)	416 (80%)	0.99	-0.0
Delusions	11 (2%)	4 (1%)	498 (96%)	0.1	-1.8
Hallucinations	12 (2%)	9 (2%)	492 (95%)	0.5	-0.7

Abbreviations: CBP = challenging behavior profile

difference between the percentage of responders to risperidone, haloperidol and placebo on behavioral problems. In this study responders were defined as those patients who improved more than 30% on the BEHAVE-AD total score. An analysis of subscales, however, proved a significant effect on the aggression subscales, a finding that dominated the conclusions (De Deyn et al., 1999). In another large RCT, Katz et al. defined responders as having a 50% reduction in BEHAVE-AD scores, and found only 12% more responders in the treatment group compared to placebo. He noted that only scores on the aggressiveness and paranoid delusion subscales were significantly reduced with antipsychotic drug use (Katz et al., 1999). A meta-analysis of all RCTs for atypical antipsychotic drugs showed overall limited effects on behavioral problems (Schneider et al., 2006a).

Figure 2 Course of Challenging behaviour after withdrawal of antipsychotics



1 higher score means deterioration of behavior.
Abbreviations: CBP=challenging behavior profile; MDS=minimum data set

Differences in the assessment scales used, however, limit comparisons across trials. As most RCTs reported a mean change from baseline scores instead of a paired t-test for each individual, the number of patients that benefit from treatment is not reported in most studies. The results of three observational longitudinal studies on the prevalence of behavioral symptoms are also comparable with our study as they suggest that patients taking antipsychotic drugs are not more likely to improve than antipsychotic drug-free patients (Ballard et al., 2001; Aalten et al., 2005; Selbaek et al., 2008). Our findings suggest that patients with severe behavioral symptoms benefit more from treatment, a finding consistent with Ballard et al. (2008). This reduction in symptoms may, however, reflect the natural course of disease.

Discontinuation of antipsychotic drugs for behavioral symptoms has been reported to be successful in the majority of patients in all published studies (Thapa et al., 1994; Bridges-Parlet et al., 1997; Cohen-Mansfield et al., 1999; van Reekum et al., 2002; Ballard et al., 2004; 2008; Bergh and Engedal, 2008; Ruths et al., 2008). Our findings suggest that behavioral problems worsen following the stopping of the antipsychotic drug in about one- third of the patients. This figure is comparable with

the results of two studies of Ballard et al. (2004; 2008) and one of Ruths et al. (2008), who both found no deterioration after discontinuation in at least 67% of patients. Our study adds to the growing evidence that antipsychotic treatment of behavioral problems of dementia is often inefficient. Given the reported high rates of adverse events such as extrapyramidal symptoms (EPS) (Lee et al., 2005), falls (Hien et al., 2005), hip fractures (Liperoti et al., 2007), venous thromboembolism (Zornberg and Jick, 2000), cerebrovascular events (Gill et al., 2005; Kleijer et al., 2008), pneumonia (Knol et al., 2008), or death (Schneider et al., 2005; Wang et al., 2005; Setoguchi et al., 2008; Ballard et al., 2009), and the high prevalence of behavioral symptoms found in this study, this finding underlines the need for new effective and safe therapies.

The results of our study must be interpreted within the context of a number of limitations. As this is a descriptive study, it does not intend to proof that individual patients did worse or better because of the treatment in question. The association of antipsychotic treatment with an increase in behavioral symptoms does suggest that the influence of this therapy is limited, but we do not know how this increase would have been without treatment. Perhaps antipsychotic drug use prevented behavioral problems to rise to extreme levels, in which case this therapy would still be effective despite the higher CBP scores. Since it is common practice to prescribe antipsychotic drugs in case of behavioral problems, there is no way we can predict the level of problems in an antipsychotic drug free situation. The high number of patients not eligible for evaluation must be considered when interpreting the results. Given the vulnerability of the study population, the substantial number of deaths is not surprising and reflects real clinical practice. Antipsychotics have been shown to be more effective for true psychotic symptoms (hallucinations and delusions) and aggression. Using the CBP and its subscales may dilute a positive effect on these symptoms. We therefore included all results on symptom level in Tables 3 and 5. We found no specific improvement of physical aggression, and a low prevalence of reported delusions and hallucinations.

Some limitations of this study relate to the inherent limitations of the RAI database. First, it relies on nursing staff for information in order to complete the assessment scales. To make sure that the patient's behavior is adequately recorded, the behavioral items of the MDS are always completed by nurses directly involved in the daily care of the patients. As in the MDS, no special emphasis is placed on the report of behavioral symptoms and these symptoms may be under-reported when compared to the use of specific research instruments such as the Cohen Mansfield Agitation Inventory (Bharucha et al., 2008). Secondly; we used reported antipsychotic drug use instead of pharmacy records. As failure to report antipsychotic drug use is possible, the use of antipsychotic drug may have been underreported. We expect any resulting bias to be non-differential. Finally, antipsychotic drugs are often started when extremes of behavior occur, but this initial increase in behavioral symptoms will not

always be captured in a quarterly assessment. This may lead to an underestimation of the initial effect of antipsychotic drugs. Nurses and staff were therefore encouraged to do an extra assessment if there was a significant change in the patient's status, which happened in 11% of cases. If, however, a MDS is recorded at a time of extreme behavioral problems, a regression to the mean phenomenon is likely to occur. In such a case, improvement is likely to occur spontaneously and is not necessarily related to the effect of antipsychotic drug treatment. This phenomenon may explain the better results of antipsychotic drug treatment in severe behavior (Table 4).

The course of symptoms after withdrawal of therapy must also be interpreted with caution, as improved behavior might be a reason to stop, which will cause selection bias. This does, however, reflect the situation in normal clinical practice. The strength of this study is that we have been able to follow a large sample of frail nursing home patients, and used a detailed assessment instrument to assess behavioral symptoms at regular intervals in a naturalistic setting.

In conclusion, these results indicate that the influence of antipsychotic therapy on the course of behavioral symptoms in nursing home patients with dementia is limited but not zero. Given these results and the current knowledge regarding major short- and long-term risks, doctors should be very reserved in prescribing antipsychotic drugs for problematic behavior. Since antipsychotic drugs may have an effect in a subgroup of patients and in specific types of problematic behavior (e.g. aggression, agitation) its use must not be prohibited. A detailed assessment of cardiovascular risk factors and goals of therapy must be made prior to starting antipsychotic drug therapy and effects on behavior should be closely monitored. Prescription figures of antipsychotic drugs in 30-40% of the nursing home patients with dementia, with a majority of these patients using antipsychotic drugs for months, can never be explained and defended based on current evidence.

Description of authors' roles

D.H.M. Frijters and M.W. Ribbe provided the data; B.C. Kleijer, R.J. van Marum an A.C.G. Egberts designed the study, analyzed the data and wrote the paper, P.A. Jansen and E.R. Heerdink assisted in the interpretation of the data. All authors reviewed the manuscript and approved the final version.

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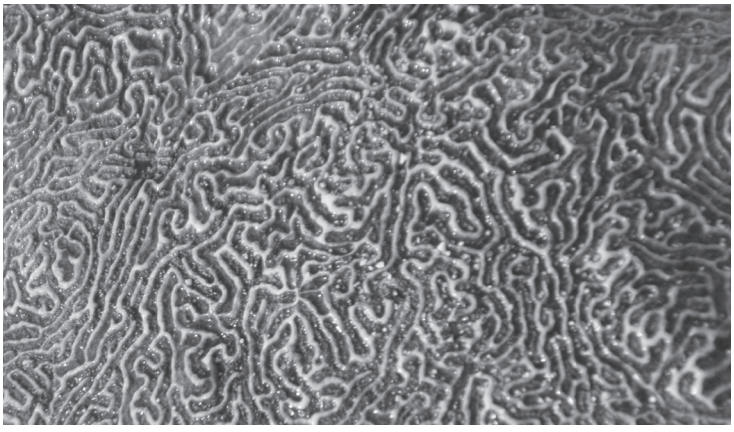
3

ADVERSE EFFECTS OF ANTI-PSYCHOTIC USE IN THE ELDERLY

3.1

RISK OF CEREBROVASCULAR EVENTS IN ELDERLY USERS OF ANTIPSYCHOTICS



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ABSTRACT

Background

It has been shown that elderly patients with dementia treated with atypical and conventional antipsychotics have a twofold increased risk of cerebrovascular adverse events (CVAE).

Methods

To investigate the temporal relationship between exposure to antipsychotics and the risk of CVAE, a case-control analysis nested within a cohort of 26,157 community-dwelling patients (mean age 76 ± 9.7) with at least one antipsychotic prescription was conducted. Data were used from Dutch community pharmacies and hospital discharge records. Five hundred and eighteen cases of hospital admission for CVAE were identified. For each case, four randomly selected controls matched by sex and age were sampled from the cohort. To evaluate the temporal relationship between antipsychotic use and the occurrence of CVAE, two measures were used: the first being a current, recent or past user, and the second for the current users, the duration of use up to the index date. In addition, the cumulative exposure was assessed.

Results

Current and recent exposure to antipsychotics were associated with an increased risk of CVAE compared with non-users (odds ratio [OR] 1.7, CI 1.4–2.2). A strong temporal relationship was found; the OR for a history of use less than a week is 9.9 (5.7–17.2). The risk decreases in time and is comparable to non-users after three months of use (OR 1.0, CI 0.7–1.3). Cumulative exposure was not associated with an increase in risk.

Conclusions

The risk of CVAE in elderly patients associated with antipsychotics is elevated especially during the first weeks of treatment. This risk decreases over time and is back on base level after three months of treatment. Chronic use is not associated with CVAE.

INTRODUCTION

Antipsychotics are widely used in the treatment of psychosis and behavioural problems in elderly patients. Antipsychotics are frequently used for the treatment of behavioural symptoms in patients with dementia although there is little evidence regarding efficacy (Schneider, et al., 2006). In contrast, it is well known that antipsychotics are frequently associated with adverse effects. For the atypical antipsychotics olanzapine, risperidone and aripiprazole, warnings have been issued in 2003 and 2004 regarding the increased risk of developing cerebrovascular adverse events (CVAEs) in patients with dementia (Kuehn, 2005; FDA, 2005; Wooltorton, 2002, 2004). On April 11, 2005, the FDA issued a health advisory for increased all-cause risk for death with atypical antipsychotics in people with dementia. These warnings were based on a post-hoc analysis of randomised controlled trials. In a meta-analysis, Haupt, et al. (2006) found 0.4% lethal CVAE with risperidone compared with 0.1% with placebo. Schneider, et al. (2005, 2006) studied 15 randomised trials of atypical antipsychotics and found a twofold increase in risk for CVAE, 1.9% versus 0.9% pooled.

Epidemiologic studies that followed showed conflicting results: Percudani, et al. (2005) found an increase in risk of CVAE in users of both atypical and conventional antipsychotics compared with non-users. In contrast, Finkel, et al. (2005), Liperoti, et al. (2005), Raivio, et al. (2007) and Suh and Shah, (2005) found no increased risk of CVAE or mortality. Kales, et al. (2007) reported a higher mortality rate for users compared with non-users but found no difference in death due to stroke after one year of treatment. It has been shown that conventional antipsychotics are equally or even more harmful compared with atypical antipsychotics (Gill et al. 2005; Herrmann, et al. 2004; Layton, et al. 2005; Wang, et al. 2005; Kales, et al. 2007). This increased risk was found in both demented and non-demented elderly patients (Wang, et al. 2005). There is no evidence that the increased risk of CVAE is unique to elderly patients with dementia. It remains unclear whether the risk of cerebrovascular events continues to be elevated during long-term treatment. Wang, et al. (2005) reported the greatest increase in risk of death soon after therapy was initiated (RR 1.6), but did not report causes of death. Schneeweiss, et al. (2007) also reported a higher risk of death (odds ratio [OR] 1.6) within 40 days after start of conventional antipsychotic drug therapy compared with atypical agents. For the risk of CVAE, these data are not available, but is should be noted that the trials consisted of new users and generally were of short duration, typically 70 days. As the greatest increase in risk seems to occur in the first weeks after initiating therapy, chronic users may have another risk profile compared with starters. In the present study, we, therefore, investigated the risk of CVAE in elderly antipsychotic users, with a special emphasis on the temporal relationship between use and the occurrence of CVAE.

Methods

To study the effect of the duration of antipsychotic use in the period preceding the CVAE, we used a time –matched case-control analysis nested within a cohort of antipsychotic users.

Setting

Data were derived from the PHARMO record linkage system. This database includes pharmacy dispensing records from community pharmacies linked to hospital discharge records of all 950,000 community-dwelling residents of 25 population-defined areas in the Netherlands from 1985 onwards (Herings, 1993). Because virtually all patients in the Netherlands are registered with a single community pharmacy, pharmacy records are virtually complete with regard to prescription drugs. Participants of the PHARMO population enter the database with the first prescription filled in a PHARMO community pharmacy and are followed until the last prescription. The computerized drug-dispensing histories contain information concerning the dispensed drug, dispensing date, amount dispensed and the prescribed number of units to be used per day. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. The hospital discharge records are obtained from PRISMANT, previously known as the Dutch Centre for Healthcare Information (LMR database), an institute that collects nationwide all hospital discharge records in the Netherlands since the 1960s into a standardised format (http://www.pharmo.nl). These records include detailed information concerning the primary and secondary diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, ninth edition (ICD-9-CM).

Cohort definition

The study was conducted in a cohort of patients of 50 years or older who started antipsychotic medication during 1986–2003. Starters were defined as those with no prescription for any antipsychotic during a period of at least 1 year. Consequently, at least 1 year of history had to be available in the PHARMO database (exposure cohort, n=26,157).

Case and control definition

Cases were defined as those patients from the cohort with a first hospital admission for ischemic or haemorrhagic stroke or transient ischemic attack (ICD–9 code 430–436). The date of admission to the hospital was taken as index date for the cases. For each case, four controls were randomly selected from the exposure cohort.

Controls were matched for age (± 5 years) and sex. Each control was assigned the index date of the corresponding case.

Exposure definition

Drug exposure was defined as current if the prescription period covered the index date, taking into account a washout period of 7 days. Past exposure was categorised as recent past (prescription period ended 8 days till 30 days before index date) and past (prescription period ended between 31 and 365 days before index date). Non-users were defined as patients with no use of antipsychotics in the year before index. Among current users, the duration of the treatment episode was calculated and divided into five categories (0–7, 8–14, 15–30, 31–90 and >90 days). A treatment episode is defined as a series of prescriptions, which are renewed just before the last prescription ends. A maximum gap of 2 weeks is allowed to compensate for possible patients delays. Cumulative exposure was measured as the total days of exposure during follow-up. Drug dosage was analysed based on last used antipsychotic and categorised into less than 0.25 DDD, 0.25–0.5 DDD and more than 0.5 DDD.

To analyse the effect of type of antipsychotic, prescriptions were divided in typical and atypical antipsychotics, in high- or low central α_1-adrenoreceptor affinity, and in high or low 5HT(2A)-affinity (Richelson, et al. 1999; Richelson and Souder, 2000). We studied α_1-adrenoreceptor affinity to consider the effect of orthostatic hypotension. The 5HT(2A) receptor plays a role in the contribution of platelet physiology to thromboembolic events. Atypical antipsychotics available in the Netherlands during the inclusion period were risperidone, olanzapine, clozapine and quetiapine. Chlorpromazine, clozapine, flufenazine, haloperidol, olanzapine, perfenazine, quetiapine, risperidone, thioridazine and zuclopentixol were classified as agents with high central α_1-adrenoreceptor affinity. We classified chlorpromazine, clozapine, perfenazine, olanzapine, pipamperon and risperidone as agents with high 5HT(2A)-affinity (Affinity <15 Ki Nm).

Potential confounders

We considered a history of previous stroke, diabetes, hypertension, hyperlipidemia, and atrial fibrillation as significant stroke risk factors. A patient was considered to have one of these risk factors if one or more of the following drugs during the year before the index date were prescribed, grouped by ATC-class: antithrombotic agents (B01), antidiabetic drugs (A10), agents acting on the renin-angiotensin system (C09), alpha-and beta blocking agents (C07), diuretics (C03), calcium channel inhibitors (C08), vasodilators (C01D), lipid modifying agents (C10), cardiac glycosides (C01A), and antiarrhythmic drugs (C01B). As both the risk of CVAE and the risk of dementia increases with age, controls were matched for age.

Statistical analysis

The strength of the association between use of antipsychotics and the occurrence of CVAE was estimated by multivariate logistic regression analysis and expressed as ORs with 95% confidence intervals (CIs), taking into account all potential confounders as covariates. To investigate the temporal relationship, we calculated the association between antipsychotic drug use and the occurrence of CVAE for difference subgroups, based on current or past use and compared with non-users. Within the group of current users, we investigated the association of duration of last exposure with the risk of CVAE, with non-users as reference. The association between total exposure time and risk for CVAE was calculated for patients with at least 2 years of available follow-up, with chronic users (exposure longer than 3 years) as a reference group. Analyses were performed with SPSS (SPSS Inc., Chicago, Illinois, USA) for windows, version 15.0.

Results

The study population comprised 518 cases of hospital admission for CVAE (54% ischemic, ICD-Codes 433–435.9; 15 % haemorrhagic, ICD-codes 431–432 and 31% non-specified cerebrovascular apoplectic events, ICD-code 436) and 2030 controls. Among cases, 94 (18%) died during hospital admission. The characteristics of the study population are shown in Table 1. There is a higher prevalence of cardiovascular medication use among cases relative to controls (79.0% vs 57.3%), indicating a worse cardiovascular risk profile among cases relative to controls. After adjustment for this difference in baseline risk, current use of antipsychotics was associated with a 60 % increase in the risk of CVAE (Table 2). Patients whose prescription ended in the recent past (7–30 days ago) also had an increased risk of CVAE compared with non-users. Past use (>31 days ago) was not associated with an increased risk of CVAE. We found a tenfold increase in risk of CVAE in the first week of use compared with controls (OR 9.9, CI 5.7–17.2). This risk decreases in time (Table 3, figure 1). Continuous use longer than 3 months is no longer associated with an increased risk compared with non-users. This pattern was the same in high and low dosage schemes. As expected, the majority of cases were ischemic events (ischemic stroke 32%, apoplexy 31%, transient cerebral ischemia 17%, intracerebral haemorrhage 10%, subdural haemorrhage 3%, occlusion of precerebral arteries with cerebral infarction 3%, miscellaneous 4%), but we found no difference in risk between ischemic and haemorrhagic events. Exclusion of transient ischemic attacks (TIAs) (89 cases) in the analysis does not change the results. Cumulative exposure does not increase the risk for CVAE, with ORs between 0.9 and 1.1 and CIs including the value of 1, for various exposure times compared with 3 years of exposure (data not shown). Finally, we analysed subgroups based on type of antipsychotic. Users of conventional antipsychotics have an increased risk compared with users of atypical antipsychotics (all patients: OR 1.6, CI 1.0–2.5; current users: OR 2.6, CI 1.3–5.0). High central α1-adreno-receptor affinity did not increase risk. (OR 1.1, CI 0.9–1.4). Agents with a high serotonin (5HT–2A) affinity showed a protective effect (current users: OR 0.5, CI 0.3–0.7).

Figure 1 Odds for CVAE plotted against time (in intervals) (current users).

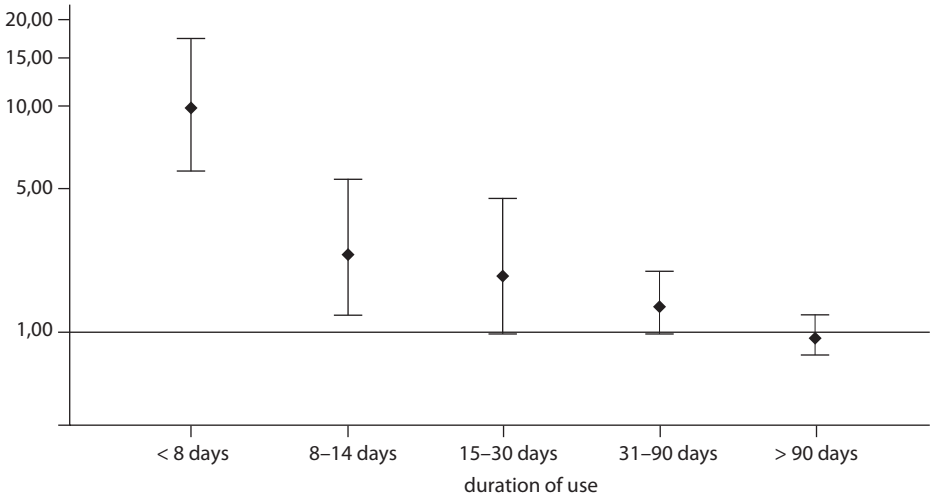

Table 1 Characteristics of patients and matched controls

	Cases	Controls
Mean age ± standard deviation (years)	76 ± 9.7	76 ± 9.7
Male (%)	44	44
Mean duration of follow-up (years)	8.0	8.2
Mean duration of last prescription among current users (days)	75	88
Mean patient daily defined dose (in proportion of ddd)	0.24	0.25
Type of antipsychotic: % with atypical antipsychotics use	4.7%	6.6%
Type of antipsychotic: % with high serotonin-2 receptor affinity	23.7%	26.7%
Type of antipsychotic: % with high central α^1 -adrenoreceptor affinity	51.4%	48.2%
Antidiabetic drugs (ATC class A10, in % present)	17%	12.7%
Antithrombotic agents (B01)	60.2%	32.6%
Lipid modifying agents (C10)	8.3%	8.4%
Calcium channel inhibitors (C08)	18.0%	11.5%
α- and β-blocking agents (C07)	29.5%	19.1%
Diuretics (C03)	34.0%	26.9%
ATII inhibitors (C09C+D)	5.4%	2.7%
ACE inhibitors (C09A+B)	21.2%	15.5%
Vasodilators (C01D)	14.7%	13.0%
Antiarrhythmic drugs (C01B)	3.1%	2.1%
Cardiac glycosides (C01A)	10.8%	8.6%
One or more cardiovascular medications (in % present)	79.0%	57.3%
Recent (< 2 weeks) hospital discharge for other diagnoses	5.8%	3.3%

ATC, Anatomical Therapeutic Chemical; ATII, angiotensin II; ACE, angiotensin-converting enzyme.

Table 2 **OR for CVAE in patients exposed to antipsychotic medication grouped by period of use, odds for CVAE against non-users, adjusted for cardiovascular risk factors**

APD use	Cases (N=518), N (%)	Controls (N=2030), N (%)	Crude OR (95%CI)	Adjusted OR (95%CI)
Current use	178 (34.4)	518 (25.5)	1.8 (1.4–2.2)	1.6 (1.3–2.0)
Recent past 8-30 days	32 (6.2)	71 (3.2)	2.3 (1.5–3.5)	2.0 (1.3–3.3)
Past >30 days	106 (20.5)	429 (21.1)	1.2 (1.0–1.4)	1.2 (0.9–1.6)
No use	202 (39)	1012 (49.9)	reference	reference

OR, odds ratio; CVAE, cerebrovascular adverse event; APD, antipsychotic drug.

Table 3 **OR for CVAE in patients currently exposed to antipsychotic medication grouped by duration of use, odds for CVAE against non-users, adjusted for cardiovascular risk factors**

Duration of use	Cases (N=380), N (%)	Controls (N=1530), N (%)	Crude OR (95%CI)	Adjusted OR (95%CI)
up to 7 days	44 (65.7)	23 (34.3)	9.6 (5.7-16.2)	9.9 (5.7-17.2)
8-14 days	14 (35.9)	25 (64.1)	2.8 (1.4-5.5)	2.6 (1.3-5.3)
15-30 days	12 (34.3)	23 (65.7)	2.6 (1.3-5.3)	2.1 (1.0-4.5)
31-90 days	40 (24.5)	123 (75.5)	1.6 (1.1-2.4)	1.5 (1.0-2.2)
>90 days	68 (17.3)	324 (82.7)	1.1 (0.8-1.4)	1.0 (0.7-1.3)
non-user	202 (16.6)	1012 (83.4)	reference	reference

OR, odds ratio; CVAE, cerebrovascular adverse event.

DISCUSSION

In this population-based study of elderly people, we showed that the increased cerebrovascular risk associated with the use of antipsychotics is concentrated in the first weeks of treatment. The risk of CVAE did not increase with increasing length of treatment and returned to baseline after 3 months of use. This temporal relationship between antipsychotics and CVAE gives further support for a causal relationship. The overall increase in risk for CVAE found in our study is comparable with the results of the study of Schneider, et al. (2006) and the reports of Wooltorton (2002, 2004). Our results indicate that in the elderly population, only the start of antipsychotic therapy is associated with an increased risk of CVAE. This may explain the difference in results previously found by placebo-controlled trials (Haupt, et al. 2006; Schneider, et al., 2005) compared with studies of longer duration (Raivio, et al., 2007; Finkel, et al., 2005; Liperoti, et al., 2005; Suh and Shah, 2005; Kales, et al., 2007). When patients use antipsychotics for more than 3 months, the increased risk

returns to baseline levels. This can be explained as only those patients who tolerated their first exposure were able to receive more prescriptions. These patients apparently are less susceptible for the adverse cerebrovascular effects of antipsychotics.

In our study, the mortality rate of hospital admission for stroke was 18%. Wang, et al. (2005) found the highest death rate at 10 days after initiating antipsychotic treatment, gradually decreasing until a plateau was reached after 40 days. They could not provide causes of death, due to insufficient data. Our findings suggest that the occurrence of CVAE may attribute to this early mortality. Our study indicates that conventional antipsychotics are more harmful than atypical antipsychotics, a finding consistent with most studies (Nasrallah, et al., 2004; Liperoti, et al., 2005; Gill, et al. 2005, 2007; Wang, et al., 2005). Potential mechanisms earlier proposed to explain this association between antipsychotics and cerebrovascular events include thromboembolic effects, altered platelet function, cardiovascular effects (e.g., orthostatic hypotension, arrhythmias) and the atherosclerotic effects of deregulation of glucose and lipid metabolism. As we found an acute increase in risk after initiating therapy, it is unlikely that atherosclerotic effects cause these cerebrovascular events. There may be direct thromboembolic effects in susceptible patients. We found no differences in the frequency of occurrence of ischemic and haemorrhagic events. However, as 30% of cases were labelled as none-specified apoplectic events, this study probably has insufficient data to detect such a difference. Platelet activation may be altered by serotonin 2A receptor inhibition. We looked selectively at strong 5HT(2A) antagonists and found a relative protective effect. This could explain the lower risk in atypical antipsychotic users, as most atypical antipsychotics used in this study were strong 5HT(2A) antagonists. Another cause we considered is orthostatic hypotension, which does occur directly after initiating treatment in susceptible patients and might cause 'water-shed' strokes. We found no significant difference in risk for medication with high or low central α_1-adrenoreceptor affinity. Finally, antipsychotics have been associated with ventricular arrhythmias that can lead to cerebral ischemia and infarction. As only eight patients were primarily referred to a cardiologist, this does not seem to be an important mechanism.

Our study is based on non-experimental data. This type of study is particularly vulnerable to several types of bias. The first to consider is selection bias. Our nested case-control design reduces selection bias as cases and controls are sampled from the same cohort of antipsychotic users. We aimed at including only new users of antipsychotics by including 1 year of non-use before the first prescription. It is possible that subjects used antipsychotics before data collection, but this misclassification is most likely non-differential. We avoided possible confounding by indication by specifically excluding data from the period after the first warnings of CVAEs were issued in 2003. Our study was designed to avoid the so-called 'depletion of susceptibles effect', where past experience with a drug may modify the risk of adverse event associated with

current use of this drug. To avoid this selection bias, we excluded from the cohort everyone with antipsychotic prescriptions in the period of 1 year before the inclusion date. We matched for age and were able to adjust for several cerebrovascular risk factors to control for these potential confounders, but given the limitations of our dataset, we could not adjust for all factors affecting the risk of stroke, such as smoking history and obesity. An episode of stroke may be followed by neuropsychiatric symptoms, behavioral symptoms and delirium that may require treatment with antipsychotics. We, therefore, restricted our analysis to the period before the hospital admission for stroke. There is a possibility that in some cases, antipsychotic agents were given for behavioural disturbances that were in fact due to the impending cerebrovascular event. We considered this protopathic bias as unlikely to occur, because stroke itself generally is an acute medical emergency without preceding symptoms, for which admission to the hospital will be arranged the same day. Misclassification of diagnosis is a possibility, as the accuracy of recording TIAs and type of stroke in hospital records have been shown to be poor in other studies. This might explain the lack of power to detect an expected higher incidence of ischemic strokes in current users. As TIAs are poorly defined and often treated as outpatients, we analyzed the data again excluding 89 cases of TIA. This did not alter the results. Misclassification of exposure status is a potential source of bias in this study. Misclassification as non-user would occur when patients receive antipsychotics while in hospital, went home without prescription for antipsychotics and were re-admitted for stroke within a few weeks. We analyzed the number of cases and controls that were discharged from hospital for other reasons not more than 2 weeks before the index date and found that 30 cases (5.8%) and 67 controls (3.3%) had been hospitalised ($p<0.01$, Table 1). Although we have no information on antipsychotic use during hospitalisation, this may indicate a misclassification of exposure. Because this misclassification is highest in the cases, this would lead to an underestimation of the risk we report.

Finally, residual confounding remains a possibility. Especially, the database does not provide psychiatric diagnoses. Both the risk of CVA and the use of antipsychotics are increased in patients with dementia, which can lead to confounding. However, there is a strong association between both Alzheimer's disease and vascular dementia with cardiovascular risk factors, for which we could adjust (Stampfer, 2006). Schizophrenia has been shown to be associated with higher cardiovascular morbidity. Because of the nested design, we think psychiatric diagnoses will be evenly distributed between cases and controls. The pattern of antipsychotic drug use is similar in cases and controls (Table 1). There is a possibility of ascertainment bias. As we used hospital records, CVAE that did not lead to admission to hospital or led immediately to death was missed. Elderly people with dementia are probably less likely to be referred to the hospital and may be underrepresented compared with the control group. As this group is also more likely to use antipsychotics, this bias

might have led to an underestimation of the risk. In our study, only community-dwelling patients were included, and this bias is more likely to occur in a nursing home population. For clinical practice, our results suggest that starting an antipsychotic increase the risk of CVAE only in the first weeks of treatment. When patients have continued treatment for 3 months, the risk of CVAE is back on baseline level and should not be a reason for discontinuation of treatment. If confirmed, these findings may be of importance for prescribing guidelines.

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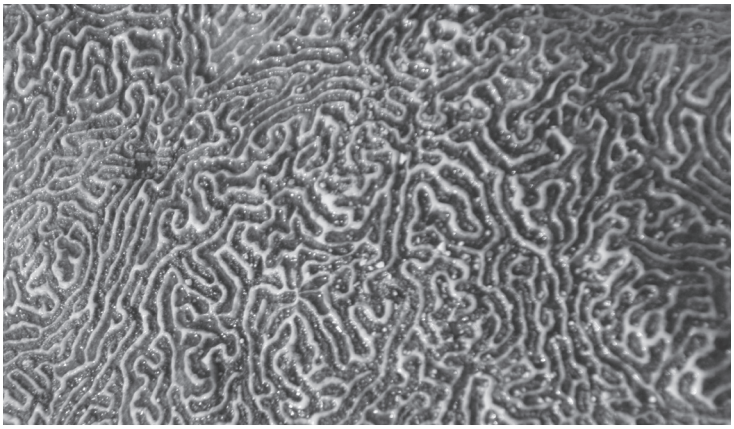
3.2

ANTIPSYCHOTIC DRUG USE AND THE RISK OF VENOUS THROMBOEMBOLISM IN ELDERLY PATIENTS



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ABSTRACT

Objective

Our aim was to investigate the relationship between exposure to antipsychotic drugs and the risk of venous thromboembolism (VTE) in elderly patients.

Methods

A time-matched case-control analysis nested within a cohort of 111,818 patients with at least 1 antipsychotic drug prescription during 1998 to 2008. Data were used from the PHARMO institute's database which contains drug dispensing data from community pharmacies and hospital admission data. The index date was for the cases defined as the date of hospital admission for VTE (deep venous thrombosis [DVT] or pulmonary embolism [PE]), or, for outpatient cases, the start of therapeutic dose low-molecular weight heparin therapy. For each case, 4 controls matched by age and sex were randomly sampled from the cohort.

Measurements

Two measures were used to evaluate the temporal relationship between antipsychotic drug use and the occurrence of VTE: being a current, recent or past user, and the duration of use up to the index date. The strength of the association was expressed as odds ratios with 95% confidence intervals, taking into account potential confounders.

Results

We identified 367 cases of hospital admission for DVT, 342 cases of hospital admission for PE, and 323 cases of outpatient treatment for DVT. Current exposure to antipsychotics was not associated with an increased risk of VTE, compared with nonusers (odds ratio, 0.9, 95% confidence interval 0.7–1.1). We found no association between dosage, the duration of use, or the type of antipsychotic drug and the risk of VTE.

Conclusion

We found no evidence of an increased risk of VTE in elderly patients using antipsychotic drugs.

INTRODUCTION

Antipsychotic drugs have been associated with an increased risk for venous thromboembolism (VTE). As both the baseline risk for VTE and a the prevalence of antipsychotic drug use increases with age, this association might be of clinical importance in the elderly population.[1,2] Several studies have reported an increased risk of sudden death with antipsychotic drug (APD) treatment.[3,4] It has been speculated that pulmonary embolism may be an under recognized cause of sudden death in these cases. Study results published so far have been contradictory, both for conventional and atypical APDs. Since 1953, sporadic case reports and case series have suggested that conventional APD use is an independent risk factor for VTE.[5] In a nested case-control study, Zornberg and Jick[6] demonstrated that current exposure to conventional APDs significantly increases the risk of idiopathic VTE. (Odds ratio [OR] 7.1; confidence interval [CI] 2.3–21.9). Kamijo et al[7] studied 16 patients with idiopathic acute pulmonary thromboembolism (mean age, 56), of whom 6 (44%) used conventional antipsychotic drugs, and 1 patient, risperidone. Parkin et al[8] found an association between current use of conventional antipsychotic drugs and idiopathic fatal PE among men and women younger than 60 years (OR, 13.3; 95% CI, 2.3–76.3). Lacut et al[9] found in a case-control study an increased risk for conventional agents (OR, 2.1; 95% CI, 1.4–3.2). Clozapine was the first atypical antipsychotic drug to be associated with VTE in a number of case reports.[5,10,11] In a cohort study monitoring the causes of death among clozapine users, a relatively large number of patients who died of PE was observed.[11] For the elderly population, Liperoti et al[12] demonstrated in a cohort study among 19,940 antipsychotic drug users an increased risk for atypical agents (Hazards Ratio [HR], 2.0; CI, 1.4–2.8), but not for conventional agents (HR, 1.0; CI, 0.5–1.9) compared with nonusers. In a study of the World Health Organization database of adverse drug reactions, Hagg et al[13] did not find an association between conventional antipsychotic drugs and VTE. Venous thromboembolism was more often reported with the atypical APD olanzapine.

Three studies reported opposite findings. In a cohort study by Ray et al[14] of 22,514 elderly antipsychotic drug users the HR of VTE was 1.1 (0.95–1.27) compared with nonusers. Alanen et al[15] studied 1334 nonagerians living in nursing homes. They did not find an association between antipsychotic drug use and deep vein thrombosis (DVT). In a surveillance program reported by Wolstein et al,[16] the difference in the incidence of VTE between users of clozapine (0.04%), users of other antipsychotics (0.03%) and nonusers (0.03%) was not statistically significant. There is no published evidence to suggest a direct biologic mechanism. Antipsychotic drugs may increase the risk for thrombosis by raising antiphospholipid and prolactin levels and enhance platelet aggregation induced by serotonin (5-HT), but all proposed mechanisms await confirmation.[17] In a laboratory study, a clear pattern of high

procoagulant factors, along with low levels of anticoagulants, was not detected.[17] Given the available evidence, it is still uncertain if APD use is an independent risk factor of VTE, especially in the elderly population. We aim to reduce this uncertainty by studying the relationship between VTE and the use of antipsychotic drugs in a cohort of elderly patients. Therefore, we performed a time-matched case-control study nested within a cohort of elderly antipsychotic drug users.

METHODS

Setting

Data were derived from the PHARMO institute's record linkage system. This database includes pharmacy dispensing records from community pharmacies linked to hospital discharge records of all 950,000 community-dwelling residents of 25 population-defined areas in the Netherlands from 1985 onwards.[18] Because virtually all patients in the Netherlands are registered with a single community pharmacy, pharmacy records are virtually complete with regard to prescription drugs. The participants of the PHARMO population enter the database with the first prescription filled in a PHARMO community pharmacy and are followed up until the last prescription. The computerized drug-dispensing histories contain information concerning the dispensed drug, dispensing date, amount dispensed, and the prescribed number of units to be used per day. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. The hospital discharge records are obtained from PRISMANT, previously known as the Dutch Centre for Healthcare Information (LMR database), an institute that collects nationwide all hospital discharge records in the Netherlands since the 1960s into a standardised format (http://www.pharmo.nl). These records include detailed information concerning the primary and secondary diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists and dates of hospital admission and discharge. All diagnoses are coded according to the *International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM)*.

Cohort definition

The base cohort consisted of patients aged 60 years or older who started with at least 1 prescription for an APD (ATC code: N05A, with the exception of lithium [N05AN01], which is not an antipsychotic drug) between January 1998 and December 2008. Starters were defined as those with no prescription for any antipsychotic drugs during a period of at least 1 year.

Case and control definition

Cases were those patients from the cohort with a primary hospital diagnosis of DVT (*ICD-9* code 453.2–9) or PE (*ICD-9* code 415.1) at admission. The date of admission to the hospital was taken as index date. In the Netherlands, heparin treatment at home in combination with vitamin K antagonists was introduced exclusively for patients with DVT of the lower extremity in the year 2000. To include this outpatient treatment, any patient who started a therapeutic dose of a low-molecular weight heparin (dalteparin, enoxaparin, nadroparin, or tinzaparine) simultaneously with prolonged use of vitamin K antagonists (acenocoumarol or fenprocoumon) was considered to be a case. For these cases, the first day of heparin use was taken as the index date. All cases had to be 60 years or older at the date of diagnosis (index date). For each case, 4 controls were randomly selected from the exposure cohort. The controls were matched for age (± 1 year), sex, and duration of registration in the database. For both cases and controls, at least 1 year of history had to be available.

Exposure definition

For each prescription, the prescription period was estimated using the dispensing date, the prescribed quantity, and the written dosage instruction. A prescription episode is defined as a continuous series of prescription periods. A gap of 1 week between the expected expiration of the prescription and the next dispensing date was allowed to avoid artificial treatment gaps. Drug exposure at the index date was categorized into 4 mutually exclusive groups. Exposure was defined as current if the prescription episode covered the index date, taking into account a washout period of 7 days. Past exposure was categorized as recent (prescription episode ended 8 days till 30 days before the index date) and past (prescription episode ended at least 1 month before the index date). Nonusers were defined as patients with no use of antipsychotic drugs before the index date.

Among current users, the duration of the prescription episode was calculated and divided in 5 categories (0–7, 8–14, 15–30, 31–90 and >90 days). Drug dosage was analyzed based on the mean dosage of the last used antipsychotic drugs and expressed in defined daily dose (DDD) equivalents. One DDD equivalent represents the recommended daily dose for an adult for the indication of schizophrenia. We categorized the DDD equivalents into less then 25% of the DDD (0.25 DDD), 0.25–0.5 DDD and greater than 0.5 DDD. To analyse the effect of type of antipsychotic drugs, prescriptions were divided in conventional and atypical antipsychotic drugs. Atypical antipsychotic drugs available in the Netherlands during the inclusion period were risperidone, olanzapine, clozapine, quetiapine, aripiprazole, tiapride and sulpiride. We also looked at 5-HT 2A affinity, as platelet function may be altered by 5-HT inhibition. We classified chlorpromazine, clozapine,

perphenazine, olanzapine, pipamperone, and risperidone as agents with high 5-HT 2A affinity (affinity, <15 Ki Nmol/L).[19,20] Histamine (H1) receptor affinity was analyzed separately because sedation resulting from H1 blockade is a known risk factor for VTE. We classified olanzapine, chlorpromazine, chlorprothixene, clozapine, periciazine, perphenazine, pipamperone and quetiapine as agents with a high H1 affinity (<15 Ki Nmol/L).[19,20]

Potential confounders

Well-known risk factors in the elderly are immobilization due to disease, recent trauma and surgery; malignancy, and hormone replacement therapy. Other proposed risk factors are hypertension, chronic obstructive lung disease, congestive heart disease, and male sex.[21-23] These risk factors for VTE were gathered from the hospital discharge record history (*ICD-9* codes) and the medication history of the previous 6 months (ATC class). We were able to study the following risk factors: prior hospitalization for any reason within 3 months; a history of cancer identified by any previous hospitalization for cancer (ICD9-CM codes 140–239), or use of antihormonal anti-cancer agents (ATC L02) or other cancer medication (ATC L01); patients who had a lower limb fracture in the three months before the index date; patients undergoing oestrogen replacement therapy (ATC G03C), patients with cardiovascular disease, identified by use of any cardiovascular drugs (agents acting on the renin-angiotensin system [ATC C09], alpha-and beta blocking agents [ATC C07], diuretics [ATC C03], calcium channel inhibitors [ATC C08], vasodilators [ATC C01D], lipid modifying agents [ATC C10], cardiac glycosides [ATC C01A], and anti-arrhythmic drugs [ATC C01B]); patients with a current or recent bacterial infection, identified by use of antibiotics (ATC J01); and patients with COPD, identified by hospitalization for COPD (*ICD9-CM* codes 491, 492, 496) in the last year or current or recent use of medication labelled for respiratory indications (ATC R03). Finally, current treatment with vitamin K antagonists or heparins (B01AB) is considered a potential confounder.

Statistical analysis

The strength of the association between the use of antipsychotic drugs and the occurrence of VTE was estimated by conditional logistic regression for matched data, taking into account the matching of cases and controls with respect to age, sex and duration of registration in the database, and controlling for comorbidity and drug use. Odds ratios and 95% CIs were calculated for each exposure category. Analyses were performed with SPSS (SPSS Inc., Chicago, Ill) for Windows, version 15.0.

RESULTS

The base cohort consisted of 111,818 patients who had at least 1 antipsychotic drug prescription. We identified 1032 cases of VTE: 367 cases of hospital admission for DVT (*ICD-9* code 453.2-9), 342 cases of hospital admission for PE (ICD-9 code 415.1, 415.11 or 415.19), and 323 cases of outpatient treatment of DVT. The mean age at diagnosis was 76 years (range, 60–104 years). All known potential risk factors for VTE were associated with an increased risk, notably recent hospitalization, cancer, the use of systemic antibiotics, tamoxifen use, and the occurrence of a lower limb fracture (Table 1). Current exposure to antipsychotic drugs was not associated with an increased risk of VTE, compared with nonusers (OR, 0.9; 95% CI, 0.7–1.1). We did not find a temporal relationship between the start of antipsychotic therapy and the occurrence of VTE. Among current users, we found no difference in risk between atypical and conventional antipsychotic drugs (adjusted OR, 1.0; 95% CI 0.5–2.1). Subanalysis of high versus low 5-HT affinity and high versus low H1 affinity did not reveal significant differences. We did not find a significant dose-effect relationship. These results are summarised in Table 2.

Table 1 Patient Characteristics

Characteristics	Cases, (n=1032; %)	Controls, (n=4125; %)
Mean age*, y	76.5	76.5
Male* ,%	43	43
Comorbidities		
Prior hospitalisation last 3 months (including surgery),%	31	8.4
History of cancer,%	14	4.9
Chronic obstructive pulmonary disease,%	20	14
Lower limb fracture last 3 months,%	0.7	0.3
Concomitant drug use		
Systemic antibiotic therapy in last 6 months,%	46	27
Cardiovascular therapy (excluding oral anticoagulants),%	68	64
Tamoxifen use in last 6 months,%	1.6	0.8
Oestrogen replacement therapy,%	2.8	2.2
Current anticoagulant therapy†,%	5.1	8.3
Any of the comorbidities or drugs mentioned previously,%	90	80

* matched for age and sex
† use of oral vitamin K antagonists or a prophylactic dose regimen of low-molecular weight heparin.

Table 2 Risk of VTE Related to Antipsychotic Drug Use

Use of Antipsychotic Medication	Cases (N=1032) n (%)	Controls (N=4125) n (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Current use	205 (19.9%)	838 (20.3%)	0.9 (0.7–1.0)	0.9 (0.7–1.1)
Recent (8-30 days)	34 (3.3%)	94 (2.3%)	1.3 (0.9–1.9)	1.1 (0.7–1.8)
Past (> 31 days)	189 (18.3%)	996 (24.1%)	0.7 (0.6-0.8)	0.8 (0.6-0.9)
Nonuse	604 (58.5%)	2197 (53.3%)	(reference)	(reference)
Duration of use†				
up to 7 days	16 (7.8%)	40 (4.8%)	1.8 (0.6-5.8)	2.9 (0.7 – 12.0)
8-14 days	20 (9.8%)	38 (4.5%)	2.5 (0.8-7.9)	1.5 (0.4 -5.9)
15-30 days	28 (13.7%)	90 (10.7%)	1.5 (0.6 – 3.4)	1.1 (0.4 – 2.8)
31-90 days	45 (22.0%)	183 (21.8%)	1.5 (0.8-2.9)	1.7 (0.8 – 3.4)
>90 days	96 (46.8%)	487 (58.1%)	(reference)	(reference)
Daily dose†				
DDD >0.5	24 (11.7%)	120 (14.3%)	1.2 (0.6 -2.4)	1.8 (0.8 -4.2)
DDD 0.25 - 0.5	53 (25.9%)	191 (22.8%)	1.4 (0.8- 2.5)	1.5 (0.8–2.9)
DDD <0.25	128 (62.4%)	527 (62.9%)	(reference)	(reference)
Type of antipsychotic†				
Atypical	47 (22.9%)	229 (27.3%)	1.2 (0.7-2.2)	1.0 (0.5 -2.1)
Multiple	1 (0.5%)	6 (0.7%)	0.5 (0.1 -4.8)	0.3 (0.1-7.9)
Conventional	157 (76.6%)	603 (72.0%)	(reference)	(reference)
5HT affinity†				
High 5HT affinity	103 (50.2%)	367 (43.8%)	1.3 (0.8–2.0)	1.4 (0.8–2.5)
Low 5HT affinity	102 (49.8%)	471 (56.2%)	(reference)	(reference)
H1 affinity†				
High H1 affinity	79 (38.5%)	296 (35.3%)	0.8 (0.5 -1 .4)	0.6 (0.3–1.0)
Low H1 affinity	126 (61.5%)	542 (64.7%)	(reference)	(reference)

*adjusted for : prior hospitalisation for any reason within 3 months; any previous hospitalisation for cancer (ICD9-CM codes 140-239), use of anti-hormonal anti-cancer agents (ATC L01, L02); patients with a lower limb fracture within three months; patients on oestrogen replacement therapy (ATC G03C), patients with any cardiovascular drug ((ATC C01A, C01B, C01D, C03, C07, C08, C09 or C10), patients with a current or recent use of antibiotics (ATC J01), patients with hospitalisation for COPD (ICD9-CM codes 491, 492, 496), patients with respiratory drugs (ATC R03), and patients with current treatment with vitamin K antagonists or heparins (B01AB).
†among current users (n = 1043).

DISCUSSION

Our findings do not support the hypothesis that antipsychotic drugs increase the risk of VTE in elderly patients. Our results are comparable with the results of the studies by Ray et al,[14] Wolstein et al,[16] and Alanen et al.[15] For conventional antipsychotic drugs, our study confirms the results of the studies by Liperoti et al[12] and Hagg

et al.[13] Liperoti et al[12] found an increased risk of VTE in elderly users of atypical APDs. In contrast to our study, their study was restricted to patients with a hospital diagnosis for VTE and he did not have information on whether patients were current users at the time of hospitalization, so both confounding by indication and misclassification of exposure may have influenced their results. Hagg et al[13] studied the World Health Organization database of adverse drug reactions and found a disproportional reporting of VTE with atypical APDs but notes that interpretation of this finding is difficult. Most previous studies reporting a positive association between APD and VTE were small and did not include an elderly population. Walker et al[11] reported 19 cases aged 10 to 54 years, Hagg et al[10] reported 12 cases with possible clozapine-related VTE, with an age range of 25 to 59 years; Zornberg and Jick[6] studied 42 idiopathic cases aged younger than 60 years, Kamijo et al[7] reported 7 patients with PE, of whom only 2 patients were aged older than 60 years; and Parkin et al[8] studied 75 cases aged 15 to 59 years.

Our study has a number of limitations. The first to consider is selection bias. Our nested case-control design reduces selection bias, as cases and controls are sampled from the same cohort of antipsychotic drug users. We aimed at including only new users of antipsychotic drugs by including one year of nonuse before the first prescription. It is possible that subjects used antipsychotic drugs before the data collection, but this misclassification is most likely nondifferential. We matched for age and sex and were able to adjust for several risk factors to control for these potential confounders, but, given the limitations of our dataset, we could not adjust for all factors affecting the risk of VTE, such as immobility, the use of restraints, and obesity. Antipsychotic drug users are often smokers, and we have no information on smoking habits. However, smoking is not an established risk factor for venous thrombosis.

We looked for and ruled out possible effect modification by current anticoagulant use. We do not have information on genetic risk factors, such as factor V Leiden. In a previous study among elderly people, 2 major and frequent inherited risk factors (factor V Leiden and prothrombin G20210A gene variation) proved to be independent risk factors.[9] It is unlikely that these factors will confound the relation between APD use and VTE. Misclassification of diagnosis is a possibility, as the accuracy of diagnosing fatal PE in hospital has been shown to be poor in autopsy studies. We were able to avoid ascertainment bias, as we included outpatient treatment of DVT that did not lead to admission to hospital. However, cases that led immediately to death at home were missed. The results of our subgroup analysis of the duration of use within the current user group should be interpreted with caution. These results seem to indicate that a shorter duration of treatment is associated with an increased risk. However, the CIs are large, which means that either there is no association or our study lacks the power to reveal this association. In our study, most patients use

low doses of antipsychotic drugs. In contrast to a younger population, where APDs are mostly used for psychiatric diagnosis such as schizophrenia, the most important indications for antipsychotic therapy in the elderly are behavioral problems associated with dementia and delirium. Doses used for these indications generally will be lower than those in cases of schizophrenia. Owing to the resulting small number of cases on high doses of antipsychotic drugs and the differences in diagnosis, our study is not directly comparable with the studies involving younger patients, and our results should not be generalized to the entire population. Another consequence of this high proportion of low-dose antipsychotic therapy is that our study might not have enough power to reveal a dose-response relationship with statistical significance. We classified antipsychotic drugs according to their 5-HT 2A and H1 receptor affinity by their Ki values. As published Ki values vary considerably and receptor blockade also depends on the actual drug concentration at the receptor site in the brain, a definite categorization is not available and our grouping might not reflect the actual antipsychotic receptor binding profiles in vivo. Finally, residual confounding remains a possibility. We expect any unknown confounder to further weaken the relationship, which we already found to be nonsignificant. We were not able to adjust for psychiatric diagnoses, as these are not available in the database. Because of the nested design and the matching for age, we think psychiatric diagnoses will be evenly distributed between cases and controls. In this population-based study of elderly people with a high baseline risk of VTE, we did not find that the use of antipsychotics is associated with VTE. This finding seemed consistent in all examined subgroups. This study adds to the existing evidence that VTE is not associated with antipsychotic drug use in the elderly population.

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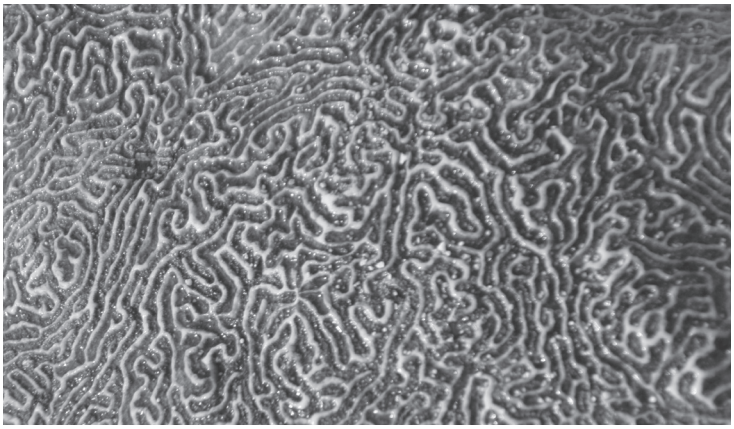
3.3

RISK OF ACUTE CORONARY SYNDROME IN ELDERLY USERS OF ANTIPSYCHOTIC DRUGS: A NESTED CASE-CONTROL STUDY



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ABSTRACT

Background

Antipsychotics have shown to increase mortality in elderly patients. It is not known if an increased risk of acute coronary syndrome (ACS) contributes to this risk.

Objectives

To examine the association between antipsychotic use and the risk of ACS in the elderly.

Methods

A community-based nested case-control study in the Netherlands. Data were derived from pharmacy dispensing records from community pharmacies and linked to hospital discharge records of 950,000 community-dwelling residents from 1998–2008. Cases were patients aged 60 or older with a first hospital admission for ACS within a cohort of persons with at least one antipsychotic prescription during the study period. For each case, four controls with no hospitalisation for ACS were randomly selected from the same cohort, matched by age, sex and duration of registration in the database.

Main outcome measures

Relative risk, expressed as odds ratios, for ACS associated with antipsychotic drug use adjusted for comorbidity.

Results

The base cohort consisted of 26,157 elderly patients with at least one antipsychotic prescription. 2,803 cases of hospital admission for ACS were identified: 1,555 cases of acute myocardial infarction and 1,248 cases of intermediate coronary syndrome. 11,024 controls were matched by age and sex. Current exposure to antipsychotics was associated with a decreased risk of hospitalisation for ACS compared to non-users (adjusted OR 0.5, 95% CI 0.5–0.6). Cumulative use up to 100 Defined Daily Doses (DDD) was also associated with a decreased risk of hospitalisation (OR 0.7, CI 0.6–0.8). No differences in risk were found between typical and atypical antipsychotics, height of the current dosage or different degrees of serotonergic, histaminergic or adrenergic affinity of the antipsychotic.

Conclusions

A decreased risk of hospitalisation for ACS in elderly patients using antipsychotics was found. Further research is needed to determine whether there is any cardioprotective effect or a high non-referral rate in elderly antipsychotic users with acute myocardial infarction.

INTRODUCTION

In 2005, the United States Food and Drug Administration (FDA) issued a warning regarding increased mortality in elderly users of antipsychotics[1]. It has been speculated that this can be explained by an increased risk of acute coronary syndrome (ACS)[2-4]. It has been shown that antipsychotics have an effect on cardiovascular risk factors. Its use is associated with increased antiphospholipid levels[5], metabolic syndrome[6], diabetes[7], hyperlipidemia[8], and with a negative influence on lifestyle-factors as smoking[9], physical activity and weight[10]. Surprisingly, there is little evidence of a negative effect of antipsychotics on hard clinical endpoints such as cardiovascular mortality, with most studies among patients with schizophrenia even finding either a reduced or normal risk, or a risk less than expected considering the increased prevalence of smoking and obesity in this population[11-20]. This finding has led to speculations about a possible protective effect of antipsychotics on ACS[21]. In recent reviews on the effect of antipsychotics on mortality, including cardiovascular mortality, it is concluded that this issue received insufficient attention[22-23]. As coronary heart disease is the single most common cause of death in the elderly population[24] and the prevalence of antipsychotic use among elderly is high[25], this issue is of particular importance for the elderly population. It is surprising that only few investigations have studied the population of elderly antipsychotic users[26-29]. Therefore, we conducted a community-based nested case-control study in the Dutch elderly population to estimate the effect of antipsychotic drug use on the risk of hospitalisation for ACS.

METHODS

Design and Setting

A nested case-control study was conducted with data derived from the PHARMO record linkage system. This database includes pharmacy dispensing records from community pharmacies linked to hospital discharge records of all 950,000 community-dwelling residents of 25 population-defined areas in the Netherlands from 1985 onwards[30]. Because virtually all patients in the Netherlands are registered with a single community pharmacy, pharmacy records are virtually complete with regard to prescription drugs. Participants of the PHARMO population enter the database with the first prescription filled in a PHARMO community pharmacy and are followed until the last prescription. The computerised drug-dispensing histories contain information concerning the dispensed drug, dispensing date, amount dispensed and the prescribed dosage regimen. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification

of the World Health Organization[31]. Patient information includes sex and date of birth. The database does not provide information concerning the indications for use. Pharmacy data are linked to hospital discharge records obtained from Prismant, an institute that collects nationwide all hospital discharge records in the Netherlands since the 1960s. These records include detailed information concerning the primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, ninth edition (ICD-9-CM)[32].

Cohort definition

The study was conducted in a cohort of patients who started antipsychotic medication (ATC code N05A, with the exception of lithium N05AN) at the age of 60 or higher during 1998–2008. Starters were defined as those with no previous prescription for any antipsychotic during a period of at least one year. Consequently, at least one year of history had to be available in the PHARMO database. This resulted in a cohort of 26,157 elderly patients starting an antipsychotic at some time during the study period.

Case and control definition

Cases were defined as patients with a first hospital admission for ACS (ICD-9-CM code 410 acute myocardial infarction, 411.1 intermediate coronary syndrome, 411.8 other acute coronary insufficiency). The date of hospital admission was taken as index date for the cases. For each patient hospitalized because of ACS, up to four controls were randomly selected from the cohort and assigned the same index date. Controls were matched for age (+/- 1 year), sex and duration of registration in the PHARMO system. For both cases and controls at least one year of history before the index date had to be available.

Exposure definition

For each case and each control, all antipsychotic drug prescriptions were identified and the duration of each prescription was estimated using the dispensing date, the prescribed quantity, and the written dosage instruction. Subsequently, individual prescriptions were transformed into prescription episodes defined as a continuous series of prescriptions. A gap of one week between the expected expiration of the prescription and the next dispensing date was allowed to avoid artificial treatment gaps. Antipsychotic drug use was defined as current use if the most recent prescription episode covered the index date or ended within

7 days before the index date. Past use was categorised in three periods based on the calculated expiration date of the most recent prescription episode: 8 days until 30 days, 31 until 180 days, and 181 until 365 days before the index date. Patients with no use of antipsychotic drugs in the year before the index date (i.e., those, given the cohort definition, who started antipsychotic use after the index date, or those with the last episode more than a year before the index date) were defined as non-users. The cumulative use was defined as the cumulative number of days of antipsychotic use preceding the index date multiplied by the patient's average prescribed daily dose. To standardise the prescribed doses of different antipsychotics, the prescribed daily dose was divided by the defined daily dose (DDD, a technical unit of measurement defined as the assumed average maintenance dose per day for a drug used for its main indication in adults[31]). Cumulative use was categorised into 4 categories (up to 100 DDD, 101–200 DDD, > 200 DDD and no use).

For current antipsychotic users the temporal association between the start of antipsychotic drug use and the risk of ACS was evaluated. The duration since the start of antipsychotics was divided into five categories (up to 7 days, 8–14 days, 15–30 days, 31–90 days and > 90 days). The association between current drug dosage and the risk of ACS was based on the last used antipsychotic and categorised into less than 0.25 DDD, 0.25–0.5 DDD and more than 0.5 DDD. To analyse the effect of type of antipsychotic, current users were divided in users of typical antipsychotic drugs, users of atypical antipsychotic drugs, and those who were using a combination of antipsychotic drugs. See the appendix for details. Finally, it was investigated whether the effect of antipsychotic drug use on the risk of ACS was modified by receptor affinity[33-34]. Histamine receptor affinity was analysed since weight gain resulting from H1-blockade is a known risk factor for ACS[35]. Adrenergic (Alpha1A) affinity was investigated as adrenergic blockade may have a preventive influence[36]. 5HT(2A) affinity was also studied as platelet function may be altered by serotonin inhibition, with a proposed antithrombotic effect[21].

Potential confounders

Controls were matched by age, sex and duration of registration. Medical conditions that have previously been associated with the risk of ACS were considered as potential confounders (smoking, a history of previous cardiovascular disease, diabetes mellitus[37], hypertension, recent hospital admission and hyperlipidemia). Since the PHARMO system does not have data on smoking, chronic obstructive pulmonary disease (COPD) was used as a proxy for smoking, as these are strongly related[38]. A patient was considered to have one or more of the risk factors if

there was a primary or secondary hospital discharge diagnosis (ICD-9-CM) of other cardiovascular disease (401–445 and subcategories, except 410, 411.1 and 411.8), diabetes mellitus (249–250), hyperlipidemia (272) or COPD (490–496) in the six months prior to the index date, any other hospital admission in the last six months, or if one or more of the following drugs were prescribed in the six months preceding the index date (grouped by ATC-class): antithrombotic agents (B01), antidiabetic drugs (A10), agents acting on the renin-angiotensin system (C09), α- and β-blocking agents (C07), diuretics (C03), calcium channel inhibitors (C08), vasodilators (C01D), lipid modifying agents (C10), antihypertensives (C02) or drugs for obstructive airway diseases (R03).

Data analysis

The strength of the association between antipsychotic drug use and the occurrence of ACS was estimated by conditional logistic regression analysis and expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). Potential confounding covariates were included in the multivariate regression model if they were univariately associated with ACS ($p<0.10$). The association between antipsychotic drug use and the occurrence of ACS for difference subgroups was calculated based on current or past use and compared with non-users. Within the group of current users, the association of duration of last exposure with the risk of ACS was investigated, with non-users as reference. Logistic regression analysis was also used to evaluate whether typical antipsychotic drug use was associated with a higher risk of ACS compared to atypical antipsychotic drug use. Furthermore, the effect of different receptor binding profiles on the risk of ACS was evaluated with logistic regression analysis. Analyses were performed with SPSS (SPSS Inc., Chicago, Illinois, USA) for Windows, version 16.0.

RESULTS

Within the cohort of antipsychotic users, 2,803 patients with a first hospital admission for ACS were identified; 1,555 cases of acute myocardial infarction and 1,248 cases of intermediate coronary syndromes. 11,024 controls were sampled. The patient characteristics are shown in Table 1. Overall, cases as well as controls had a mean age of 76 years and 57% were male. As expected, all investigated cardiovascular risk factors were associated with an increased risk of ACS. Current use of antipsychotics was associated with a decreased risk of hospitalisation for ACS,

Table 1 Patient characteristics

Characteristic	Cases (n=2803)	Controls (n=11024)	p-value for difference*
Age** (years, mean, SD)	75.9 (8.1)	75.9 (8.1)	
Male** (%)	56.7	56.7	
Concomitant disease (%)			
Diabetes mellitus**	19.4	13.8	<0.001
COPD***	18.1	15.2	<0.001
Hospitalisation for cardiovascular disease (excluded ACS) in last six months	10.4	2.8	<0.001
Hospitalisation for other reasons in last six months	19.4	15.2	<0.001
Concomitant drug use (%)			
Use of any medication on prescription in the last 6 months	91.4	91.4	0.96
Any antithrombotic agent****	53.5	38.3	<0.001
Any cardiovascular agent	75.9	63.2	<0.001
Antilipemic agents	22.2	13.4	<0.001
ACE-inhibitors and AT-antagonists	28.7	21.1	<0.001
Beta-blocking agents	36.2	21.4	<0.001
Diuretics	32.2	25.8	<0.001
Nitrates	33.5	9.7	<0.001
Antihypertensives other than categories above	1.7	1.2	0.04

abbreviations: COPD chronic obstructive pulmonary disease, ACS acute coronary syndrome, ACE angiotensin converting enzyme, AT angiotensine, SD standard deviation.
* chi-square test
** matched by age, sex and duration of registration.
*** any hospital admission or use of medication for this disease in the last six months.
**** e.g. platelet aggregation inhibitors and vitamin K antagonists.

compared to no use (adjusted OR 0.5, 95% CI 0.5–0.6) (Table 2). This association was also found for past use during up to 180 days before the ACS (adjusted OR 0.6, 95% CI 0.5–0.7). Cumulative use up to 100 DDD was also associated with a decreased risk of hospitalisation (OR 0.7, 95% CI 0.6–0.8), but use above 100 DDD was not associated with a significantly decreased risk (OR 0.9, CI 0.7–1.0). For current users, no dose-response relationship, and no temporal relationship between the start of antipsychotic therapy and hospitalisation for ACS were found. No differences in risk were found between different types of antipsychotic drugs or between different degrees of serotonergic, histaminergic or adrenergic affinity (Table 3).

Table 2 Risk of ACS related to antipsychotic use

Use of antipsychotic medication	Cases (N=2803) N (%)	Controls (N=11024) N (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Current use	271 (9.7)	1836 (16.7)	0.5 (0.5–0.6)	0.5 (0.5–0.6)
Past use (8-30 days ago)	33 (1.2)	228 (2.1)	0.5 (0.4–0.7)	0.5 (0.3–0.7)
Past use (31-180 days ago)	99 (3.5)	566 (5.1)	0.6 (0.5–0.8)	0.6 (0.5–0.7)
Past use (181-365 days ago)	87 (3.1)	377(3.4)	0.8 (0.6–1.0)	0.8 (0.7–1.1)
No use	2313 (82.5)	8017 (72.7)	(reference)	(reference)
Cumulative use**				
1 - 100 DDD	245 (15.3)	1228 (19.5)	0.7 (0.6–0.8)	0.7 (0.6–0.8)
100 - 200 DDD	112 (7.0)	528 (8.4)	0.7 (0.6–0.9)	0.8 (0.6–1.0)
> 200 DDD	226 (14.1)	992 (15.7)	0.8 (0.7–0.9)	0.9 (0.7–1.0)
No use	1022 (63.7)	3553 (56.4)	(reference)	(reference)

abbreviations: ACS acute coronary syndrome, OR odds ratio, CI confidence interval, DDD defined daily dose, COPD chronic obstructive pulmonary disease, ICD international classification of diseases, ATC anatomical therapeutic chemical.
* adjusted for COPD as a proxy for smoking, measured by admission for COPD (ICD9-CM 490-496), or the use of medication for COPD (R03), cardiovascular disease (measured by any use of cardiovascular medication in the last six months, by ATC class: antithrombotic agents (B01), agents acting on the renin-angiotensin system (C09), α- and β-blocking agents (C07), diuretics (C03), calcium channel inhibitors (C08), vasodilators (C01D), lipid modifying agents (C10), antihypertensives (C02), or by non – ACS related cardiovascular hospital admissions (ICD9-CM 401-445 and subcategories) in the last six months), diabetes mellitus (measured by the use of antidiabetic drugs (A10) and hospital admissions for diabetes mellitus in the last six months (ICD9-CM 249-250), and any hospital admission in the last six months.
** among cases and controls with at least 4 years of medication history available (n =7,906).

Table 3 Risk of ACS for current users of antipsychotics: relation with duration, dose and type of antipsychotic

Use of antipsychotic medication	Cases (N=271) N (%)	Controls (N=1836) N (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Duration of use				
> 90 days	123 (45.4)	959 (52.2)	0.8 (0.5–1.2)	1.0 (0.6–1.6)
31 – 90 days	61 (22.5)	464 (25.3)	0.8 (0.5–1.3)	0.9 (0.5–1.5)
15 – 30 days	39 (14.4)	181 (9.9)	1.3 (0.7–2.2)	1.4 (0.7–2.5)
8 – 14 days	26 (9.6)	102 (5.6)	1.5 (0.8–2.8)	1.9 (1.0–3.6)
up to 7 days	22 (8.1)	130 (7.1)	(reference)	(reference)
Daily dose				
DDD > 0.5	49 (18.1)	323 (17.9)	1.0 (0.7–1.4)	1.2 (0.8–1.6)
DDD 0.25 - 0.5	21 (7.8)	138 (7.6)	0.9 (0.6–1.5)	1.1 (0.6–1.7)
DDD < 0.25	200 (74.1)	1347 (74.5)	(reference)	(reference)
Type of antipsychotic				
Atypical	61 (22.5)	493 (26.9)	0.8 (0.6–1.1)	0.9 (0.6–1.2)
Multiple	9 (3.3)	59 (3.2)	1.0 (0.5–2.0)	1.1 (0.5–2.3)
Conventional	201 (74.2)	1284 (69.9)	(reference)	(reference)

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Table 3 (Continued)

Use of antipsychotic medication	Cases (N=271) N (%)	Controls (N=1836) N (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
5HT(2A) affinity				
High HT affinity	107 (39.5)	853 (46.5.)	0.8 (0.6–1.0)	0.8 (0.6–1.0)
Low HT affinity	164 (60.5)	983 (53.5.)	(reference)	(reference)
H1 affinity				
High H1 affinity	86 (31.7)	735 (40)	0.7 (0.5–0.9)	0.7 (0.6–1.0)
Low H1 affinity	185 (68.3)	1101 (60)	(reference)	(reference)
Adrenergic affinity				
High α 1A affinity	174 (12.4)	1225 (87.6)	0.9 (0.7–1.2)	0.9 (0.7–1.2)
Low α 1A affinity	97 (13.7)	611 (86.3)	(reference)	(reference)

abbreviations: ACS acute coronary syndrome, OR odds ratio, DDD defined daily dose, 5HT 5-Hydroxytryptamine (serotonin), H histamine, A adrenergic COPD chronic obstructive pulmonary disease, ICD international classification of diseases, ATC anatomical therapeutic chemical.
* adjusted for COPD (as a proxy for smoking, measured by admission for COPD (ICD9-CM 490-496), or use of medication for COPD (R03), cardiovascular disease (measured by any use of cardiovascular medication in the last six months, by ATC class: antithrombotic agents (B01), agents acting on the renin-angiotensin system (C09), α- and β-blocking agents (C07), diuretics (C03), calcium channel inhibitors (C08), vasodilators (C01D), lipid modifying agents (C10), antihypertensives (C02), or by non – ACS related cardiovascular hospital admissions (ICD9-CM 401-445 and subcategories, except 410, 411.1 and 411.8) in the last six months), diabetes mellitus (measured by the use of antidiabetic drugs (A10) or hospital admissions for diabetes mellitus (ICD9-CM 249-250) in the last six months), and any other hospital admission in the last six months.

Appendix Classification of antipsychotics as used for this study*.

	5HT(2A) affinity	Central α 1-adrenoreceptor affinity	Histamine (H1) affinity	Type of antipsychotic
aripiprazole	low	low	low	atypical
chlorpromazine	high	high	high	typical
chlorprothixene	low	low	high	typical
clozapine	high	high	high	atypical
fluphenazine	low	high	low	typical
haloperidol	low	high	low	typical
levomepromazine	high	low	low	typical
olanzapine	high	high	high	atypical
periciazine	low	low	high	typical
perphenazine	high	high	high	typical
pipamperone	high	high	high	typical
risperidone	high	high	low	atypical
sulpiride	low	low	low	atypical
tiapride	low	low	low	atypical
thioridazine	low	high	low	typical
quetiapine	low	high	high	atypical
zuclopentixol	low	high	low	typical

*only antipsychotics used in the study population which were classified as either strong receptor-antagonists[33-34] or classified as atypical are shown.

DISCUSSION

This large community based nested case control study suggests that the observed increased mortality among elderly users of antipsychotics in randomised controlled trials (RCTs) cannot be explained by an increased risk of acute coronary events. Current users of antipsychotics had a 50% lower risk of being admitted to hospital for ACS, when compared with non-users of antipsychotics. Our results suggest that current antipsychotic drug use either directly reduces the risk of ACS in elderly patients, or is associated with underreferral to hospital for myocardial infarction.

Comparison with other studies

A number of studies investigating the association between cardiovascular morbidity or overall mortality and antipsychotic use also reported an equal or lower incidence of these outcomes among antipsychotic users[11 13-20 26-29], but these results were contradicted by others[3 39-41]. As most of these studies included middle-aged schizophrenia patients, these results can not easily be extrapolated to the elderly population, as schizophrenia and schizo-affective disorders account for only a small minority of antipsychotic use in the elderly[42-43]. In a meta-analysis of RCTs of elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs, Schneider et al. found an 1.5 times increased risk of death compared to placebo, but it is not known to what extent ischemic cardiovascular disease contributes to these deaths[3]. Osborn et al. found an increased risk of death due to coronary heart disease with antipsychotic use in elderly aged 50–75 years (RR 1.8, 95% CI 1.5–2.0) in a large retrospective cohort study. However, no increased risk due to atypical agents was observed (RR 0.9, 95% CI, 0.5–1.4)[40]. Nakagawa et al. found no association between current use of antipsychotics and hospitalisation for myocardial infarction in a Danish case-control study (mean age 69 years, RR 1.0, 95% CI: 1.0–1.0)[11]. Raivio et al. found a lower overall mortality rate and a lower hospital admission rate in antipsychotic users compared to non-users among elderly demented patients, especially for atypical antipsychotics (OR 0.5, 95% CI 0.2–1.0), but did not specify cardiovascular events[28]. Simoni-Wastila et al. found a significant lower overall mortality and hospital admission rate in residents of nursing homes aged 65 years or older who used antipsychotics, but again the data did not specify cardiovascular diagnoses[29]. In a large naturalistic study of 3,111 elderly psychiatric inpatients, Barak et al. found that treatment with antipsychotics did not increase their risk of hospitalisation for cerebro- and cardiovascular events, but did not specify between these two groups[26]. Huybrechts et al. found no increased risk for ACS or heart failure in patients admitted to nursing homes who initiated antipsychotic therapy, compared to those who initiated benzodiazepine therapy[27].

Possible protective effect

The observation that cardiovascular mortality was reduced in mental institutions after the introduction of antipsychotics in 1955 has led to speculations that antipsychotics may have a protective effect[44]. In 1995, a possible protective effect of antipsychotics on the risk of ACS was suggested by Canoso et al. Although he found high levels of antiphospholipid antibodies in patients treated with chlorpromazine, a strong 5HT(2A) receptor antagonist, he found an absence of thromboembolic consequences in these patients[45]. Recently, it has been suggested that antipsychotics may have a protective cardiovascular effect through 5HT(2A) inhibition on clot aggregation[21]. Platelets can induce acute ischemia by clot-forming, and are also involved in the process of atherosclerosis[46]. The increase of ACS in patients with depression has been linked to an increase in 5HT(2A) receptor sensitivity[47]. Many antipsychotics have 5HT(2A) antagonistic activity, and 5HT(2A) antagonists have been shown to have a strong antiplatelet-aggregation-effect in vitro[48], to reduce coronary thrombosis in animal models[49-50] and to reduce cardiovascular mortality by 23% in a large RCT[51]. In a previous study concerning the risk of current antipsychotic use on acute cerebrovascular ischemia, a protective effect of high 5HT(2A) affinity was found, compared to low affinity (OR 0.5, 95% CI 0.3–0.7)[52]. In the study presented here, however, we did not find a protective effect of strong 5HT(2A) antagonists (OR 0.8, CI 0.6–1.1). The absence of a strong association with any type of antipsychotic in our study argues against a specific receptor-mediated protective effect. Also, we did not find a dose dependency, and the rate of decline in protection after quitting use seems to slow to support a biologic mechanism.

Another proposed protective mechanism of antipsychotics exerts effects on a more psychological level. An ACS occurs when a trigger suddenly provokes atherosclerotic plaque disruption which causes coronary thrombosis. The timing of the event is strongly related to mental stress, with an estimated 18–37% of patients relating their heart attack to acute mental stress in the two hours before the attack[53-55], and a 33–50% rise in risk of getting an ACS on Monday, the first work-day of the week, compared to Sunday[56]. It is speculated that mental stress invokes a hemodynamic and catecholamine surge that increases physical stress on the atherosclerotic plaque[57-58]. Emotional stress may also directly influence platelet aggregation[59]. Established triggers are vigorous physical exercise[60], anger[60], acute depressed mood[61] and sexual activity[62]. The use of antipsychotics may reduce the incidence and severity of these triggers[63]. In a single case report, chlorpromazine was reported to stop repeated myocardial injury in a patient with mental stress[64]. It has been shown that psychosocial interventions aiming at reducing stress and providing a more relaxed lifestyle may protect against the effects of triggering events[65]. This mechanism might explain our findings with current antipsychotic use, but does not explain why the risk of hospital referral for ACS remains low in patients up to six months after use. However,

if this mechanism is a class-effect of all sedative drugs, a shift to other sedative drugs or a reduction in stress level after antipsychotic therapy is likely and might explain the prolonged effect. Antipsychotics are associated with an increased risk of acute ischemic stroke[66]. This does not necessarily contradicts a possible protective effect on ACS, as the pathophysiology of this effect remains unknown and both diseases may have different triggers[67]. In our study, a high cumulative use brings the risk to the level of non-users. This may reflect the slow atherosclerotic effects of antipsychotic-induced metabolic syndrome counteracting a protective effect of current drug use.

Limitations and strengths of our study

There are several potential sources of bias to consider in this study. First, protopathic bias is unlikely to occur, as ACS is an acute event, requiring immediate hospital treatment. There is a possibility of ascertainment bias, as we only included hospital admissions for ACS. Patients with cardiac arrests who died before reaching the hospital were not included. Death due to cardiac arrest has been associated with current antipsychotic use, but it is not known whether these sudden deaths are ischemia-related or due to QTc prolongation leading to ventricular fibrillation[68]. Furthermore, elderly people with dementia or psychosis are less likely to be referred to the hospital with an ACS and may be underrepresented compared with the control group. Unrecognised myocardial infarction is a common event in the elderly, with an estimated incidence of 20–40%[69]. Especially in elderly demented or psychotic patients under-reporting or under-diagnosing of ACS can be an important factor since interpretation and presentation of complaints can be altered. Although all patients in the cohort had at some moment during follow-up a mental illness requiring antipsychotic therapy, it is possible that elderly patients with a current or recent mental illness requiring antipsychotic treatment were less likely to seek medical help when having an ACS. If this inadequate help-seeking behaviour persists for some time after antipsychotic treatment, it might explain the lower risks found up to six months after treatment in our study. Also, ACS may present with atypical symptoms in these patients. Antipsychotics are known to reduce the pain accompanying an ACS, increasing the risk that the physician misinterprets the signs of ACS[51, 70]. We performed a separate analysis of 57 patients admitted for precordial pain of non-cardiac origin (ICD-9-CM code 786.50), and again found that cases tended to be less likely to use antipsychotics (OR 0.5, 95% CI 0.2–1.5), although nor statistically significant (data not shown). It is possible that elderly patients with psychiatric problems requiring antipsychotic therapy more often refrain from hospital admission and choose to receive palliative care in their home environment. This referral bias might have led to an overestimation of the protective effect of antipsychotics.

Laursen demonstrated the existence of such a referral bias against cardiac catheterization and revascularization among patients with schizophrenia[71-72]. However, in elderly patients without schizophrenia, a choice for palliative care is more likely in advanced dementia, and we did not include patients residing in nursing homes in this study. Confounding by contraindication is possible as most patients with an ACS were already identified as being at risk for cardiovascular disease (Table 1) and physicians familiar with the warnings concerning cerebrovascular events in 2002[73-74], metabolic syndrome[75] (2004) and increased mortality[1] (2005) may have withdrawn antipsychotics in an attempt to reduce this risk. To account for this bias we looked at cumulative use, and found no significant positive association between cumulative use and the occurrence of ACS. Also, if this bias occurs, we would expect patients with heart failure to be withdrawn from antipsychotics. We looked if patients recently treated for heart failure (identified by the simultaneous use of ace-inhibitors, loop diuretics and antithrombotics) were withdrawn from antipsychotics, but found an opposite effect: patients treated for heart failure were more often current antipsychotic users (OR 1.2, 95% CI 1.0–1.3). As especially atypical antipsychotics are expected to raise the long-term risk for heart failure, we did a separate analysis for this subgroup, but did not find a significant increase in risk (data not shown). Misclassification of exposure status is a potential source of bias in this study. As we have no information on antipsychotic use during hospitalisation, misclassification as non-user would occur when patients recently received antipsychotics while in hospital, and were re-admitted for ACM within a week after discharge. We analyzed the number of cases and controls that were discharged from hospital not more than one week prior to the index date and found that 89 cases (3.2%) and 156 controls (1.4%) had been discharged recently ($p<0.01$). This may indicate a misclassification of exposure. However, the number of possible misclassifications is too small to alter our results significantly (data not shown). The PHARMO database does not provide outpatient psychiatric diagnoses. Elderly patients with schizophrenia may have used antipsychotics for decades and are likely to have a different cardiovascular risk than elderly patients starting with an antipsychotic for delirium or the behavioural symptoms of dementia. As we were particularly interested in the latter, we required patients entering the cohort to be at least one year without antipsychotic therapy, which ensured exclusion of schizophrenics on chronic antipsychotic therapy from the cohort. Strengths of our study include the size of the study and the ability to correct for a large number of possible confounders. In contrast to previous studies, our data are based on a cohort of patients starting antipsychotic use at the age of 60 or older, which gives the opportunity to study the effects of antipsychotic use in this particularly vulnerable population.

CONCLUSIONS

We found a decreased risk of hospitalisation for ACS in elderly patients using antipsychotics. This implies either a biological or psychological protective effect of antipsychotics, a high incidence of unrecognised myocardial infarction or a high incidence of non-referral of elderly antipsychotic users. These possibilities have important clinical consequences. If antipsychotics do have some protective effect, there would be no reason to restrict its use in patients with coronary risk factors. If the prevalence of untreated myocardial infarction among elderly antipsychotic users is increased, early recognition and timely treatment of these patients would improve the individual prognosis and might substantially reduce health care costs[76]. Further research is needed to solve this issue.

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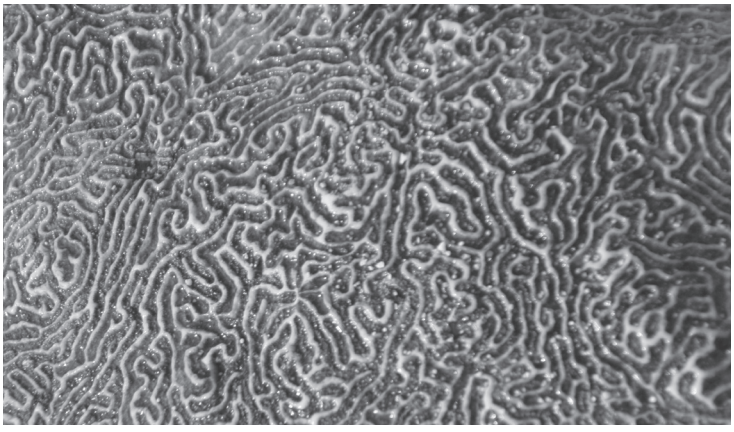
4

GENERAL DISCUSSION



GENERAL DISCUSSION

Introduction

In the introduction of this thesis, we have outlined the history of the high prevalence of antipsychotic use in the treatment of behavioural symptoms in patients with dementia in nursing homes. We concluded that while evidence-based medicine emphasises the limited effectiveness of antipsychotic treatment and the risk of serious adverse effects when used in the elderly population, a gap exists with daily clinical practice, as (inappropriate) antipsychotic use is still common. In this thesis, we aimed to reduce this gap. In chapter 2.1, we looked for practice variation in prescribing. In our sample of 20 nursing homes, we found a large variation in antipsychotic use. A large variation in prescribing indicates potentially inappropriate use and is associated with differences in prescribing culture between facilities[1]. Apparently, prescribers within a setting share their beliefs, including their perception of the effectiveness of antipsychotics and the optimal treatment of behavioural disorders. In chapter 2.2 we investigated the reasons for prescribing antipsychotics for behavioural and psychological symptoms of dementia (BPSD) among patients in LTCFs by interviewing elderly care physicians. We aimed to understand why prescription rates remain high despite the limited efficacy in this patient group. Only a few articles have been published so far concerning the reasons for prescribing APDs in BPSD. In these studies, pressure by nurses to 'do something' and the lack of nursing staff and resources was found to be of importance in the process of decision-making. Although we found these factors to play a role, the belief that antipsychotics do actually work in about half of the patients to alleviate behavioural symptoms, was often mentioned as the main reason to try antipsychotic treatment. We found a large variation in this expected success rates (standard deviation 25%), which may partly explain the variability in antipsychotic prescription rates between nursing homes. To investigate the effectiveness of antipsychotic therapy, we studied behavioural symptoms before and after starting antipsychotics in a sample of Dutch nursing home patients (chapter 2.3). In contrast to the physicians' positive expectations of antipsychotic therapy, but in line with results from other studies, we found improvement of symptoms in only one out of six patients who started antipsychotic therapy. After withdrawal of therapy, 68% of patients remained stable. In chapter 3, we extended our knowledge on cardiovascular adverse effects of this treatment in elderly patients, focussing on thromboembolic adverse effects that could explain the raised mortality among antipsychotic users in clinical dementia trials: cerebrovascular events (CVAE), venous thrombosis with subsequent pulmonary embolism (VTE), and acute coronary syndrome. The incidence of CVAE was increased, compared with non-users of antipsychotics (odds ratio [OR] 1.7, confidence interval [CI], 1.4–2.2). The risk was elevated especially during the first weeks of treatment

(chapter 3.1). This result is in line with other studies. In three RCTs that examined the safety and efficacy of risperidone for the management of agitation in dementia, approximately half of the cerebrovascular events occurred within the first weeks of treatment[2]. Sacchetti published a replication study, based on our study, comprising 2,824 cases of new-onset stroke and found that antipsychotic use was associated with an increased risk of CVAE (OR 12.4, 95% CI 8.4–18.1) during the first month of treatment, with no significant increase in risk after the first month of use[3]. The overall incidence of CVAE was reported to rise from 1.6 % to 3.9% in a risperidone RCT[4], from 0.8 to 2.2% in a post-hoc analysis of RCTs[5], and in a pooled analysis by Schneider[6] from 0.9 to1.9%. In a Cochrane systematic review, Ballard[7] concluded that especially risperidone increased the risk of CVAE from 1 to 3%. From this evidence, the estimated number needed to harm (NNH) is approximately 60. In our study, the risk of CVAE was elevated during the first three months of treatment, with a mortality of 18% during hospital admission. Therefore, the increased risk can account for a proportion of the raised mortality among antipsychotic users in the first three months of treatment. It has been speculated that pulmonary embolism may be an under recognized cause of sudden death in elderly patients using APDs, but study results published so far have been contradictory, both for conventional and atypical APDs. We did not confirm the raised incidence of VTE, found in other studies[8-10] (chapter 3.2). Our study adds to the existing evidence that antipsychotic drug use is not associated with VTE in the elderly population. Surprisingly, we found a decreased risk of hospitalisation for acute coronary syndrome in elderly patients using antipsychotics (chapter 3.3). This finding raises the possibility of a cardioprotective effect of antipsychotics, or a high non-referral rate in elderly home-dwelling antipsychotic users with acute myocardial infarction.

In this general discussion, we will further elaborate on two issues associated with our findings: the difficulties of research in elderly patients with dementia, in particular those residing in long term care facilities (LTCF) , and the increased mortality as an adverse effect of antipsychotic drug use in elderly patients. Finally, we present some implications for clinical practice and future research.

Difficulties of research in elderly patients with dementia

Research on psychotropic drug use in this patient group is difficult for several reasons. In patients with dementia, it is necessary to get consent for this type of study by the patient's legal representative. This poses an important barrier, and, especially in intervention studies, is often difficult to obtain, as there are ethical barriers to approval[11]. In a family representative survey in the US, 15% of the representatives felt that, as their relative with dementia does not have the ability to make the decision, he or she should not be included in a clinical trial[12]. For the Netherlands, these figures are not available. Ethical barriers are more easy to overcome in observational studies.

However, to study the effect and adverse effects of psychotropic drugs, patients need to be followed for the duration of use, which can last months or even years. During follow-up, the behavioural symptoms, which can occur at any time during the day and at night, need to be well documented. Adequate observation and reporting of these symptoms is dependent of nurses already occupied by clinical care. Therefore, the use of an already available assessment instrument in residents of LTCFs is a practical solution. The Resident Assessment Instrument (RAI) is such an instrument, and has been shown to be useful for research purposes[13], although the reliability is dependent on the performance of the participating facilities. Patients or their representatives are informed about the RAI instrument at admittance to the LTCF, and asked to consent that RAI data may be used for research purposes, so informed consent is pre-arranged with both the patients and at facility level. This is advantageous, as LTCF approval procedures can be time and resource consuming, as we have seen in our study on the reasons to prescribe antipsychotics (chapter 2.2). Although the number of LTCFs participating in the Dutch RAIview initiative (www.nedrai.nl) is still relatively small, limiting the generalizability of the results, the international (interRAI) database is sufficiently large for research purposes.

Another difficulty of research in this population is that the effect of treatment on the behavioural symptoms is not judged 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. For instance, it is likely that caregivers, rather than the patient itself, suffer from the patient's behavioural problems such as unwillingness to take a shower, or to obey to bedtime-rules. An improvement on behavioural scales does therefore not necessarily mean that the patient feels better. In general, the effect of psychotropic drug use on behaviour is assessed by comparing behaviour scales before and during therapy. Several rating scales have been developed for this use[14]. Ideally, these rating scales are sensitive enough to detect clinically relevant changes, but it has been shown that methodological issues limit the possibility to detect (minor) changes with these scales[15]. When used on a group level, as is done in most randomised controlled trials, more problems arise in the interpretation of the results: does a significant decrease in symptoms mean a small decrease in all of the patients, or a large decrease in a few patients? Ideally, RCTs provide both results, but mostly, only mean changes are given. To assess behaviour (chapter 2.1, 2.3) we used the data from the RAI Database. Inherent limitations include the low (three monthly) frequency of the assessments, although extra assessments are performed if the patient's condition changes significantly. Also, patients with dementia can exhibit a wide range of behaviour, and not all of these are sampled with the MDS. Furthermore, MDS items measure the frequency of the observed behaviour but do not assess the intensity of the behaviour. It is therefore possible that the RAI does not detect small changes in behaviour, while the behaviour is subjectively improved

or worsened. These limitations may explain the apparent discrepancy between the expected success rate among physicians and nurses (chapter 2.2) and the actually measured effects (chapter 2.3). Other often used clinical outcome scales, however, do have the same limitations. The Cohen – Mansfield Agitation Inventory (CMAI) is comparable to the RAI as it also measures the frequency of behaviour[16]. The Neuropsychiatric Inventory-Nursing Home (NPI-NH) measures both severity and frequency, but it measures only 12 symptoms, including symptoms that are not targets for antipsychotic use, e.g. appetite change, euphoria and depression. Its capability to detect clinical changes in behavioural symptoms in dementia has been shown to be limited[15 17].

The measurement of psychotropic drug exposure in Dutch nursing homes provided other challenges. Up to 2007, medication prescription details were not systematically collected in the RAI database. After 2007, medication details are available, but registered only at the time of the assessment. This cross-sectional approach limits its use, as short-term therapy can be missed, and a precise temporal relationship between behavioural symptoms and psychotropic drug use is more difficult to assess. To address this problem, pharmacies delivering medication to the LTCFs under study were approached and asked to provide the medication history of the residents. Although a number of pharmacies voluntarily participated and a data collection was established, the heterogeneity of the pharmacist's medication distribution software and the lack of possibilities to export medication files in some of these systems, combined with changes of commercial software providers made the data-collection incomplete. Another problem poses the anonymity of the dataset. LTCFs are asked to inform their residents and their representatives that RAI MDS data can be used anonymously for research purposes. This includes registry of their medication use. As it would have been time-consuming to obtain written informed consent from all representatives, we asked the pharmacists to deliver the medication history anonymously. The lack of a common identifier in these separate datasets poses practical problems in linking these two sets. For the purposes of this study, we therefore used the categorical information on psychotropic drug use provided by the RAI MDS before 2007, and the more detailed information on psychotropic drug use provided after 2007.

In conclusion, research in elderly patients with dementia is challenging. More prospective, long-term randomised trials with quality of live outcomes and good registration of adverse effects are needed to evaluate the effect of psychotropic drug use, including long-term antipsychotic use. Observational studies with large groups of patients can be useful, but rely on nurses to provide essential information on the behavioural symptoms and adverse effects of their patients. This will only succeed if the collected information is useful for the nurses or the LTCF itself. The RAI instrument, provided that it is well implemented, is suitable for this purpose.

Increased mortality as an adverse effect of antipsychotic drug use in elderly patients

Since the warning by the FDA[18] of an increased mortality, several studies have been conducted to explore this increase in mortality. In Schneider's[19] meta-analysis of RCTs 3.5% of antipsychotic users versus 2.3% of the placebo groups died during a mean of three months of follow-up. The FDA has reported that 5,106 elderly patients with dementia treated with atypical antipsychotics in 17 randomized controlled trials had a 1.6 fold increase in mortality (4.5% vs. 2.6%) compared with those receiving placebo[18]. The relatively low over-all mortality risk in these randomised trials, combined with the equal distribution of covariates makes it possible to detect this small increase in risk, which is easily obscured by confounders in observational studies. Although the increase in risk of death is significant, with a NNH of 100, it is not known whether this small increase in risk in the first three months continues to exist, or disappears with long-term therapy due to the depletion of susceptibles, or a better tolerability. Gill et al.[20-21] found a significant, adjusted hazard ratio (HR) of 1.2 [CI, 1.1–1.5] at 180 days of follow-up, but noted that unmeasured, unevenly distributed confounders that increase the risk for death could easily diminish the observed association. Ballard et al.[22] reported a marked mortality risk in the second year of follow-up in 64 patients continuing antipsychotics compared with 64 who withdrew from therapy, with 18 deaths in the treatment group, versus 15 deaths in the placebo group after one year of treatment, and 13 versus 3 deaths in the second year. Limitations of this study are the low numbers and the lack of accurate antipsychotic exposure data in the entire open label follow-up period of four years. Kales et al.[23] found a relative risk of death of 1.5 (CI 1.0 –2.3) in the first year for antipsychotic users in an outpatient clinic.

Several studies did not confirm an increased mortality associated with antipsychotic use. Livingston et al.[24] did not find a higher mortality rate in those treated with antipsychotics at the maximum of six months follow-up, when taking into account age and severity of dementia. In a large cohort of American veterans with dementia, Rossom et al.[25] also found that no antipsychotic was associated with greater mortality after the first 30 days. During the first 30 days, she found a significant increase in mortality in subgroups prescribed a higher than average dose of haloperidol (5.4% deaths vs. 1.7% in controls), olanzapine (2.7% vs. 1.7%) and risperidone (2.8% vs. 2.0%), but not for quetiapine. Simonis-Wastila et al.[26] found a reduced mortality rate among antipsychotic users (HR 0.83 [95% CI 0.69–1.00], when controlled for gender, age, delirium and functional impairment. Raivio et al.[27] also found a protective effect of use of atypical antipsychotics on mortality, HR 0.49 [95% CI 0.24–0.99], and no effect on mortality of the use of conventional antipsychotics. Scarmeas et al.[28] found no association between antipsychotic use and mortality, when controlled for sex, age, cognition, functional impairment and a

comorbidity index among patients with Alzheimer's disease during a 4 year follow-up. Nonino et al.[29] showed that older age at entry, male gender, severe dementia and functional impairment were associated with a higher risk of death after one year, but atypical antipsychotic use was not. Finally, Suh and Shah[30] reported a reduced mortality (HR0.78, [95%CI 0.7–0.9]) in a one year prospective study in a LTCF.

In this thesis we presented three studies related to this issue. We hypothesised that part of the increased risk of death found in RCTs could be caused by an increased risk of venous thrombosis and subsequent pulmonary embolus, an increased risk of acute coronary syndrome, or an increased risk of CVAE. We did not find an increase in risk of venous thrombosis, and found a possible protective effect of antipsychotics on the risk of acute coronary syndrome. For CVAE, an increased risk was found (OR 1.6); but especially shortly after the start of therapy, and 18% of patients admitted for CVAE died while in hospital. We concluded that the increase in risk for CVAE can partly explain the increase in mortality.

In conclusion, although the results of the meta-analysis of RCTs give unequivocal evidence of a raised mortality, it was not possible to detect this increased risk in most of the observational studies mentioned above. This finding raise the question whether the increased risk of death is clinically relevant in this patient group. In 2009, the UK government commissioned an independent report on the use of antipsychotic medication for people with dementia[31]. In this report, a NNH of 100 was derived from the existing evidence from RCTs of an increased mortality and an increased incidence of cerebrovascular events, and than extrapolated for all 720,000 patients with dementia, of which an estimated 25% use antipsychotic drugs. A 1% increase in mortality in 180,000 people gives a conservative estimate of 1,800 extra deaths per year. In the Netherlands, extrapolation of these figures for an approximate 220,000 persons with dementia, would lead to estimation of an extra 550 deaths per year.

To put these figures into perspective, it is important to realize that the mortality rate of patients with dementia living in LTCFs is high. Xie et al.[32] estimated the median survival time from the time of first diagnosis at 4.5 years, dependent on the age at onset (age <60, median survival 11 years, age >80, median survival 4 years, 75% percentile 7 years). In the Netherlands, Zuidema et al.[33] reported a median duration of stay of 20 months in a sample of 1,319 residents with dementia with a mean age of 84 years. Liperoti et al.[34] reported that 20% of LTCF residents with dementia had died after 6 months of follow-up. An absolute increase in the risk of death of 1% in one year can therefore be seen as clinically irrelevant in this patient group. This may explain the attitude towards the use of antipsychotic drugs in our study among elderly care physicians in 23 LTCFs in the Netherlands (chapter 2.2). Although physicians were aware of the warnings of serious adverse effects, the more severe adverse effects as stroke, pneumonia, or death, were seldom mentioned as a

potential problem, and did not withhold them from starting antipsychotic therapy. The assumption that use of antipsychotic drugs in elderly patients with dementia is both ineffective and harmful needs to be carefully nuanced. Although the presence of a variation in prescribing between practices indicates that reducing antipsychotic use is possible, and our observational study of the course of behavioural symptoms did not find beneficial effects of treatment with antipsychotic drugs in the large majority of patients, it is possible that minor improvements in the behaviour of patients are still relevant for patients, their family and their professional care givers. Although especially the start of antipsychotic therapy raises the risk of cerebrovascular events by a tenfold, the baseline risk is very low. We did not find an increase in risk of both venous thrombosis and myocardial infarction. The morbidity and mortality caused by antipsychotic therapy is small in comparison with the existing morbidity, and the already high mortality rate among institutionalised patients with dementia. Advanced dementia can be seen as an incurable, progressive disease with a short live expectancy. Most elderly patients with dementia die within seven years, of which the last two to three years are spent in an LTCF[32 35-36]. In those last years, most patients choose to receive palliative treatment. In palliative care, improvement of the quality of live by symptom control is more important than prognosis. A minority of patients seem to benefit from antipsychotic therapy. Therefore, given that informed consent has been obtained, the possibility of serious adverse effects, including a raised mortality, do not justify a complete ban on antipsychotic use.

Implications for clinical practice

The raised risk of CVAE in the first weeks of treatment found in our study has clinical implications. In elderly patients, especially those with pre-existing cardiovascular or cerebrovascular disease, antipsychotic use should be restricted to those patients for which the treatment is judged to be absolutely necessary. The patient's legal representative should be informed about this risk. The large variability in antipsychotic prescribing in our sample of twenty nursing homes is also found in several other countries and indicates inappropriate prescribing, with no rational explanation why similar patients with the same symptoms are treated differently[37-38]. Practices with a low prevalence of APD use report the same variance in behavioural symptoms as practices with a high prevalence, a finding that is suggestive of a modest treatment effect (chapter 2.1), and stopping APDs did not worsen behavioural symptoms in most of the patients (chapter 2.3). Therefore, we recommend to add an evaluation date to any new prescription of antipsychotics, and to plan ahead to taper the dose at any increment of dosage. A computerised decision support system for prescribing drugs (DSS) can help physicians to implement this in their daily routine[39]. Automated prescribing systems containing diagnoses and indications can be specially

designed to give elderly care physicians reminders and suggestions for appropriate APD use. More awareness of the variation between practices, the possibility to exchange information, and the possibility to compare their own practice to 'best practices' (so-called benchmarking) might help to reduce antipsychotic overuse. Peer group meetings of elderly care physicians should be used to discuss their APD prescribing habits, their opinions on APD use in general and the issues that arise for them in attempting to discontinue their use. To change routine antipsychotic prescribing patterns, regular medication reviews are useful. As most LTCFs have an established relationship with a pharmacist this should be easy to implement. It is recommended that the Dutch association of elderly care physicians (Verenso) gives attention to the high prevalence of APD use by developing a directive in this area. In addition, appropriate APD use should get special attention during the elderly care physician's 3-year training in geriatric and psychogeriatric medicine. Rapid computerised access to relevant guidelines may also help, and is currently developed by a collective of practices of nursing home physicians (www.gerimedica.nl). Although physicians are able to reduce their number of antipsychotic prescriptions, physicians believe the quality of non-pharmacological treatment of BPSD needs to be improved before this can be done on a large scale (chapter 2.2). The LTCFs management can help to reduce the urgency to prescribe antipsychotic drugs by ensuring the availability of more and better-trained nursing staff. It should be part of the LTCFs policy to promote education for nurses who provide care to patients with dementia. More expertise in psychogeriatric nursing would also improve accurate monitoring and better reporting to the elderly care physician. An adequate provision of daytime activities, individual or in small groups, may also help[40-41]. We recommend the Dutch association of elderly care physicians (Verenso) to give high priority to the improvement of the dementia care practice.

Implications for future research

In this thesis, we showed that the RAI assessments could be used for observational studies on the prevalence and effects of antipsychotic use in patients with dementia. The RAIview instrument provides the unique possibility for ongoing observational research on the use of antipsychotic drugs in patients with dementia in the Netherlands and Belgium. International research is possible with the interRAI database. Better and more detailed results can be obtained if researchers succeed to link both the complete pharmacy medication records and the hospital records of the patients to the assessments. For intervention studies, however, a qualitative evaluation of the behaviour is necessary, and (among others) should include if the patient-caregiver interaction improves, and if APD use facilitates the effect of non-pharmacological interventions. Despite the many publications on this subject, it has been shown both nationally and internationally that the use of APDs is difficult

to influence. This calls for research into stimulating and obstructing factors that influence adherence to policy guidelines. The raised mortality found in RCTs in 2005 did not reduce the high prevalence of APD use in LTCFs in most countries, including the Netherlands. The raised mortality does not withhold elderly care physicians from prescribing APDs (chapter 2.2). This is possibly related to the already high mortality in advanced dementia. This finding requires further research into the relationship between APD use, mortality and multi-morbidity. The InterRAI database would be ideally suited to provide further insight into these factors. In chapter 2.1, we concluded that the association between high prevalence of APD use and low quality of care as is worrisome and warrants further investigation. To further understand this rather alarming finding both quantitative and qualitative research is needed. If confirmed, further analyses of the care programmes of facilities with a high and low prevalence of APD use may result in best practice models that can help to reduce APD use. Interventions to reduce behavioural symptoms in patients with dementia should ultimately aim to reduce the distress of the patient with dementia. In daily practice, the judgement whether a patient is in distress while showing challenging behaviour, and whether this distress is less with antipsychotic therapy, even when the behaviour itself is still present, is routinely made but not easily quantified. The gap between the believe in antipsychotic therapy (chapter 2.2) and the observed effects (chapter 2.3) raises the possibility that the currently used instruments to measure behavioural symptoms do not detect clinically relevant changes in this distress, thereby underestimating the effects of treatment. Ultimately, the result of treatment on the distress of the patient depends on the balance of both benefits and adverse effects. This outcome is not captured with a count of the behavioural symptoms alone. To address this issue, future research should include outcome scales derived from research on the quality of life in dementia[42-45]. Over 75% of patients diagnosed with dementia in the Netherlands are not institutionalized and receive home-care by the general practitioner. In chapter 2.3, we have seen that over 50% of users of antipsychotic drugs already used antipsychotic drugs when admitted to the LTCF, and antipsychotic drug use was often not initiated, but simply continued by the elderly care physician. Future research should therefore also focus on the prevalence and adverse effects of antipsychotic use for the behavioural symptoms of dementia in general practitioner's practices in the Netherlands. Finally, the possibility of undertreatment of APD users with an acute coronary syndrome (chapter 3.3) warrants further investigation, as untreated myocardial infarction may cause heart failure[46] and lower the patient's quality of live[47]. The possibility of a protective effect of antipsychotic drugs on the occurrence of coronary plaque rupture (either by a direct effects on platelets or by reducing the catecholamine surge caused by sudden mood changes) also raises interesting questions for future research.

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SUMMARY

Antipsychotics are often used to treat behavioral problems in dementia. This use is controversial: while scientists warn of the high risk of side effects, including death, and emphasize the limited efficacy for this indication, antipsychotics are still commonly used in long term care facilities (LTCF). This thesis aims to bridge the gap between practice and scientific evidence by increasing knowledge about prevalence, expectations and effectiveness of antipsychotics among patients with dementia in Dutch LTCFs, and by examining three potentially serious cardiovascular side effects of antipsychotics in the elderly.

Chapter 2 describes studies that have been done using the VU University Resident Assessment Instrument Database (VURAI-DB). This database contains more than 400 Minimum Data Set (MDS) items related to 13 domains, including functional, cognitive and behavioral items. It includes a dichotomous recording of the use of antipsychotic drugs in the last week before the assessment. The data were collected with the RAI Version 2.0. The VURAI-DB contained at the end of 2010 more than 60,000 assessments of 9387 patients from 48 LTCFs, collected from 1997 onwards. Patents were assessed on admission and then quarterly. Additional evaluations were performed in the event of a major change in the condition of a resident. The staff that performed the MDS assessments had received a standardized training.

Chapter 2.1 dealt with differences in the prevalence of antipsychotic use among patients with dementia in different LTCFs in the Netherlands. The prevalence of the use of antipsychotics in Dutch nursing homes has been estimated previously at around 35%. Previous studies in the United States and Canada revealed a wide variation in the frequency of prescribing of antipsychotic drugs in patients with dementia. When antipsychotic drugs are prescribed for the treatment of behavioral symptoms of dementia, we expect similar prevalences of antipsychotic use in comparable groups of patients with dementia. When large differences are found, this may indicate differences in preference of prescribers (the prescribing culture within a LTCF) or perhaps differences in the living conditions of patients, which influences the need to prescribe antipsychotics. We investigated the existence of these differences using LTCF and resident characteristics collected with the VURAI-DB and information on organizational resources and facility-level resident satisfaction surveys from the National Institute for Public Health and the Environment (RIVM), an independent government funded institute. We found that a discrepancy existed between the large range in prevalence of antipsychotic use among the facilities in the lowest and highest tertile of antipsychotic use (13% compared to 41%), and the small range in prevalence of behavioral symptoms in these facilities (for example: at least one symptom present; 54% compared to 62%). The remarkable large variability in antipsychotic drug use found in our study (5%-52%) cannot be fully explained by differences in the prevalence of behavioral symptoms between the facilities. A high prevalence of antipsychotic use was associated with average to below

average satisfaction with staff, personal care and choice of activities. Facilities with a high prevalence of antipsychotic use were often large and located in an urban area.

The available scientific evidence demonstrates that the effectiveness of antipsychotics is limited, with on average an improvement in one out of eight patients. This low success rate cannot explain the high prevalence of antipsychotic use. In Chapter 2.2 we investigated the reasons why experienced elderly care physicians prescribe antipsychotics, and asked them about their expectations of the intended effects and side effects. Physicians, nurses and caregivers believed that the potential benefits of antipsychotics generally outweigh the risk of side effects. Key reasons to begin therapy were agitation and aggression. Doctors felt pressured to prescribe in 17% of cases. Elderly care physicians felt supported by the guideline 'Problem Behavior' of the Dutch Association of Elderly care Physicians (Verenso). Elderly care physicians estimated the average success rate in the cases discussed (the patient is expected to improve on the target symptom) to be 50%, nurses on average expected 53% improvement and family 55%. The most anticipated side effects were increased risk of falls, sedation, and Parkinsonism. Nurses often called cognitive decline as expected side effect. The family felt inadequately informed about the side effects in 44% of cases. We concluded that the interviewed elderly care physicians expect that almost half of their patients with dementia and behavioral problems benefit from antipsychotics. Serious side effects are thought to occur only sporadically. These ideas will play a role in the high prevalence of antipsychotic use in these patients.

In **Chapter 2.3** we describe the course of behavioral problems during treatment with antipsychotics in a large sample of elderly patients with dementia residing in LTCFs. Data were used from the VURAI-DB. A total of 556 patients who initiated antipsychotics were studied. The behavioral score improved in 101 patients (18%), while the score deteriorated in 260 patients (47%) after three months of antipsychotic therapy, compared to the score before therapy. Patients with severe behavioral problems showed more improvement than patients with mild problems. After discontinuation of antipsychotic drugs, 352 (68%) of the 520 patients remained stable or improved after three months compared with their scores before discontinuation. This figure is 58% after six months. During antipsychotic treatment of LTCF residents with dementia the severity of behavioral problems in most patients still increased, with only one in six patients improving. Although we do not know how this increase would have been without treatment, these results indicate that the effect of antipsychotics on the course of behavioral symptoms in LTCF residents with dementia is limited. Given these results and current knowledge on important short-and long-term risks, physicians should be very reluctant with prescribing antipsychotics for behavioral problems in elderly patients.

In 2005 the U.S. Food and Drug Administration (FDA) stated that the use of atypical antipsychotics in elderly patients with dementia leads to an approximately 1.6 fold higher mortality. This warning was based on a post-hoc analysis of randomized controlled

trials (RCTs). During a typical 10-week RCT on the effects of atypical antipsychotics for behavioral symptoms of dementia, the incidence of mortality in patients receiving antipsychotics was 4.5%, compared to 2.6% in the placebo group. The causes of death varied, with most of the deaths from cardiovascular (heart failure, sudden death) or infectious nature. Based on these results, the FDA issued a so-called 'black box' warning in which it stated not to approve the use of antipsychotics in dementia. In 2008, this warning was extended to all antipsychotics. It is possible that the increased risk also exists in elderly people without dementia. The underlying mechanisms of the increased mortality risk associated with antipsychotics in patients with dementia remains to be elucidated. In **Chapter 3** we examined three possible cardiovascular complications of antipsychotic use in elderly patents witch may contribute to this increased mortality. These studies were conducted using the PHARMO database. This database contains information from public pharmacies that are linked to hospital discharge data from all 950,000 people in 25 defined areas in the Netherlands since 1985. Since almost all patients in The Netherlands are registered with one pharmacy, the pharmacy data are virtually complete with regard to prescription medicines. Participants in the PHARMO system are followed from the first prescription that is dispensed at a pharmacy affiliated with PHARMO. The medication history includes information about the date, amount delivered, strength and the required number of units per day. The medication was coded according to the Anatomical Therapeutic Chemical (ATC) classification. Hospital discharge data were obtained from Prismant (LMR database), a national institute that collects discharge data from all hospitals in the Netherlands since the 60s in a standardized format (www.pharmo.nl). These data include detailed information about the primary and secondary diagnosis, possible diagnostic and surgical procedures and treatment, and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM). The studies were conducted in a cohort of patients aged 50 years or older (Chapter 3.1) or 60 years and older (Chapters 3.2 and 3.3) that started an antipsychotic medication in the period 1986-2003 (Chapter 3.1) or between 1998 and 2008 (Chapters 3.2 and 3.3).

In a meta-analysis of RCTs for patients with dementia, Schneider found a 1.9% risk of cerebrovascular adverse events, compared to 0.9% with placebo. In most epidemiological studies, this increased risk is not found. In **Chapter 3.1**, we have contributed to the existing evidence that use of antipsychotics in the elderly increases the risk of cerebrovascular adverse events (CVAE). A case-control analysis nested within a cohort of 26,157 community-dwelling patients (mean age 76 ± 9.7) with at least one antipsychotic prescription was conducted. The study population comprised 518 cases of hospital admission for CVAE (54% ischemic; 15 % hemorrhagic and 31% non-specified cerebrovascular apoplectic events), and 2030 controls. Among cases, 94 (18%) died during hospital admission. Current and recent exposure to antipsychotics was associated with an increased risk of CVAE compared to nonusers (odds ratio [OR] 1.7,

confidence interval (CI) 1.4-2.2). A novel finding was the strong temporal relationship; the OR for use less than one week was 9.9 (CI 5.7 to 17.2). The risk decreases over time and is comparable to non-users after three months of use (OR 1.0, CI 0.7-1.3). Cumulative exposure was not associated with increased risk.

The increase in the risk of venous thrombosis and subsequent pulmonary embolism is controversial. It has been suggested that massive pulmonary embolism is an unrecognized cause of increased mortality. The mechanism of increased thrombosis is unexplained. In **Chapter 3.2** we examine the risk of venous thrombosis and pulmonary embolism in elderly patients taking antipsychotics. We identified 367 cases of hospitalization for deep venous thrombosis, 342 cases of hospitalization for pulmonary embolism, and 323 cases of outpatient treatment for deep vein thrombosis. Current exposure to antipsychotic drugs was not associated with an increased risk of venous thromboembolism, compared to nonusers (odds ratio 0.9, 95% CI 0.7 to 1.1). We found no relationship between dose, duration of use, or type of antipsychotics and the risk of venous thromboembolism.

Antipsychotic use is associated with an increased risk of developing metabolic syndrome, diabetes and hyperlipidemia. Therefore, antipsychotic use has been associated with an increased risk of cardiovascular disease in the elderly. An increased risk of acute coronary syndrome may contribute to increased mortality. The available literature on this subject is surprisingly scarce and the results are contradictory. In **Chapter 3.3** we therefore looked at the risk of acute coronary syndrome in elderly antipsychotic users. 2,803 hospitalizations for ACS were identified: 1,555 cases of acute myocardial infarction and 1,248 cases of intermediate coronary syndrome. 11,024 controls were matched by age and gender. Current exposure to antipsychotics was associated with a decreased risk of hospitalization for ACS compared with nonusers (adjusted OR 0.5, 95% CI 0.5 - 0.6). Cumulative use of more than 100 Defined Daily Doses (DDD) was also associated with a decreased risk of hospitalization (OR 0.7, CI 0.6 - 0.8). No differences in risk were found between typical and atypical antipsychotics, dosage, or level of serotonergic, histaminergic or adrenergic affinity. In conclusion, we found a reduced risk of hospitalization for ACS in elderly patients who use antipsychotics. Further research is needed to determine whether there is a true cardioprotective effect of antipsychotics or the results are biased by a low referral rate among elderly antipsychotic drug users with acute myocardial infarction.

In **Chapter 4** the results of the previous chapters are discussed in a broader perspective. The problems of research in this population are discussed and we found that the RAI instrument is well suited for research purposes. We mention some methodological limitations associated with the RAI. We conclude that the assertion that the use of antipsychotics in elderly patients with dementia is both ineffective and harmful needs to be carefully nuanced. Although the presence of a variation in prescribing between practices indicates that a reduction of antipsychotic drug use is

possible, and in our observational study of the course of behavioral symptoms the vast majority of patients had no beneficial effects of antipsychotic treatment, it is still possible that small, undetected improvements in patient behavior are relevant to the patients themselves, their families and caregivers. Although at the start of antipsychotic therapy the risk of cerebrovascular events increased by a tenfold, the absolute risk is very low. We found no increased risk of venous thrombosis and myocardial infarction. Morbidity and mortality due to antipsychotics is small compared to the existing morbidity, and the already high mortality rate of institutionalized patients with dementia. Advanced dementia can be seen as an incurable, progressive disease with a short life expectancy. Most older patients with dementia die within seven years, with the last two to three years spent in a long term care facility. In these last years, most patients or their representatives choose a palliative treatment. In palliative care the improvement of quality of life through symptom management is more important than the life expectancy. A minority of patients appears to benefit from antipsychotic therapy. A complete ban on antipsychotic use in dementia is therefore, despite the risk of serious side effects such as increased mortality, not justified.

For most of the patients with dementia treated with antipsychotics, the treatment is probably not effective or no longer necessary and potentially harmful. Therefore we present some recommendations. We recommend to add an evaluation date to any new prescription of antipsychotics, and to plan ahead to taper the dose at any increment of dosage. A computerised decision support system for prescribing drugs (DSS) can help physicians to implement this in their daily routine. Automated prescribing systems containing diagnoses and indications can be specially designed to give elderly care physicians suggestions for appropriate APD use. More awareness of the variation between practices, the possibility to exchange information, and the possibility to compare their own practice to 'best practices' (so-called benchmarking) might help to reduce antipsychotic overuse. Peer group meetings of elderly care physicians should be used to discuss their antipsychotic prescribing habits, their opinions on APD use in general and the issues that arise for them in attempting to discontinue their use. To change routine antipsychotic prescribing patterns, regular medication reviews are useful. Appropriate antipsychotic use should get special attention during the elderly care physician's 3-year training in geriatric and psychogeriatric medicine. Rapid computerised access to relevant guidelines may also help. The LTCFs management can help to reduce the urgency to prescribe antipsychotic drugs by ensuring the availability of more and better-trained nursing staff and to provide daytime activities, individual or in small groups. It should be part of the LTCFs policy to promote education for nurses who provide care to patients with dementia. More expertise in psychogeriatric nursing would also improve accurate monitoring and better reporting to the elderly care physician. We recommend the Dutch Association of elderly care physicians to give high priority to the improvement of the dementia care practice.

SAMENVATTING

Antipsychotica worden vaak gebruikt voor de behandeling van gedragsproblemen bij dementie. Dit gebruik is omstreden: terwijl wetenschappers waarschuwen voor het hoge risico op bijwerkingen - waaronder sterfte - en wijzen op de beperkte werkzaamheid voor deze indicatie, worden de middelen in de dagelijkse praktijk in verpleeg- en verzorgingshuizen veelvuldig voorgeschreven. Dit proefschrift beoogt de kloof tussen de praktijk en de wetenschap te verkleinen door de kennis te vergroten over prevalentie, verwachtingen en effectiviteit van antipsychotica bij patiënten met dementie in Nederlandse verpleeg- en verzorgingshuizen, en door een drietal veronderstelde ernstige cardiovasculaire bijwerkingen van antipsychotica in een populatie van ouderen nader te onderzoeken.

In **Hoofdstuk 2** worden onderzoeken beschreven die zijn gedaan met behulp van de Vrije Universiteit Resident Assessment Instrument Database (VURAI-DB). De VURAI-DB bevat meer dan 400 Minimale Data Set (MDS) items met betrekking tot 13 domeinen, met inbegrip van functionele, cognitieve en gedragsmatige items. Het omvat een dichotome registratie van het gebruik van antipsychotica in de laatste week voor iedere beoordeling. De gegevens zijn verzameld met de RAI versie 2.0. De VURAI-DB bevatte aan het eind van 2010 meer dan 60.000 MDS van 9387 inwoners van 48 verpleeg- en verzorgingshuizen, verzameld vanaf 1997. Bewoners werden beoordeeld bij opname en vervolgens driemaandelijks door direct betrokken verzorgenden. Extra evaluaties werden uitgevoerd in het geval van een belangrijke verandering in de toestand van een bewoner. Het personeel dat de MDS-evaluaties verricht, heeft een gestandaardiseerde opleiding gekregen.

Hoofdstuk 2.1 behandelt verschillen in de prevalentie van antipsychoticagebruik onder patiënten met dementie in verschillende verpleeg- en verzorgingshuizen in Nederland. De prevalentie van het gebruik van antipsychotica in de Nederlandse verpleeghuizen is in eerder onderzoek geraamd op ongeveer 35%. Uit eerdere onderzoeken in de Verenigde staten en Canada bleek dat er een grote variatie is in de frequentie van het voorschrijven van antipsychotica bij patiënten met dementie. Wanneer antipsychotica worden voorgeschreven voor gedragssymptomen bij dementie, zou je, bij vergelijkbare groepen verpleeghuispatiënten, vergelijkbare prevalenties van antipsychoticagebruik verwachten. Wanneer er grote verschillen worden gevonden, kan dit duiden op verschillen in voorkeur van de voorschrijvende artsen (de voorschrijfcultuur binnen een verpleeg- of verzorgingshuis) of wellicht op verschillen in de omstandigheden van de patiënten, die de noodzaak van het voorschrijven van antipsychotica beïnvloeden. We onderzochten dit in 20 verpleeg- en verzorgingshuizen door gegevens uit de VURAI-DB te koppelen aan door het centrum klantervaring zorg (CKZ) openbaar gemaakte gegevens van onderzoek naar klantervaringen in deze verpleeg- en verzorgingshuizen. We vonden dat er een discrepantie bestond tussen de grote spreiding in prevalentie van

antipsychoticagebruik onder de verpleeg- en verzorgingshuizen in de laagste en hoogste tertiel van antipsychoticagebruik (13 t.o.v. 41%) enerzijds, en de kleine spreiding in prevalentie van gedragssymptomen bij deze verpleeg- en verzorgingshuizen anderzijds (bijvoorbeeld: ten minste een symptoom aanwezig; 54 t.o.v. 62%). De opmerkelijke grote variabiliteit in antipsychoticagebruik in onze studie (5–52%) kan dus niet volledig worden verklaard door de verschillen in de prevalentie van gedragssymptomen tussen de huizen. Een hoge prevalentie van antipsychoticagebruik blijkt geassocieerd met gemiddelde tot onder gemiddelde tevredenheid over het personeel, persoonlijke verzorging en aanbod van activiteiten. Huizen met een hoge prevalentie van antipsychoticagebruik waren vaker grootschalig en gelegen in een stedelijk gebied.

In de wetenschappelijke literatuur is beschreven dat de effectiviteit van antipsychotica op probleemgedrag veelal gering is, met een verbetering in gemiddeld één op de acht patiënten. De hoge prevalentie van antipsychoticagebruik is onverklaarbaar uit dit lage succespercentage. In **Hoofdstuk 2.2** onderzochten we daarom welke redenen ervaren specialisten ouderengeneeskunde hebben om antipsychotica voor te schrijven, en vroegen naar hun verwachtingen ten aanzien van het beoogde effect en de bijwerkingen. Zowel artsen als verzorgenden en mantelzorgers vonden de mogelijke voordelen van antipsychotica meestal opwegen tegen het risico van bijwerkingen. Belangrijkste redenen om te beginnen met therapie zijn agitatie en agressie. Artsen voelden zich in 17% van de gevallen door verzorgenden onder druk gezet om voor te schrijven. Zij voelden zich ondersteund door de richtlijn Probleemgedrag van de vereniging van specialisten ouderengeneeskunde en sociaal geriaters (Verenso). Het door de arts geschatte gemiddelde slagingspercentage in de besproken gevallen (de patiënt zal naar verwachting verbeteren op het doelsymptoom) was 50%; verzorgenden verwachtten gemiddeld in 53% van de gevallen verbetering en familieleden verwachtten een slagingspercentage van 55%. De meest verwachte bijwerkingen waren verhoogd valrisico, sedatie en parkinsonisme. Verzorgenden noemden vaker cognitieve achteruitgang als verwachte bijwerking. De familie voelde zich onvoldoende geïnformeerd over de bijwerkingen in 44% van de gevallen. We concludeerden dat de geïnterviewde specialisten ouderengeneeskunde en verzorgenden verwachten dat ongeveer de helft van hun patiënten met dementie en gedragsstoornissen profiteren van antipsychotica. Ernstige bijwerkingen worden verondersteld slechts sporadisch op te treden. Deze opvattingen zullen een rol spelen bij de hoge prevalentie van antipsychoticagebruik bij deze patiënten.

In **Hoofdstuk 2.3** beschrijven we het beloop van gedragsproblemen tijdens de behandeling met antipsychotica van oudere verpleeghuispatiënten met dementie, gebruikmakend van de VURAI-DB. In totaal werden 556 patiënten die begonnen met antipsychotica onderzocht. Van hen verbeterde de gedragsscore bij 101 patiënten

(18%), terwijl de score verslechterde bij 260 patiënten (47%) na drie maanden, vergeleken met de score vóór de therapie. Patiënten met ernstige gedragsproblemen lieten vaker een verbetering zien dan patiënten met milde stoornissen. Na het staken van het gebruik van antipsychotica bleven 352 van de 520 patiënten (68%) stabiel of verbeterden zelfs na drie maanden in vergelijking met hun scores vóór het staken. Zes maanden na staken was nog steeds 58% stabiel of verbeterd. Tijdens de behandeling van verpleeghuisbewoners met dementie met antipsychotica neemt de ernst van de meeste gedragsproblemen bij de meeste patiënten toe, met slechts bij één op de zes patiënten verbetering. Alhoewel dit een beschrijvend onderzoek is, waarbij onbekend is hoe het beloop van de gedragsproblemen zou zijn geweest zonder de inzet van antipsychotica, geven deze resultaten aan dat de invloed van antipsychotica op het beloop van gedragssymptomen bij verpleeghuisbewoners met dementie beperkt is. Gezien deze resultaten en de huidige kennis over belangrijke korte- en langetermijnrisico's zouden behandelaars zeer terughoudend moeten zijn met het voorschrijven van antipsychotica voor probleemgedrag.

In 2005 heeft de Amerikaanse Food and Drug Administration (FDA) verklaard dat het gebruik van atypische antipsychotica bij oudere patiënten met dementie leidt tot een ongeveer 1,6 maal hogere mortaliteit. Deze waarschuwing was gebaseerd op een post-hoc analyse van gerandomiseerde gecontroleerde studies (RCTs). Tijdens een typische 10-weekse RCT over het effect van atypische antipsychotica op de gedragssymptomen van dementie was de incidentie van sterfte bij patiënten die antipsychotica gebruikten ongeveer 4,5%, vergeleken met 2,6% in de placebogroep. De oorzaken van de dood varieerden, met de meeste doodsoorzaken van cardiovasculaire (hartfalen, plotseling overlijden) of van infectieuze aard. Op grond hiervan werd het gebruik van atypische antipsychotica bij dementie door de FDA ontraden. In 2008 werd deze waarschuwing uitgebreid tot alle antipsychotica. Het is mogelijk dat dit verhoogde risico ook bestaat bij ouderen zonder dementie. Er is veel onduidelijkheid over de oorzaken van het verhoogde sterfterisico. In **Hoofdstuk 3** wordt onderzocht of drie mogelijke cardiovasculaire complicaties van antipsychoticagebruik bij ouderen bijdragen aan de verhoogde mortaliteit. Deze drie onderzoeken zijn verricht met de Nederlandse PHARMO database. Deze database bevat gegevens van openbare apotheken van ongeveer 950.000 inwoners in 25 gedefinieerde gebieden in Nederland vanaf 1985 welke o.a. zijn gekoppeld aan ontslaggegevens uit het ziekenhuis. Aangezien vrijwel alle patiënten in Nederland zijn geregistreerd bij een enkele apotheek, zijn de apotheekgegevens vrijwel compleet met betrekking tot de receptgeneesmiddelen. Deelnemers aan de PHARMO database worden geregistreerd vanaf het eerste recept dat wordt afgehaald in een bij PHARMO aangesloten apotheek en worden gevolgd tot het laatste voorschrift. De geautomatiseerde medicatiehistorie bevat gegevens over de datum, afgeleverde hoeveelheid, sterkte en het voorgeschreven aantal eenheden per dag. De medicatie is gecodeerd volgens

de Anatomical Therapeutic Chemical (ATC) classificatie. Ontslaggegevens uit het ziekenhuis zijn verkregen van Prismant (LMR database), een instituut dat sinds de jaren zestig in een gestandaardiseerd formaat landelijk alle ontslaggegevens verzamelt uit de ziekenhuizen in Nederland. Deze gegevens bevatten gedetailleerde informatie over de primaire en secundaire diagnose, eventuele diagnostische en chirurgische procedures en de behandeling, en de data van opname in het ziekenhuis en ontslag. Alle diagnoses worden gecodeerd volgens de International Classification of Diseases, 9e editie (ICD-9-CM). De studies werden uitgevoerd in een cohort van patiënten van 50 jaar of ouder (Hoofdstuk 3.1) of 60 jaar en ouder (Hoofdstukken 3.2 en 3.3) die begonnen zijn met antipsychotische medicatie in de periode van 1986-2003 (Hoofdstuk 3.1) of 1998 - 2008 (Hoofdstuk 3.2 en 3.3).

In een meta-analyse van RCT's voor antipsychotica voor probleemgedrag bij patiënten met dementie vond Schneider een risico van 1,9% op cerebrovasculaire bijwerkingen, vergeleken met 0,9% bij placebogebruikers. In een aantal epidemiologische studies werd dit verhoogde risico echter niet gevonden. In **Hoofdstuk 3.1** hebben we een bijdrage geleverd aan het bestaande bewijs dat antipsychoticagebruik bij ouderen het risico op CVA verhoogt. Binnen het cohort oudere antipsychoticagebruikers identificeerden we 518 patiënten die werden opgenomen met een CVA: 54% ischemisch, 15% hemorragisch en 31% niet gespecificeerd. 2030 controles werden gematcht naar leeftijd en geslacht. De sterfte onder patiënten tijdens ziekenhuisopname bedroeg 18%. Huidige en recente blootstelling aan antipsychotica gingen gepaard met een verhoogd risico op cerebrovasculaire bijwerkingen in vergelijking met niet-gebruikers (odds ratio [OR] 1.7, betrouwbaarheidsinterval (BI) 1.4-2.2). Een nieuwe bevinding was, dat er een sterke tijdsrelatie bestaat tussen de duur van de therapie en het risico. De OR voor een gebruik korter dan een week is 9.9 (BI 5.7 tot 17.2). Het risico neemt af in de tijd en is na drie maanden van gebruik vergelijkbaar met dat van niet-gebruikers (OR 1.0, BI 0.7-1.3). Cumulatieve blootstelling werd niet geassocieerd met een toename van het risico.

De toename van het risico op veneuze trombose en daaruit voortvloeiende longembolie is controversieel. Het is gesuggereerd dat massale longembolie een niet onderkende oorzaak van de verhoogde sterfte bij antipsychoticagebruikers is. Het mechanisme van verhoogde trombose is echter onverklaard. In **Hoofdstuk 3.2** onderzoeken we het risico op veneuze trombose en longembolie onder thuis- en in het verzorgingshuis wonende ouderen die antipsychotica gebruiken. We identificeerden 367 gevallen van ziekenhuisopname voor diep-veneuze trombose, 342 gevallen van ziekenhuisopname voor longembolie, en 323 gevallen van poliklinische behandeling voor diep-veneuze trombose. 4125 controles werden gematcht naar leeftijd en geslacht. De huidige blootstelling aan antipsychotica werd niet geassocieerd met een verhoogd risico op veneuze trombo-embolie, in vergelijking met niet-gebruikers (OR 0.9, 95% BI 0.7 tot 1.1). We vonden geen relatie tussen de dosering, de duur van het gebruik, of het type antipsychotica en het risico van veneuze trombo-embolie.

Antipsychoticagebruik wordt geassocieerd met een verhoogd risico op het ontwikkelen van een metabool syndroom, diabetes en hyperlipidemie. Daarom wordt antipsychoticagebruik geassocieerd met een verhoogd risico op hart- en vaatziekten bij ouderen, waarbij een verhoogde kans op een acuut coronair syndroom mede zou kunnen bijdragen aan de verhoogde mortaliteit. De beschikbare literatuur over dit onderwerp is verrassend schaars en de resultaten zijn tegenstrijdig. In **Hoofdstuk 3.3** kijken we daarom naar het risico op acuut coronair syndroom onder oudere antipsychoticagebruikers. Er werden 2803 ziekenhuisopnames voor ACS geïdentificeerd: 1555 gevallen van acuut myocardinfarct en 1248 gevallen van intermediair coronair syndroom. 11024 controles werden gematcht naar leeftijd en geslacht. De huidige blootstelling aan antipsychotica was geassocieerd met een verminderd risico op ziekenhuisopname voor ACS in vergelijking met niet-gebruikers (gecorrigeerde OR 0.5, 95% BI 0.5 - 0.6). Cumulatief gebruik tot 100 Defined Daily Doses (DDD) was ook geassocieerd met een verminderd risico op ziekenhuisopname (OR 0.7, BI 0.6 - 0.8). Er zijn geen verschillen in risico gevonden tussen typische en atypische antipsychotica, hoogte van de huidige dosering, of mate van serotonerge, histaminerge of adrenerge affiniteit. Samenvattend vonden we een verminderd risico op ziekenhuisopname voor de ACS bij oudere patiënten die antipsychotica gebruiken. Verder onderzoek is nodig om te bepalen of er sprake is van cardioprotectief effect of een laag verwijscijfer onder oudere antipsychoticagebruikers met een acuut hartinfarct.

Hoofdstuk 4 is een nabeschouwing. Er wordt ingegaan op de problematiek van het doen van wetenschappelijk onderzoek bij deze patiëntengroep en we constateren dat het instrument van de RAI hiervoor goed gebruikt kan worden. We noemen enige methodologische beperkingen en bespreken de bevindingen in een breder perspectief. We concluderen dat de stelling dat het gebruik van antipsychotica bij oudere patiënten met dementie zowel ineffectief als schadelijk is, moet worden genuanceerd. Hoewel de aanwezigheid van een variatie in voorschrijffrequentie tussen praktijken aangeeft dat het verminderen van antipsychoticagebruik mogelijk is, en onze observationele studie van het verloop van gedragssymptomen in de grote meerderheid van de patiënten geen gunstige effecten van behandeling met antipsychotica vond, is het mogelijk dat kleine verbeteringen in het gedrag van patiënten wel relevant blijken voor patiënten, hun familie en hun professionele zorgverleners. Hoewel in het begin van de behandeling met antipsychotica het risico op beroerte sterk verhoogd is, is het absolute risico zeer laag. We vonden geen verhoging van het risico op zowel veneuze trombose als myocardinfarct. De morbiditeit en mortaliteit ten gevolge van antipsychotica is klein in vergelijking met de reeds bestaande morbiditeit, en het toch al hoge sterftecijfer onder geïnstitutionaliseerde patiënten met dementie. Gevorderde dementie kan worden gezien als een ongeneeslijke, progressieve ziekte met een korte levensverwachting. De meeste oudere patiënten met

dementie overlijden binnen zeven jaar, waarvan de laatste twee tot drie jaar worden doorgebracht in een verpleeg- of verzorgingshuis. In die laatste jaren kiezen de meeste patiënten of hun vertegenwoordigers voor een palliatieve behandeling. In de palliatieve zorg is verbetering van de kwaliteit van leven door symptoombestrijding belangrijker dan verlenging van de levensduur. Een minderheid van de patiënten lijkt te profiteren van antipsychotische therapie. Een algeheel verbod op antipsychoticagebruik bij dementie is daarom, ondanks het risico op ernstige bijwerkingen zoals een verhoogde mortaliteit, niet gerechtvaardigd.

Voor een groot deel van de thans vaak langdurig met antipsychotica behandelde patiënten met dementie is de behandeling echter waarschijnlijk niet of niet meer effectief en mogelijk schadelijk. We doen daarom een aantal aanbevelingen. We raden aan standaard een evaluatiedatum toe te voegen aan ieder nieuw antipsychoticarecept. Een geautomatiseerd beslissingsondersteunend systeem voor het voorschrijven van geneesmiddelen (DSS) kan artsen hierbij helpen. Geautomatiseerde receptsystemen die diagnoses en indicaties bevatten kunnen speciaal worden ontworpen om specialisten ouderengeneeskunde suggesties te geven voor juist antipsychoticagebruik. Meer bewustwording van de variatie tussen de praktijken, de mogelijkheid om informatie uit te wisselen, en de mogelijkheid om de eigen praktijk te vergelijken met 'best practices' (de zogenaamde benchmarking) kan helpen om overmatig antipsychoticagebruik te verminderen. Binnen toetsingsgroepen van specialisten ouderengeneeskunde kunnen voorschrijfgewoontes, meningen over antipsychoticagebruik in het algemeen en de problemen die ontstaan bij pogingen om het gebruik te staken worden besproken. De meeste verpleeginstellingen hebben regelmatig farmacotherapeutisch overleg met een vaste apotheker. Het antipsychoticagebruik kan daarin regelmatig geëvalueerd worden. Het verdient aanbeveling dat de Nederlandse vereniging van specialisten ouderengeneeskunde (Verenso) aandacht geeft aan de ongewenst hoge prevalentie van antipsychoticagebruik. Daarnaast moet antipsychoticagebruik speciale aandacht krijgen tijdens de opleiding tot specialist ouderengeneeskunde. Snelle geautomatiseerde toegang tot de relevante richtlijnen kan ook helpen, en wordt momenteel ontwikkeld door een collectief van praktijken van specialisten ouderengeneeskunde (www.gerimedica.nl). Psychogeriatrische instellingen zullen meer en beter opgeleid verplegend personeel moeten inzetten om non-farmacologische interventies toe te passen bij probleemgedrag. Het onderwijs voor verpleegkundigen die de zorg aan patiënten met dementie geven, moet structureel verbeterd worden. Meer expertise bij de psychogeriatrische verpleging zal ook leiden tot verbeterde observatie en rapportage aan de arts. Een goed aanbod aan dagbestedingactiviteiten, individueel of in kleine groepen, kan ook helpen. De Nederlandse vereniging van specialisten ouderengeneeskunde raden wij aan om hoge prioriteit te geven aan de verbetering van de dementiezorg.

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