A STUDY OF BALANCE, GAIT AND PSYCHOTROPIC DRUG USE IN RELATION TO FALL RISK IN NURSING HOME RESIDENTS WITH DEMENTIA

Carolyn Shanty Sterke

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ONDERZOEK NAAR BALANS, LOOPPATROON EN GEBRUIK VAN PSYCHOTROPE MEDICATIE IN RELATIE TOT VALRISICO BIJ VERPLEEGHUISBEWONERS MET DEMENTIE

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CHAPTER 1

General introduction
Falls in nursing home residents with dementia

FALLS IN THE ELDERLY

Falls are a major health problem among the elderly,[1-2] particularly in nursing homes,[3-6] and are associated with considerable morbidity and mortality,[2, 7-8] and with substantial economic costs.[9-10] In nursing homes 30% to 70% of the residents experience at least one fall per year,[11] with one-third of all falls resulting in an injury.[10] Nursing home residents are three times more likely to fall compared with their community-dwelling counterparts, approximately 1.5 falls per bed per year occur in somatic nursing homes and more than 2 falls per bed per year in psychogeriatric nursing homes.[12-13] In summary, nursing home residents with dementia are at particular risk of falling and this group has the highest fall incidence.

RISK FACTORS

Previous research has identified numerous risk factors for falls.[1, 3, 14-20] The risk factors can be classified as either intrinsic or extrinsic.[1, 7] Intrinsic risk factors are related to the individual, for example balance and gait impairments,[1, 6, 14-15] lower extremity weakness,[1, 6, 14] use of psychotropic drugs (antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants),[21-24] dementia and cognitive impairment,[3, 14, 25-26] and medical conditions (e.g. cardiovascular disease, stroke, urinary incontinence, visual impairment).[1, 7, 14] Extrinsic risk factors for falls are environmental factors like thresholds, stairs, poor lighting and so on.[27-28] The risk of falling increases linearly with the number of risk factors.[1]

Because of the magnitude of the problem of falls in nursing home residents with dementia, it is important to systematically evaluate the fall risk profile of each individual resident so that for each resident tailor-made preventive measures (e.g. physical

therapy, drug withdrawal, hip protectors) can be taken in time. A systematic evaluation of fall risk should include an assessment of all major contributing components, such as a history of previous falls, impaired balance and gait, use of fall risk increasing drugs, and existing medical problems.[29] Each single risk factor should be assessed with the help of specific instruments, which have proven feasibility, reliability and validity in the target population.

In nursing home residents with dementia, there is a high prevalence of balance and gait impairments,[30-31] and of neuropsychiatric symptoms and behavioral disturbances.[32-34] The prevalence of balance and gait impairments can increase to over 70% in patients with dementia.[30-31] Furthermore, 63% to 79% of nursing home residents with dementia are treated with psychotropic drugs[35-37] because of neuropsychiatric symptoms or behavioral disturbances, which occur in more than 80% of this population.[32-34]

Therefore, special efforts should be made in such a population to identify potentially modifiable risk factors, such as balance and gait impairments,[38] and psychotropic drug use.[39-40] More knowledge of these highly prevalent risk factors might provide clues to designing effective interventions.

FALL RISK AND BALANCE AND GAIT IMPAIRMENTS

Balance and gait impairments are strong predictors for falling.[1, 11, 28, 41] Gait impairments are associated with severity of dementia.[42] To assess balance and gait, the Tinetti Performance Oriented Mobility Assessment (POMA) can be used. The POMA is a widely used clinical measure that provides an insight into the impairments in balance and gait, and which has the ability to predict fall risk in nursing home residents.[43] Clinimetric properties like reliability and validity of the POMA have been well demonstrated.[43-46] The POMA has been recommended as part of a multidisciplinary evaluation tool for fall risk in nursing home patients with dementia in the Netherlands.[11, 47]

The original test was developed and used in an institutionalized population of intermediate care residents with chronic diseases, who were independent or required minimal assistance in activities of daily living.[43] However, the POMA has not yet been tested in nursing home populations with dementia. Dementia is a process of progressive deterioration in memory, judgement, attention and executive functions, and may be accompanied by aphasia and apraxia.[48] Therefore, this type of population presents special problems when testing physical performance. This could make the POMA less suitable for persons with severe cognitive impairment.

An electronic walkway system that objectively quantifies walking function[49-50] is less dependent on cognition. Quantitative studies of walking in older fallers have found gait parameters that distinguish fallers from non-fallers. It has been shown that increased

stride-to-stride variability in stride length, stride time, speed, stride width, and in double-support time are associated independently with falling in community-dwelling older adults,[19, 51] and that decreased cadence (steps/minute) is associated independently with falling in nursing home patients with advanced Alzheimer disease.[52] The advantage of studying gait parameters with an electronic walkway system is that there is no executive functioning required like in the POMA items. Therefore, an electronic walkway system might be more feasible and valid than the POMA to predict fall risk in a population of nursing home residents with dementia. However, this has not been tested yet.

FALL RISK AND PSYCHOTROPIC DRUG USE

Drugs constitute a major part of modifiable risk factors for falls.[39-40] Previous reviews and meta-analyses have shown an increased fall risk for the use of psychotropic drugs.[21, 23-24] The use of two or more psychotropic drugs increased the incidence of falls further.[23] Several studies have shown that benzodiazepines, antidepressants, and antipsychotics were independent fall risk factors.[23-24, 53]

However, none of the studies in the above mentioned meta-analyses was done in the specific population of nursing home residents with dementia. The contribution of psychotropic drugs to fall risk in nursing home residents with dementia must still be quantified. When this study was initiated, it was unknown whether psychotropic drug use remains an independent fall risk factor in high risk patients with dementia, who might function better because of these drugs. In addition, it was unknown whether dose-response relationships existed between psychotropic drug use and falls.

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CHAPTER 2

Aim of the thesis

As described in the introduction of this thesis, nursing home residents with dementia are at particular risk of falling. Psychotropic drug use, and balance and gait impairments are strong predictors for falling.

As a clinical physiotherapist, my interest in the possible relationship between psychotropic drug use, and gait and falls was aroused when a nursing home physician asked me to judge whether a certain resident walked better after a dose reduction of a psychotropic drug, in this case haloperidol. The dose of haloperidol was reduced because of the falls that this resident had experienced. Then came a few questions to me. First, although it is generally known that nursing home residents with dementia have an increased fall risk, I was interested whether psychotropic drug use was an independent fall risk factor in this high risk population. Second, I wondered whether the dose reduction would reduce the fall risk. In other words, is fall risk dependent on the dose of a psychotropic drug? The idea arose to investigate the precise contribution of psychotropic drugs to fall risk. Third, I wondered whether this resident actually walked better after the dose reduction, and to what extent walking patterns are predictive of future falls. This stressed the need for a suitable instrument to measure gait and mobility. Then I experienced that mobility tests for the prediction of fall risk, which are recommended in the international literature[1-2] and in the Dutch national guideline for the prevention of fall incidents in older people,[3] are difficult to apply in everyday practice in nursing home residents with dementia. Moreover, the Dutch national guideline highlighted that there was a lack of research on mobility tests and falls in Dutch nursing homes.[3] So, it seemed necessary to investigate whether there was an appropriate test to monitor balance and gait, and to predict fall risk in this highly vulnerable group.

This thesis describes our work in two major parts. The objective described in the first part of this thesis was to gain more knowledge about the assessment of balance and gait with regard to fall risk in residents of a psychogeriatric nursing home. We addressed the following research questions:

1. Is the Tinetti Performance Oriented Mobility Assessment (POMA) a feasible and valid instrument to predict short-term fall risk in ambulatory nursing home residents with dementia?
2. Is an electronic walkway system a feasible and valid instrument to predict short-term fall risk in ambulatory nursing home residents with dementia?
3. Which of the gait parameters has the best predictive value with regard to fall risk in this specific population?

In the second part of this thesis we describe the contribution of psychotropic drug use to fall risk in a psychogeriatric nursing home. We addressed the following research questions:

1. Which psychotropic drugs increase fall risk and what is known about the influence of these drugs on gait in nursing home residents with dementia?
2. What is the magnitude of the associations between specific psychotropic drugs and fall risk in nursing home residents with dementia?
3. Are there dose-response relationships between specific psychotropic drugs and fall risk in nursing home residents with dementia; and between specific psychotropic drugs and the risk of an injurious fall?

Figure 1 shows the outline of this thesis schematically. Part I (chapter 3 and chapter 4) deals with the prediction of fall risk by balance and gait parameters in nursing home residents with dementia. In chapter 3, we describe the results of a prospective cohort study in which we evaluated the feasibility and examined the inter-rater reliability and the predictive ability of the POMA to predict fall risk. We focused on the prediction of fall risk in the short term (i.e. three months). In chapter 4, we report the results of a prospective cohort study on the validity of gait parameters as measured with an electronic walkway system, the GAITRite® walkway, in predicting short-term fall risk. Furthermore, we present which of the GAITRite® parameters had the best predictive value with regard to fall risk.

Part II (chapter 5, 6 and 7) deals with the contribution of psychotropic drug use to fall risk in nursing home residents with dementia. In chapter 5, we describe a systematic review of the literature. We investigated which psychotropic drugs increased fall risk, and what was known about the influence of these drugs on gait parameters in nursing home residents with dementia. In chapter 6, we present an analysis of the magnitude of the associations between specific psychotropic drugs and fall risk. Furthermore, we describe our exploration of the dose-response relationships between specific psychotropic drugs

and fall risk. Chapter 7 describes our analysis of the dose-response relationship between the use of specific psychotropic drugs and injurious falls. Finally, in chapter 8, we reflect on our main findings, and discuss the implications of our results for daily health care practice and for future research.

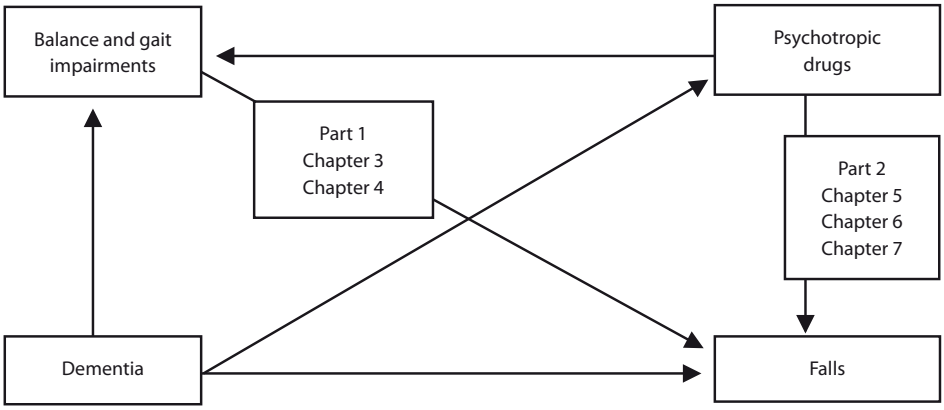

Figure 1 Outline of this thesis

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PART 1

Fall risk and balance and gait impairments

CHAPTER 3

Is the Tinetti Performance Oriented Mobility Assessment (POMA) a feasible and valid predictor of short-term fall risk in nursing home residents with dementia?

Sterke CS, Huisman SL, van Beeck EF, Looman CW, van der Cammen TJ. Int Psychogeriatr 2010;22:254-63.

ABSTRACT

Background The feasibility and predictive validity of balance and gait measures in more severe stages of dementia have been understudied. We evaluated the clinimetric properties of the Tinetti Performance Oriented Mobility Assessment (POMA) in nursing home residents with dementia with a specific objective of predicting falls in the short term.

Methods Seventy-five ambulatory nursing home residents with dementia, mean age 81 ± 8 years, participated in a prospective cohort study. All participants underwent the full POMA-test. Fall statistics were retrieved from incident reports during a three-month follow-up period. The predictive validity was expressed in terms of sensitivity and specificity. Loglinear regression analysis was used to examine the relationship between POMA scores and the occurrence of a fall.

Results The POMA showed several feasibility problems, with 41% of patients having problems in understanding one or more instructions. The inter-rater reliability of the instrument was good. The predictive validity was acceptable, with a sensitivity of 70–85% and a specificity of 51–61% for the POMA and its subtests, and an area under the curve (AUC) of 0.70 for POMA-Total (95% CI: 0.53–0.81), 0.67 for POMA-Balance (95% CI: 0.52–0.81), and 0.67 for POMA-Gait (95% CI: 0.53–0.81). After loglinear regression analysis, only POMA-Total was significant in predicting a fall (adjusted HR=1.08 per point lower; 95% CI 1.00–1.17).

Conclusions Application of the POMA in populations with moderate to severe dementia is hampered by feasibility problems. Its implementation in clinical practice cannot therefore be recommended, despite an acceptable predictive validity. To refine our findings,

large prospective studies on the predictive validity of the POMA in populations with mild, moderate and severe dementia are needed. In addition, the performance of mobility assessment methods that are less dependent on cognition should be evaluated.

INTRODUCTION

Falls are a major health problem among older people, particularly in nursing homes.[1-2] Drug use, and gait and mobility impairments are strong predictors for falling.[3-7] Studies examining the relationship between falls and gait function in nursing home residents with dementia indicate that the number of falls and gait impairments increases with advancing severity of dementia.[8-9]

The Tinetti Performance Oriented Mobility Assessment (POMA) is a widely used clinical measure that provides an insight into the abnormalities in balance and gait, and which has the ability to predict fall risk. Clinimetric properties like reliability and validity of the POMA have been well demonstrated.[10-13]

The original test was developed and used in an institutionalized population of intermediate care residents with chronic diseases, who were independent or required minimal assistance in activities of daily living.[10] A recent study of the validity and reliability of the POMA revealed that this test is also suitable for measuring gait and mobility in patients with mild to moderate dementia.[14] However, the POMA has not yet been tested in populations with moderate to severe dementia. It is therefore not clear if the POMA can be used in a population of nursing home residents with moderate to severe dementia. This type of population presents special problems when testing physical performance. Dementia is a process of progressive deterioration in memory, judgment, attention and executive functions, and may be accompanied by aphasia and apraxia.[15] The POMA items require the ability to perform executive functions, so this could make the POMA less suitable for persons with severe cognitive impairment. Because of the magnitude of the problem of falls in nursing home residents with dementia, it is important to have a test available which is feasible and reliable and has predictive abilities to identify those at increased risk of a fall in the short term. This will allow early recognition and intervention in this specific population, in order to prevent falls in a practical way. It is important to evaluate systematically the fall risk profile of each individual resident so that tailor-made preventive measures (e.g. physical therapy, drug withdrawal, hip protectors) can be readily applied to each resident. A systematic evaluation of fall risk should include an assessment of all major contributing components, such as a history of previous falls, use of drugs known to increase the risk of falls, existing medical problems (e.g. with visual impairment, incontinence) and impaired balance and mobility. Each single risk factor should be assessed with the help of specific instruments, which have proven feasibility,

reliability and validity in the target population. In populations with moderate to severe dementia, impaired balance and gait are a major component with respect to increased fall risk. However, assessment methods for this component, such as the POMA, have not yet been tested in these populations. Nevertheless, the POMA has been recommended as part of a multidisciplinary evaluation tool for nursing home patients with dementia in the Netherlands.[4, 16] Internationally, there seems to be a need for an evidence-based advice on the best method to asses balance and gait in populations with moderate to severe dementia, as part of a multifactorial evaluation.

We therefore evaluated the feasibility, and examined the inter-rater reliability and the predictive ability of the POMA to predict fall risk in a population of nursing home residents with moderate to severe dementia. We focused on the prediction of fall risk in the short term (i.e. three months) because we tested the performance of the POMA in a frail population where early recognition is of paramount importance. Identifying those patients who have increased fall risk in the short term could allow the timely application of preventive measures.

METHODS

Design and setting

This design was a prospective cohort study with a three-month follow-up. The Medical Ethics Committee of the Erasmus University Medical Center approved the study.

Population and study period

We included nursing home residents with a diagnosis of moderate to severe dementia, living in the psychogeriatric nursing home Smeetsland from the De StromenOpmaat-Groep, Rotterdam, The Netherlands.

Residents living in the chronic care psychogeriatric department because of a diagnosis of dementia,[15] and who were able to walk independently, were asked to participate in the study after written informed consent had been obtained from their legal guardians.

Residents who were not able to stand without the aid of a person or walk independently, or who had other types of cognitive impairment such as Korsakoff's syndrome, as well as those without written informed consent from their legal guardians, were excluded.

Of the 220 residents with dementia who were resident at the start of the inclusion period (1 May until 31 July 2008), 109 were eligible to participate in the study; 111 residents were not eligible because of the exclusion criteria. The legal guardians of 87 residents gave their informed consent. Before the test took place, six residents were no

longer ambulatory and hence not able to participate further, four residents died and two residents refused to participate. Finally 75 residents participated in the study (Figure 1).

Baseline data abstracted from medical records and nursing home charts were: age, gender, medication use and comorbid conditions considered potentially causative of falls. These comorbid conditions included: visual impairment, urinary incontinence, Parkinson's disease, arthritis and other joint diseases, depression and cardiovascular diseases.[3, 17] Severity of dementia was defined as stage 5 or 6 on the Global Deterioration Scale,[18] and was based on the regular multidisciplinary team assessment by the nursing home staff, including the nursing home physician. This multidisciplinary team assessment takes place six weeks after admission to the nursing home and thereafter twice a year. The most recent assessment before the test date was taken into account.

Falls were recorded on a standardized incidence registration form,[19] which is part of the incidence registration system. This standard procedure is a national instrument to monitor the quality of care in nursing homes in the Netherlands.[20] The staff are trained to complete the forms immediately that a fall has been witnessed or after a resident is found on the floor or any lower level.[21] A committee collects the forms and makes incidence reports. Falls data were gathered from these reports after a three-month follow-up period.

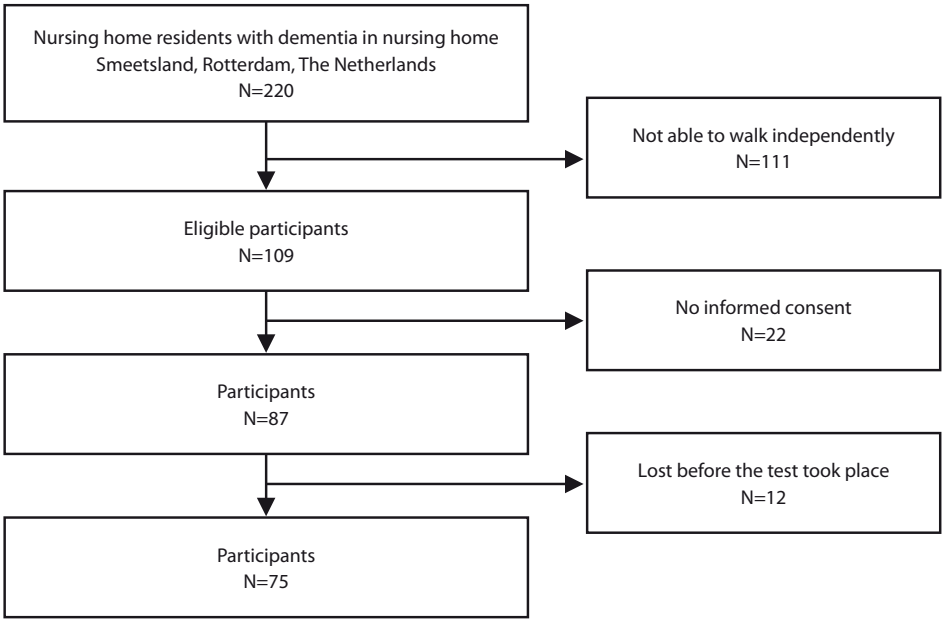

Figure 1 Flow diagram of participants included and excluded in the study

POMA

The total POMA scale (POMA-T) consists of a balance scale (POMA-B) and a gait scale (POMA-G), and was administered between 1 May and 31 July 2008. The balance subtest includes eight positions and position changes that stress stability such as sitting balance, rising up from a chair, immediate and prolonged standing balance, withstanding a nudge on the sternum, balance with eyes closed, turning balance and sitting down. The gait subtest reflects gait maneuvers used during normal daily activities. The eight gait items are initiation, step length and height, step continuity, symmetry, path deviation, trunk sway, walking stance and turning while walking. Some items are graded dichotomously (can/cannot perform) whereas other items are scored 0, 1 or 2 points to denote quality of performance. The total score can range from 0 to 28 points, with lower scores indicating increased fall risk.[10]

To assess the inter-rater reliability, one investigator (SH), who received eight hours of training on scoring the POMA, and one investigator (CS), with 17 years' experience in physical testing of nursing home residents with dementia, conducted the test on 75 participants. Both investigators (CS and SH) recorded the findings simultaneously without discussion.

First, each participant was invited to perform the eight maneuvers of the POMA-B as described in the original protocol.[10] If a participant had difficulty in understanding and following verbal instructions, we allowed the examiner to use any combination of verbal persuasion, physical cueing, and physical assistance required to get the participant to stand up from the chair, to turn 360° and to sit down. The participants were encouraged to rest between the maneuvers as necessary. If a participant was frightened, uncertain or unable to perform certain maneuvers, he or she could proceed to the next item and was scored 0 for that maneuver.

Second, we invited each participant to walk 6 meters at his or her natural walking speed, turn and walk back as described in the original protocol.[10] The gait subtest was performed without a walking aid since, in our experience, many older people with dementia usually forget their walking aid. To test with a walking aid would not be a true reflection of the daily practice in the nursing home. We allowed the examiners to use any combination of verbal persuasion, physical cueing, and physical assistance required to perform the gait subtest.

A note was made of movements or gestures that suggested that verbal instructions of the POMA-B or the POMA-G were not understood; for example, when a participant began walking immediately after rising, and didn't follow the instruction to stand for 3–5 seconds. In that case it was not possible to score the item "immediate standing balance." In the gait subtest it was not possible to test the item "turning while walking" if a participant walked straight ahead and failed to follow the instruction to turn and walk back.

In order to gain insight into the effect of our assessment method, an independent physiotherapist with 18 years' experience in physical testing of nursing home residents with dementia, but who did not know this specific study group, conducted additional tests on a random subsample of 11 participants after one month. The two investigators (CS and SH) recorded their findings without discussion during the assessment. The independent physiotherapist recorded her findings without discussion after performance.

Statistical analysis

Frequencies were calculated for items in which participants had difficulty in following instructions, due to cognitive impairment.

For the POMA-T, as well as for the subscales, intraclass correlation coefficients (ICCs) (2,1) were calculated to examine agreement between raters.[22]

The inter-observer agreement of the individual items of the POMA-B and the POMA-G was derived by kappa statistics because of categorical data. An inter-observer agreement of k=0.41 to 0.60 represents moderate agreement. An inter-observer agreement of k=0.61 to 0.80 represents a good agreement, while k=0.81 to 1.00 represents a very good agreement.[23]

The predictive validity was expressed in terms of sensitivity and specificity. The sensitivity was defined as the percentage of fallers within three months who were correctly identified. Specificity was defined as the percentage of non-fallers within three months who were correctly identified. Optimal cut-off values were determined by plotting Receiver Operating Characteristic (ROC) Curves for the POMA-T, and for the subtests, to determine the point that provided the best trade-off between sensitivity and specificity. The Area under the ROC Curves (AUCs) for the POMA-T, as well as for the subtests, were computed, with larger AUC indicating better predictive ability. It is a general rule that a test does not discriminate if ROC=0.5; is acceptable if $0.7 \leq ROC < 0.8$; is excellent if $0.8 \leq ROC < 0.9$; and is outstanding if $ROC \geq 0.9$.[24] Positive and negative predictive values were calculated for each cut-off score for the POMA and the subtests.

Loglinear regression analysis was used to examine the relationship between each participant's POMA-T, POMA-B and POMA-G scores and the occurrence of a fall within three months. Because a considerable proportion of the participants (n=14) did not complete the follow-up at three months we had to correct for time-at-risk by way of an offset parameter. The time at risk ended at the moment of the first fall or at the end of the observation period (i.e. three months or earlier). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for POMA-scores, falls history, comorbidities and medication use. POMA-T, POMA-B and POMA-G scores were included in multivariate models, with adjustments for variables which were significantly associated with a fall in the univariate analysis.

To examine if the prediction of a fall differs between participants who had no difficulty in understanding verbal instructions and those who did have difficulty in understanding the instructions of the test, the interaction between test scores and understanding was added to the regression model. All statistical analyses were performed using SPSS software (version 15.0, SPSS INC., Chicago, IL, U.S.A.).

RESULTS

The mean age ± standard deviation (sd) of the participants was 81 ± 8 years, and 64% were female.

The scoring of the POMA-T ranged from 6 to 28 points (mean=18.7, sd=5.9). The scoring of the balance subtest ranged from 0 to 16 points (mean=9.2, sd=4.1). The scoring of the gait subtest ranged from 3 to 12 points (mean=8.7, sd=2.5). Twenty residents (26.7%) experienced at least one fall during the follow-up period. Of the 75 residents who participated in the study, 14 were lost during follow-up. Three participants died, two were no longer ambulatory, and left the facility.

Feasibility

Despite the fact that we allowed the examiner to use verbal persuasion, physical cueing and physical assistance whenever a participant had difficulty in understanding the instructions, we encountered several problems with regard to the feasibility of the POMA in this population with dementia. Thirty-one participants (41%) had difficulty following one or more instructions of the POMA due to cognitive impairment. For example, when testing the item "immediate standing balance" of the POMA-B, some participants did not stand for 3-5 seconds as required but began walking immediately after rising, or were holding the chair and it was not clear whether they could stand without holding the chair. When testing the item "turning while walking" of the POMA-G some participants did not turn but walked straight ahead. Hence it was not possible to score these items.

Inter-rater reliability

The inter-rater reliability expressed as ICCs and *k* coefficients is shown in Table 1. The ICC of the POMA-T scored 0.97, the POMA-B showed an ICC of 0.97, and the POMA-G an ICC of 0.88.

Kappa coefficients between the two raters varied for the POMA-B between k=0.65 (withstanding a nudge on the sternum) and k =0.92 (standing balance with eyes closed). Kappa coefficients for the POMA-G varied between k=0.47 (step height), k=0.50 (walking stance), k=0.54 (symmetry) and k=0.83 (step length). No k statistic could be computed

Table 1 Intra-class correlation coefficients of the POMA-T, the POMA-B, and the POMA-G and Kappa coefficients of the individual POMA-items rated by two raters

Test	ICC	p-value
POMA-T	0.97	0.00
POMA-B	0.97	0.00
POMA-G	0.88	0.00
POMA items	***k*-value**	**p-value**
Balance		
sitting balance[a]	-	
rising up from a chair	0.88	0.00
standing balance in the first 5 seconds	0.90	0.00
standing balance with feet together	0.87	0.00
standing balance with eyes closed	0.92	0.00
withstanding a nudge on the sternum	0.65	0.00
turning through 360°	0.75	0.00
sitting down	0.69	0.00
Gait		
initiation[b]	-	
step length	0.83	0.00
step height	0.47	0.00
step continuity	0.71	0.00
symmetry	0.54	0.00
path deviation	0.81	0.00
trunk sway	0.81	0.00
walking stance	0.50	0.00
turning while walking	0.82	0.00

[a]No kappa (κ) statistic was computed because sitting balance was a constant.
[b]No κ statistic was computed because initiation was a constant.

for the items "sitting balance" and "initiation of gait", since these items were scored 2 and 1 respectively for all participants, and thus were treated as a constant.

In the additional testing with the independent assessor, the ICC for the POMA-T scored 0.80, the POMA-B showed an ICC of 0.75, and the POMA-G scored an ICC of 0.83.

Predictive validity

For the prediction of a fall in the short term, i.e. within three months, the optimal cut-off points for each assessment are presented in Table 2. The point with the best predictive value for the POMA-T was the score of ≤ 21 with a sensitivity of 85% and a specificity of 56%. The positive predictive value for a score of ≤ 21 was 38%, which means that the probability that a resident with a POMA-T score of ≤ 21 will experience a fall within three months is 38%. For the POMA-B, the best predictive value was a score of ≤ 11 points

Table 2 The predictive validity of the POMA-T, the POMA-B, and the POMA-G

	AUC (95% CI)	p-value	cut-off score	sensitivity	specificity	PPV	NPV
POMA-T	0.70 (0.53-0.81)	0.01					
			19	65%	61%	36%	81%
			20	75%	61%	28%	84%
			21*	85%	56%	38%	89%
			22	85%	51%	36%	88%
POMA-B	0.67 (0.52-0.81)	0.04					
			10	55%	61%	34%	78%
			11*	70%	51%	35%	81%
			12	80%	44%	34%	84%
			13	85%	34%	32%	84%
POMA-G	0.67 (0.53-0.81)	0.03					
			8	45%	68%	37%	78%
			9*	70%	61%	37%	81%
			10	90%	39%	34%	89%
			11	90%	17%	29%	80%

Abbreviations: PPV=positive predictive value; NPV=negative predictive value.
*Cut-off score with the best predictive value.

with 70% sensitivity and 51% specificity. The positive predictive value for a score of ≤ 11 was 35%. For the POMA-G, the best predictive value was a score of ≤ 9 points with a sensitivity of 70% and a specificity of 61%. The positive predictive value for a score of ≤ 9 was 37%.

The ROC curves for the POMA-T, the POMA-B, and the POMA-G are plotted in Figure 2. The AUC for the POMA-T was 0.70 (95% CI 0.53-0.81, p=0.01). The AUC for the POMA-B and POMA-G was 0.67 (95% CI 0.52-0.81, p=0.04) and 0.67 (95% CI 0.53 -0.81, p=0.03) respectively.

In the univariate analysis, falls history (HR=2.32; 95% CI 1.00-5.46), POMA-T (HR=1.09; 95% CI 1.01-1.17) and POMA-B (HR=1.11; 95% CI 1.01-1.23) scores were significantly associated with a fall within three months. For participants who had no problem understanding verbal instructions (n=44) each point lower on the POMA-T was associated with a 10% increase in fall risk. For participants who did have problems understanding at least one item of the verbal instructions (n=31) each point lower on the POMA-T was associated with a 7% increase in fall risk. However, the interaction term was not found to be significant (p=0.73). There was no difference in the prediction of a fall between those who had difficulties in understanding instructions and those who did not. POMA-G scores, comorbidities and medication use were not found significant in the univariate analysis.

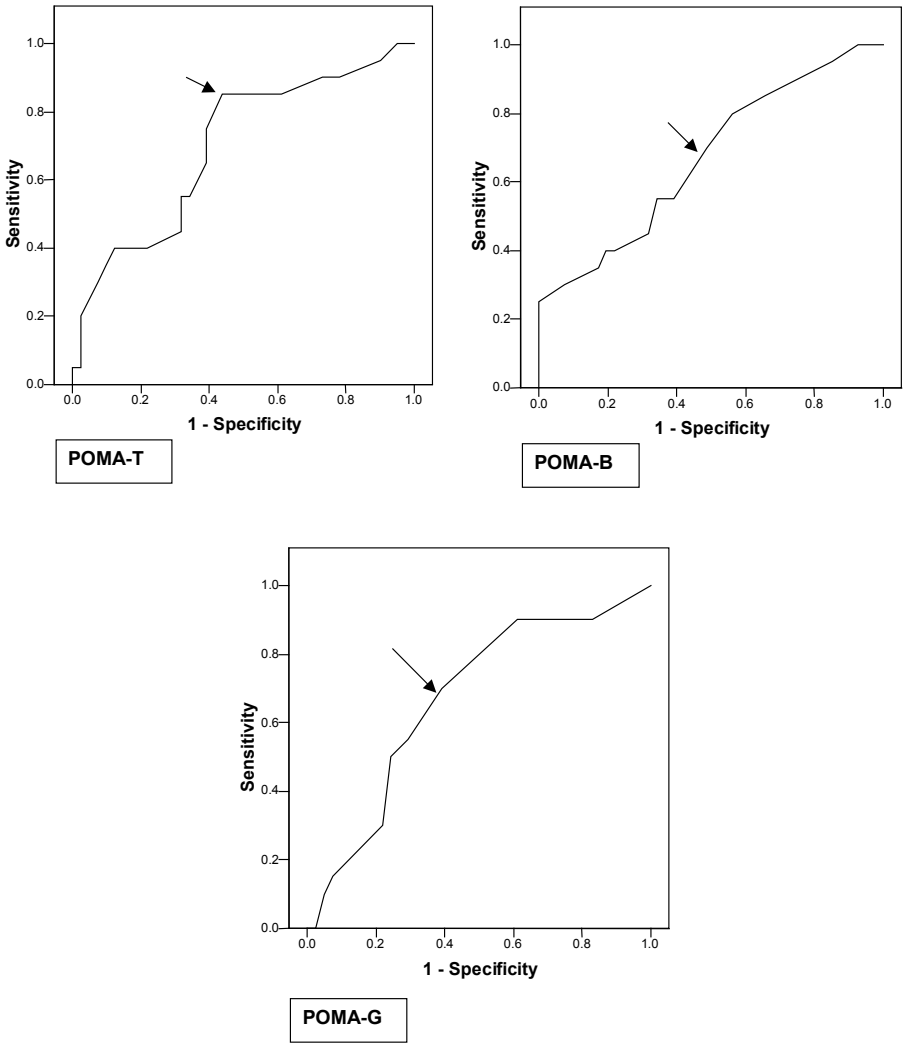

Figure 2 Receiver operating characteristic curves for POMA-T, POMA-B and POMA-G
Arrows indicate optimal cut-off points.

In the multivariate model with POMA-T, falls history, age and gender, POMA-T remained significantly associated with a fall within three months (Table 3). Each point lower on the POMA-T was associated with a 7.9% increase in fall risk. In the multivariate model with POMA-B, falls history, age and gender, the POMA-B subtest did not remain significant. In the multivariate model with POMA-G, falls history, age and gender, the POMA-G subtest was not significant.

Table 3 Associations between POMA-scores and the occurrence of a fall

	Unadjusted HR (95% CI) (per point lower)	p-value	Adjusted* HR (95%CI) (per point lower)	p-value
POMA-T	1.09 (1.01-1.17)	0.03	1.08 (1.00-1.17)	0.05
POMA-T[a] (n=44)	1.10 (1.00-1.20)	0.05		
POMA-T[b] (n=31)	1.07 (1.07-1.21)	0.34		
POMA-B	1.11 (1.01-1.23)	0.03	1.11 (1.00-1.23)	0.06
POMA-G	1.15 (0.97-1.36)	0.10	1.15 (0.96-1.38)	0.12

*Adjusted HR for age (continuous variable), gender and falls history.
[a]POMA-T scores for those without problems in understanding verbal instructions.
[b]POMA-T scores for those with problems in understanding at least one item of the verbal instructions. Interaction term p-value=0.73.

DISCUSSION

In this study population of nursing home residents with a diagnosis of moderate to severe dementia, we found a POMA-T score ranging from 6 to 28 (mean=18.7, sd=5.9), a POMA-B score ranging from 0 to 16 (mean=9.2, sd=4.1), and a POMA-G score ranging from 3 to 12 points (mean=8.7, sd=2.5). We found a good inter-rater reliability and an acceptable validity to predict a fall within three months. Nevertheless, the POMA can not be recommended yet as an assessment method for balance and gait in populations with moderate to severe dementia, because several feasibility problems were observed. We found that 41% of the participants had some degree of difficulty in following the instructions of the POMA due to cognitive impairment. The performance of the test is dependent on how well the participant can understand instructions. In this regard, the items of the balance subtest were particularly difficult to perform because they contain dual tasks. If a participant was unable to perform a certain item, he or she scored 0 points. When the score of a specific item is zero because of major cognitive problems, severity of dementia could have been the predictor of a fall rather than the balance or gait impairment. This stresses the need for further studies, focusing on the differences in performance of the POMA between persons who do or do not understand the instructions.

In our study, we did not find that the association between the test scores and fall risk was different in those who had difficulty in following verbal instructions and those who did not, but this could be due to lack of power. We found that participants with no problems in understanding verbal instructions had an increased fall risk of 10% per point lower on the POMA-T, whereas participants with problems in understanding verbal instructions showed a 7% increase of fall risk for each point lower. However, these differences were not significant. With larger samples, perhaps, significant differences in

results between participants who understand verbal instructions and those who do not would be identified.

Because of the low feasibility of the POMA in severe dementia, the performance of assessment methods that are less dependent on cognition should be evaluated, such as, for example, electronic walkway systems.[25]

The POMA has the advantage of ease of administration and low cost and was therefore chosen for initial testing, but our results show that its application is hampered by feasibility problems and alternatives should be considered after careful evaluation.

Other potential limitations of our study are related to our method of assessing inter-rater reliability. First, two raters working in the same room with a patient might provide opportunities for mutual influences. However, in the additional testing we observed that the inter-rater reliability between three raters remained good. Second, the reliability outcomes of the study might be overestimated, since reliability is likely to be influenced by variability in the tester's instructions, tone of voice, encouragement, and so on.

Our results support previous findings that, in general, the inter-rater reliability of the POMA is good to very good. In a study in cognitively intact community-dwelling older people, an inter-rater reliability for the POMA-T, as well as for the subscales, of over 0.95 was reported.[11] In another study in 30 residents living in either self-care or nursing-care resides, with a mean age 84.9 years, inter-rater reliabilities for the POMA-T and the subscales ranged from 0.80 to 0.93. In this study, none of the participants had dementia, or they had only mild cognitive impairment. Residents with moderate dementia were excluded.[13] In one study of 29 hospital inpatients and nursing home residents focusing on the inter-rater reliability of scores on the eight individual items of the POMA-B, *k* coefficients ranging from 0.40 to 1.00 were reported, indicating fair to good reliability.[26] None of the aforementioned studies on the inter-rater reliability of the POMA was carried out in a population of residents with dementia. One study on the reliability of a physiological test battery designed to assess fall risk in a population of 21 community-dwelling older people with mild to moderate Alzheimer's disease, reported an ICC of 0.90 for the balance range test.[27]

Our results on predictive validity are also comparable to previous studies. With regard to the predictive validity observed in our study, given optimal cut-off criteria, sensitivity ranged from 70% to 85% and the specificity ranged from 51% to 65%, with better predictive validity for the POMA-T than for the subtests only. In our opinion, the high sensitivity we found is more important than the lower specificity in our study. The identification of a large percentage of fallers within three months creates the opportunity for efficient intervention. For example, physical exercise has been shown to improve physical performance and reduce fall risk in a population of ambulatory nursing home residents with mild to severe Alzheimer's disease (n=134).[28] The consequences for the false positives, i.e. non-fallers who were not correctly identified, would not be harmful.

They will probably experience a fall during a longer follow-up period, and the interventions (e.g. physical exercise) are not likely to have any damaging side effects. A cut-off value of ≤ 21 for POMA-T therefore seems excellent.

In a study in which the same version of the POMA scale was used, a sensitivity of 64% for the POMA-T, as well as for the subscales, a specificity ranging from 62.5% to 66.1%, and cut-off values of 19 for POMA-T, 10 for POMA-B, and 9 for POMA-G were reported. In this study, a follow-up of 10 months was chosen.[13] In another study, a sensitivity of 70%, and a specificity of 52% were found for a group of 225 community-dwelling older people with a mean age of 80.0. In this study, the 40-point version and a one-year follow-up were chosen.[12]

With regard to the predictive accuracy, our study also has limitations. First, all residents were tested without their usual walking aid, which could have lowered the predictive accuracy. However, there are no studies known which show that walking with a walking aid can reduce falls.[4] Second, sampling error could have influenced our results on predictive validity. Although we obtained a high consent rate (87 of 109 eligible patients), consent may perhaps have been lower among legal guardians of residents in more severe stages of dementia and the predictive validity of the POMA may have been overestimated. Finally, a three-month follow-up is inconsistent with studies of other high risk populations, such as older people presenting to Emergency Departments after a fall, in which a one-year follow-up was chosen. However, the results of such studies cannot be extrapolated to people in residential care.[29]

Despite the described limitations, our results regarding the predictive validity are comparable with other studies and other populations, where longer follow-up times have been chosen. We expected that during a longer follow-up period almost the whole population would experience at least one fall or would be lost to follow-up. A three-month follow-up period was chosen, in the first place, to test the performance of the POMA for the timely recognition of fall risk in a frail population. In addition, a 12-month follow-up period, as recommended for community-dwelling older persons,[30] would have caused much difficulty in interpretation, since in our study population many participants would have shown changes in medication and physical status over such a period.

We conclude that application of the POMA in populations with moderate to severe dementia is hampered by feasibility problems. Its routine implementation in clinical practice cannot therefore be recommended, despite good reliability and an acceptable predictive validity.

To the best of our knowledge, this is the first study to assess the POMA in nursing home residents with moderate to severe dementia. However, because of the possible lack of sufficient power in our study, we do not know in detail if and how the prediction of fall risk differs between those who understood the instructions and those who did

not. To refine our findings, a large prospective study on the predictive validity of the POMA in a population with moderate tot severe dementia is needed, and should focus on the differences in understanding of instructions between those with mild, moderate and severe dementia. In addition, the performance of mobility assessment methods that are less dependent on cognition, and might therefore be more feasible, should be evaluated in nursing home residents with dementia.

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CHAPTER 4

An electronic walkway can predict short-term fall risk in nursing home residents with dementia

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ABSTRACT

Objectives To evaluate the feasibility and validity of gait parameters measured with an electronic walkway system in predicting short-term fall risk in nursing home residents with dementia.

Methods 57 ambulatory nursing home residents with moderate to severe dementia participated in this prospective cohort study. We used the GAITRite® 732 walkway system to assess gait parameters. Each measurement was followed by a three-month follow-up period, resulting in 176 measurements. Falls were retrieved from incident reports. The predictive validity of the GAITRite® parameters was expressed in terms of sensitivity and specificity. Logistic regression analysis was conducted to examine the association between these parameters and falls occurrence within three months.

Results Velocity (OR=1.22; 95% CI 1.04-1.43) and mean stride length (OR=1.19; 95% CI 1.03-1.40) were the best significant gait predictors of a fall within three months, with a sensitivity of 77-84% for velocity and 75-89% for mean stride length, and a specificity of 46%-53% for velocity and 47-60% for mean stride length. The test procedure took an average of 5 minutes per participant. Some verbal persuasion or physical cueing was necessary in 142 measurements (80.7%).

Conclusion Gait parameters as measured with an electronic walkway system can be used for the prediction of short-term fall risk in nursing home residents with moderate to severe dementia.

INTRODUCTION

Nursing home residents are at high risk of falls,[1-2] and the risk increases with concurrent dementia.[1]

However, if tailor-made preventive measures are taken in time, the number of falls in this population can be reduced significantly.[3] In order to take tailored preventive measures, the fall risk profile of each individual nursing home resident should be periodically evaluated. A systematic evaluation of fall risk should include an assessment of all major contributing components, including gait and mobility impairments.[4-6] Therefore, it is important to have an assessment method available, which can identify those at increased risk of a fall in the short term in this high risk population.

Gait parameters as measured with an electronic walkway system, the GAITRite® walkway, have been shown to be able to identify those at risk of a fall in the short term in a cohort of hospitalized older patients in an acute care geriatric department.[7] The feasibility and predictive validity of gait parameters as measured with the GAITRite® walkway, in predicting short-term fall risk in nursing home residents with moderate to severe dementia, however, has not yet been investigated. We focused on the prediction of fall risk in the short term (i.e. within three months after the test procedure), because in a frail population early recognition is of paramount importance.

The purpose of this study was to answer the following questions:

1. Is the GAITRite® walkway a feasible instrument to predict short-term fall risk in ambulatory nursing home residents with moderate to severe dementia?
2. Which of the GAITRite® parameters has the best predictive value with regard to fall risk in this specific population?

METHODS

Design and setting

This design was a prospective cohort study. The study took place over a period of 15 months, from April 11th 2006 till September 10th 2008 inclusive. The Medical Ethics Committee of the Erasmus University Medical Center approved the study.

Population and study period

Residents who lived in the psychogeriatric nursing home Smeetsland of the De StromenOpmaatGroep, Rotterdam, The Netherlands, and who were able to walk over a distance of at least 10 meters independently, were asked to participate in the study. Written informed consent was obtained from their legal guardians. All residents in the

nursing home met the DSM-IV-TR criteria for the diagnosis of dementia,[8] and were classified as dementia severity stage 5 or 6 on the Global Deterioration Scale (GDS).[9] We collected data between April 11th 2006 and September 10th 2008. Of the 220 nursing home residents who were resident in the study period, 110 were excluded because they were not able to walk over a distance of at least 10 meters independently, and 110 were eligible to participate in the study. The legal guardians of 59 residents gave their informed consent. Two residents fell and had a hip fracture before the first test took place. Finally 57 nursing home residents participated in the study.

Baseline data

We abstracted the following baseline data from medical records and nursing home charts: age, gender, and comorbid conditions that are considered potentially causative of falls. These comorbid conditions included: visual impairment (i.e. vision loss that could not be optically corrected), urinary incontinence, Parkinson's disease, arthritis and other joint diseases, depression and cardiovascular diseases.[10-11] The detailed methods of collecting baseline data are described elsewhere.[12]

Medication use

Daily medication use and dosage were recorded for each participant throughout the period that participant was in the study. We extracted data on the use and dose of antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants from the prescription database in the medical records.

GAITRite®

We used the GAITRite®-732 system (Biometrics France) to measure and record temporal and spatial parameters of gait. It has previously been demonstrated that the GAITRite®-system has good reliability.[13-14] The GAITRite®-system is a portable computer based electronic roll-up walkway with an overall dimension of 823 cm x 90 cm x 0.6 cm connected to a personal computer with application software for calculation of temporal and spatial parameters of gait. The active area of the walkway is 732 cm x 61 cm. Pressure sensors are embedded into the carpet in a horizontal grid. We followed the guidelines for clinical applications of spatial-temporal gait analysis in older adults.[15]

An experienced physiotherapist asked all participants to walk without a walking aid at their preferred walking speed across the carpet. The participants wore their own footwear. If the participant had difficulty in understanding the instruction, we allowed the physiotherapist to use any combination of verbal persuasion or physical cueing required to perform the walk. For each individual test, we noted the amount of verbal persuasion and physical cueing. Time needed to perform the whole testing procedure was recorded.

Spatial gait parameters used in this study were: stride length, and heel-to-heel base of support or base width. Temporal parameters used were: cadence (steps/minute), stride time, velocity, double support time. Variability in the GAITRite® parameters stride length, heel-to-heel base support, stride time, and double support time was expressed as coefficients of variation (CV).

The GAITRite® measurements were done with a maximum of five times per participant, once at the beginning of the study and then after three, six, nine, and twelve months. Each measurement was followed by a three-month follow-up period.

Falls

The staff in the nursing home, where the present study was conducted, are trained to record falls on a standardized incidence registration form,[16] as used in the national incidence registration to monitor quality of care in nursing homes in the Netherlands.[17] They complete the forms immediately when a fall has been witnessed or after a resident is found on the floor or any lower level.[18] A committee collects the forms and makes incidence reports. We gathered falls data from these reports from April 12th 2006 till December 10th 2008 inclusive.

Falls history

Because a positive falls history is a known risk factor for further falls,[10] we also collected data on falls in the previous year before the start of the study from this computer system, i.e. from April 12th 2005 till April 12th 2006.

Statistical analysis

We examined the relationship between each participant's Gaitrite® parameters at baseline and the occurrence of at least one fall within a three-month follow-up period. Because in this population physical status may change during one year, we repeated this procedure for each participant every three-months. Each time, a Gaitrite® measurements was done, it was considered as baseline measurement for the following three months. Because residents were tested repeatedly, we used logistic regression analysis based on the method of generalized estimating equations (GEE), in order to control for the correlated response data. Every three-month period was an observation unit with predictors and outcome; Participant id was used as the clustering variable. Odds ratios (ORs) with 95% confidence intervals (CI's) were calculated for Gaitrite® parameters, age, gender, falls history, comorbidities, and medication use.

Gaitrite® parameters that were significantly associated with a fall in the univariate analysis were included in multivariable models. We adjusted for age, gender, and other variables that were significantly associated with a fall in the univariate analysis.

The predictive validity was expressed in terms of sensitivity and specificity. The sensitivity was defined as the percentage of fallers within three months who were correctly identified. Specificity was defined as the percentage non-fallers within three months correctly identified. Optimal cut-off values were determined by plotting Receiver Operating Characteristic (ROC) Curves for the significant Gaitrite® parameters to determine the points that provided the best trade off between sensitivity and specificity. The Area under the Receiver Operating Characteristic Curves (AUCs) for the Gaitrite® parameters were also computed, with larger AUC indicating better predictive ability. It is a general rule that a test does not discriminate if ROC=0.5, is acceptable if 0.7≤ROC<0.8, is excellent if 0.8≤ROC<0.9, and is outstanding if ROC≥0.9.[19] Positive and negative predictive values were calculated for each cut-off score for the Gaitrite® parameters.

All data were analysed using SPSS statistics software, version 16.0 (SPSS INC. Chicago. Il).

RESULTS

Fifty-seven residents participated in the study, 28 were lost during the study period. Fifteen persons died, ten became dependent on a wheelchair, 3 refused further participation. We obtained a total of 176 measurements. Ten participants were tested five times, 17 were tested four times, ten were tested three times, eight were tested two times, and 12 participants were tested one time.

The mean age (sd) of the participants was 81.7 (7.0) years. Thirty-five times (19.5%) a participant experienced one fall during a three month follow-up period, 33 times (18.8%) a participant experienced more than one fall during a three-month follow-up period. The subject characteristics as well as GAITRite® performance data are shown in Table 1.

Feasibility

With regard to the feasibility of the GAITRite®, the test procedure took an average of 5 minutes (range 3-10 minutes) per participant to complete. Some verbal persuasion or physical cueing was necessary in 142 measurements (80.7%) to perform the test. In 111 (63.1%) measurements verbal persuasion was needed (the physiotherapist kept repeating: "walk on" to prevent that the participant stopped walking before or at the end of the walkway). In 87 (49.4%) measurements physical cueing was needed (the physiotherapist took the participant by the hand to prevent him/her from stopping before or at the end of the walkway).

Table 1 Subject characteristics and GAITRite® performance data

Characteristic	
Demographic data	
Mean age [years] (SD)	81.7 (7.0)
Female [n] (%)	104 (61.2%)
Visual impairment [n] (%)	39 (22.9%)
Urinary incontinence [n] (%)	67 (39.4%)
Arthrosis and other joint diseases [n] (%)	42 (24.7%)
Cardiovascular diseases [n] (%)	105 (61.8%)
Parkinson's disease [n] (%)	1 (0.6%)
Psychotropic drug use	
Antipsychotics [n] (%)	83 (48.8%)
Anti-anxiety drugs [n] (%)	41 (24.1%)
Hypnotics [n] (%)	36 (21.2 %)
Antidepressants [n] (%)	28 (16.5%)
GAITRite® parameters	
Velocity (cm/s) [mean] (sd)	62.8 (24.6)
Cadence (steps/min) [mean] (sd)	99.2 (16.0)
Stride-to-stride average	
Stride length (cm) [mean] (sd)	76.3 (26.2)
Heel-to-heel base of support (cm) [mean] (sd)	10.7 (4.0)
Stride time (sec) [mean] (sd)	1.3 (0.38)
Double support time (sec) [mean] (sd)	0.5 (0.4)
Stride-to-stride variability CV %	
Stride length [mean] (sd)	9.3 (5.4)
Heel-to-heel base of support [mean] (sd)	19.1 (11.7)
Stride time [mean] (sd)	9.6 (32.7)
Double support time [mean] (sd)	14.2 (35.6)

CV=coefficients of variation.
Total n=176 measurements.

Predictive validity

In the univariate analysis falls history (OR=2.77; 95% CI 1.34-5.71), age (OR=1.10; 95% CI 1.03-1.17), velocity (OR=1.27; 95% CI 1.07-1.51), mean stride length (OR=1.24; 95% CI 1.07-1.46), stride length variability (OR=2.16; 95% CI 1.13-4.14), heel-to-heel base of support variability (OR=1.54; 95% CI 1.16-2.03), and double support time variability (OR=1.50; 95% CI 1.03-2.44) were significantly associated with a fall within three months.

In the multivariable model falls history, age, velocity, mean stride length, heel-to-heel base of support variability, and double support time variability remained significantly associated with a fall within three months (Table 2).

Table 2 Multivariable odds ratios for falls

Characteristic	Unit of change	OR[a]	(95% CI)	p-value
Age (continuous variable)		1.09	1.03-1.16	<0.01
Gender				
Male		1.16	0.53-2.51	0.71
Female		ref		
Falls history		2.77	1.34-5.71	0.01
GAITRite® parameters				
Velocity (cm/s)	10 cm/s decrease	1.22	1.04-1.43	0.01
Mean stride length (cm)	10 cm decrease	1.19	1.03-1.40	0.02
Stride length variability (%CV)	10% increase	1.82	0.98-3.35	0.06
Heel-to-heel base of support variability (%CV)	10% decrease	1.49	1.15-1.93	<0.01
Double support time variability (%CV)	10% increase	1.54	1.05-2.25	0.03

[a]adjusted for age, gender, and falls history.

In Figure 1, as an example, the linear relationships between the significant Gaitrite® parameters (velocity, mean stride length, heel-to-heel base of support variability, and double support time variability) and fall risk are plotted for a male and a female participant at age 80 and 85 years. For the prediction of a fall in the short term, i.e. within three months, cut-off points for the Gaitrite® parameters velocity, mean stride length, heel-to-heel base of support variability, and double support time variability are presented in Table 3. The best predictive values were a velocity of 65-72cm/s (with a sensitivity of 77-84% and a specificity of 46-53%), a mean stride length of 81-91cm (with a sensitivity of 75-89% and a specificity of 47-60%), a covariance of 14-20% for the heel to heel

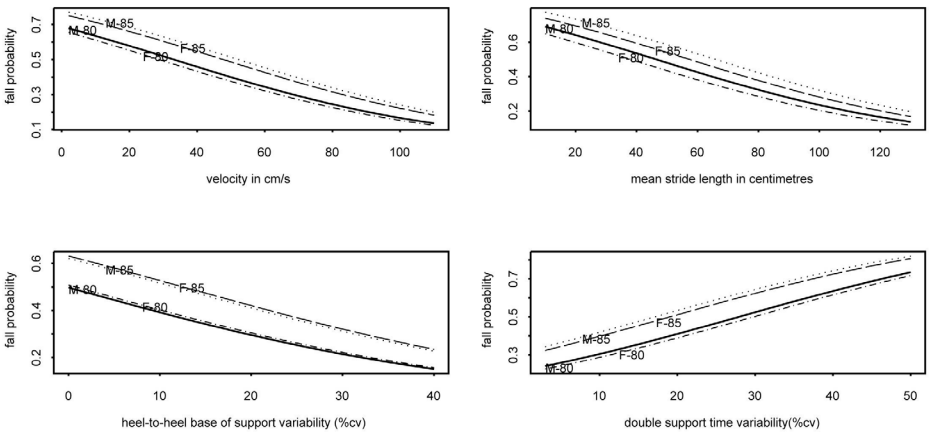

Figure 1 Linear relationships between the significant Gaitrite® parameters and fall risk
Linear relationships stratified at age 80 and 85 for a male and a female participant.

Table 3 Predictive validity of the significant Gaitrite® parameters

	AUC (95% CI)	p-value	cut-off score	sensitivity	specificity	PPV	NPV
Gait parameters							
Velocity (cm/s)	0.66 (0.58-0.74)	<0.01	65	77%	53%	48.0%	78.9%
			68	82%	52%	49.0%	81.9%
			72	84%	46%	46.8%	81.5%
Mean stride length (cm)	0.67 (0.59-0.75)	<0.01	81	75%	60%	49.5%	79.0%
			85	86%	52%	50.0%	84.3%
			91	89%	47%	48.2%	85.4%
Heel-to-heel base of support variability (%CV)	0.59 (0.51-0.68)	0.05	14	57%	33%	42.9%	67.3%
			17	60%	56%	43.5%	70.3%
			20	68%	46%	41.6%	70.1%
Double support time variability (%CV)	0.59 (0.50-0.68)	0.05	8	74%	41%	27.7%	58.6%
			9	63%	51%	29.6%	57.9%
			10	50%	61%	31.3%	57.1%

Abbreviations: AUC=Area under the Receiver Operating Characteristic Curve; PPV=positive predictive value; NPV=negative predictive value.

base support variability (with a sensitivity of 57-68% and a specificity of 33-46%), and a covariance of 8-10% for the double support time variability (with a sensitivity of 50-74% and a specificity of 41-61%).

The ROC curves for the Gaitrite® parameters velocity, mean stride length, heel-to-heel base of support, and double support time variability, are plotted in Figure 2. The AUC for velocity was 0.66 (p<0.01), for mean stride length 0.67 (p<0.01), for heel-to-heel base of support variability 0.59 (p=0.05), and for double support time variability 0.59 (p=0.05).

DISCUSSION

In this study population of nursing home residents with a diagnosis of moderate to severe dementia, we found that the GAITRite® is a feasible instrument to assess short-term fall risk. With regard to the predictive validity we found that the Gaitrite® parameters velocity, mean stride length, heel-to-heel base of support variability, and double support time variability were significant predictors of a fall within three months.

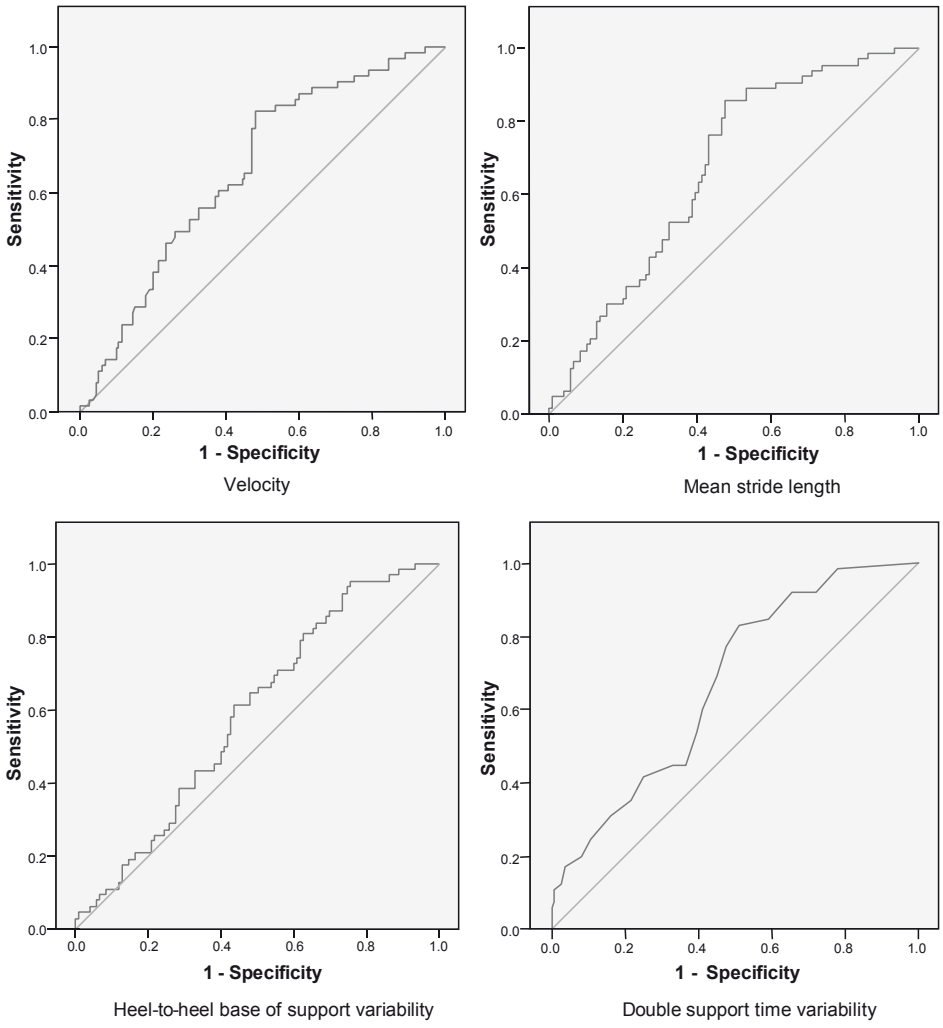

Figure 2 Receiver operating characteristic curves velocity, mean stride length, heel-to-heel base of support variability and double support time variability

As far as we are aware from the literature, this is the first study to report a positive predictive validity of the Gaitrite® system in predicting short-term fall risk in nursing home residents with moderate to severe dementia. The Gaitrite® parameters velocity and mean stride length performed comparable with the Tinetti Performance Oriented Mobility Assessment (POMA)[20] with regard to the predictive ability.[12] The POMA is an instrument to monitor gait and mobility, and is recommended as part of a multidisciplinary evaluation tool for fall risk in nursing home residents in the Netherlands.[4] However, in this population the use of the GAITRite® walkway is preferable because this instrument saves time

and is not hampered by feasibility problems and information losses as met with the application of the POMA.[12]

A potential limitation of this study concerns the small sample of 57 participants. However, by examining the relationship between GAITRite® scores and falls every three months, and controlling for the fact that participants were tested repeatedly, we extended the sample to 176 measurements.

With regard to the predictive accuracy, our study also has limitations. Sampling error could have influenced our results on predictive validity. Maybe consent was lower among legal guardians of residents in more severe stages of dementia, so the predictive validity of the Gaitrite® parameters may have been overestimated.

Another potential limitation concerns the possible differences in the amount of verbal persuasions and physical cueing. This might have influenced the psychometric properties of this task. However, each participant managed to complete the walk on the walkway without interruptions, so that for each participant we had the same measure while walking on the walkway.

Within the analysis, the cut-off values for determining sensitivity and specificity are based on post hoc examinations of the ROC curves. This might introduce a bias into the assessed performance (sensitivity and specificity). There could also be a bias in the performance of the logistic model as it is being used to derive the regression and demonstrate its performance.

In contrast with studies done in community dwelling older adults, we found that the reduced velocity and mean stride length were better predictors of falls than variability of gait parameters.[21-23] The results of our study also differ from other studies with comparable populations.[24-25] In a study of 97 nursing home residents with Alzheimer's disease (AD) (mean age 75.2), there was no significant difference between fallers and non-fallers in velocity and mean stride length over a two-year follow-up period.[25] In another study of patients with AD, velocity and mean stride length were not significant for predicting falls, probably due to a relatively small sample (n=42) compared with our sample of 176 measurements.[24]

The predictive validity of the GAITRite® parameters velocity and mean stride length is modest. The conventional fall risk predictor previous falls has a stronger association with fall risk than the gait variables. However, previous falls cannot be influenced and this study aimed to identify which potentially modifiable risk factors were most strongly associated with a fall in the next three months. We think that in spite of finding only modest relations, the GAITRite® parameters velocity and mean stride length create the opportunity for efficient and individualized tailor-made interventions. For example, physical exercise can improve physical performance and reduce fall risk in ambulatory nursing home residents with mild to severe AD.[26] Physical exercise has cognitive and physical benefits besides reducing fall risk, and should be applied to all nursing home

residents with dementia. However, because of healthcare costs, not every resident can get individual instructions from a physiotherapist. In physical therapy, gait training may focus on increasing gait velocity, which may also change other important factors of gait.[27] Given the high risk of falls in nursing home residents with dementia, we imagine that a retained ability to increased velocity and mean stride length, may be ideal candidates for interventions aimed at preventing falls.

If the use of the GAITRite® walkway in practice is hindered because of cost constraints, we believe that gait velocity can alternatively be measured using a stopwatch. Previous research has shown that the concurrent validity of gait velocity determined from a timed corridor walk compared with velocity using the GAITRite® walkway is excellent, with an intraclass correlation coefficient of 0.95.[27] Using a stopwatch could be an alternative for identifying nursing home residents at risk of a fall within three months.

Conclusion

Gaitrite parameters as measured with an electronic walkway system can be used for the prediction of short-term fall risk in nursing home residents with moderate to severe dementia.

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PART 2

Fall risk and psychotropic drug use

CHAPTER 5

The influence of drug use on fall incidents among nursing home residents: A systematic review

Sterke CS, Verhagen AP, van Beeck EF, van der Cammen TJ. Int Psychogeriatr 2008;20:890-910.

ABSTRACT

Background Falls are a major health problem among the elderly, particularly in nursing homes. Abnormalities of balance and gait, psychoactive drug use, and dementia have been shown to contribute to fall risk.

Methods We conducted a systematic review of the literature to investigate which psychoactive drugs increase fall risk and what is known about the influence of these drugs on gait in nursing home residents with dementia. We included studies with a prospective cohort design on psychoactive drug use in nursing homes with dementia residents and with falls as an outcome measure.

Results Seventeen studies were included in the review. Pooled risk estimates were not calculated because there was no homogeneity across studies. We assessed the strength of evidence for psychoactive drugs as a prognostic factor for falls by defining four levels of evidence: strong, moderate, limited or inconclusive. Strong evidence was defined as consistent findings (≥ 80%) in at least two high quality cohorts. We found strong evidence that the use of multiple drugs (3/3 cohorts, effect sizes 1.30-10.30), antidepressants (10/12 cohorts, effect sizes 1.10-7.60), and anti-anxiety drugs (2/2 cohorts, effect sizes 1.22-1.32) is associated with increased fall risk. The evidence for the association of other psychoactive drug classes with fall risk was limited or inconclusive.

Conclusions Research on the contribution of psychoactive drugs to fall risk in nursing home residents with dementia is limited. The scarce evidence shows, however, that multiple drugs, antidepressants and anti-anxiety drugs increase fall risk in nursing home populations with residents with dementia.

INTRODUCTION

Falls are a major health problem among the elderly, particularly in nursing homes.[1-4] Abnormalities of balance and gait,[5-7] psychoactive drug use,[5, 8-9] and dementia[10-11] have been shown to contribute to fall risk. Gait and balance problems usually occur in the more advanced stages of dementia,[12] and might be due to the use of psychoactive drugs such as antipsychotics, antidepressants and sedatives.[13]

It is generally known that nursing home residents with dementia have an increased fall risk, however, the additive effect of psychoactive drugs to fall risk in such residents is not known. Also, the mechanisms by which psychoactive drugs increase fall risk (i.e. the influence on gait) are not known. As a high proportion of nursing home residents with dementia are treated with psychoactive drugs, better knowledge of the influence of these medications on fall risk might be useful to prevent further falls. If we know the influence of psychoactive drugs on gait, we can use gait measurements to evaluate the influence of drugs on gait and on subsequent fall risk. We therefore undertook a systematic review of the literature to investigate which psychoactive drugs increase fall risk and what is known about the influence of these drugs on gait in nursing home residents with dementia.

METHODS

Search strategy

Between 1980 and 31 October 2007 inclusive we performed a broad literature search of Medline, Cinahl, Cochrane, and Psychlit. The following search terms were used: dementia, cognitive impairment, nursing home resident, elderly, older adult; fall, gait, mobility test; drugs, psychoactive medication, psychotropics, antidepressants, benzodiazepines, antipsychotics, sedatives. Randomized controlled trials on drug withdrawal as an intervention and prospective cohort studies published until November 2007 were eligible for inclusion in the review.

Study selection

Two reviewers independently performed the study selection (CS and TC). Differences in opinion were resolved by discussion between the two reviewers. First, titles and abstracts of identified published articles were reviewed in order to determine their relevance. Next, full papers were screened for eligibility. Studies were selected if they met the following criteria: (1) residents with dementia were included in the study population of nursing home residents; and (2) psychoactive medication use was studied. The outcome measures selected were: (1) falls (our primary outcome measure), and (2) gait

parameters (our secondary outcome measure, as a possible predictor of risk of falling). If residents with advanced dementia were excluded from participation in a study, we excluded that study from our analysis.

The two reviewers (CS and TC) independently appraised each full text article that passed the first eligibility screening, using a structured form to record our selection criteria. Excluded studies and reasons for exclusion were recorded. The references of all identified relevant studies were individually searched for additional potentially relevant publications. For feasibility reasons, the publication had to be written in English, French, German, or Dutch.

Quality assessment

The two reviewers (CS and TC) assessed the methodological quality of the studies independently, using the nine-item checklist for quality assessment of prospective cohort studies from the Dutch Cochrane Centre website.[14] Each item was scored as positive, negative (potential bias), or "not enough information provided," if the paper provided insufficient information on a specific item. Differences in scores were resolved by discussion between the two reviewers, and a third reviewer (AV) was consulted if disagreements could not be resolved.

At item nine of the checklist it was decided if the results of the study were valid and applicable. Item nine was scored as positive if six or more items scored positive. The study was then considered as high quality. Item nine was scored as dubious or negative if fewer than six items scored positive, and the study was then considered as low quality.

Data extraction

One reviewer (CS) extracted data concerning population characteristics (mean age, gender, cognitive status, dementia severity) and sample size using a structured data collection form. Two reviewers (CS and AV) extracted information and data regarding primary (falls) and secondary (gait parameters) outcome measures, determinants (psychoactive drug use), follow-up period, associations, and adjustments for confounding if reported by the authors, using a standardized form for data extraction from prospective cohort studies from the Dutch Cochrane Centre website.[14] In case of disagreement, consensus was achieved by discussion between the two reviewers.

Analysis

The inter-observer agreement of quality assessment was derived by kappa statistics because of dichotomous values. An inter-observer agreement of k=0.60 to 0.80 represents a good agreement. An inter-observer agreement of k=0.80 to 1.00 represents a very good agreement.[15]

Pooled risk estimates were not calculated because there was no homogeneity across studies concerning similar drug classes and outcome measures.

Four levels of evidence were defined to assess the strength of evidence for prognostic factors, i.e. strong, moderate, limited and inconclusive (Table 1). Strong evidence was defined as consistent findings (≥ 80%) in at least two high quality cohorts.[16-17] In the case of dichotomous outcomes, positive clinical relevant findings were considered relative risks (RRs), odds ratios (ORs) or hazard ratios (HRs)>2.0 or <0.5 or else significant associations ($p<0.05$).[18] If provided by the authors, positive findings were derived from the multivariate results. If only univariate results were available, we used these findings to determine the level of evidence.

Table 1 Levels of evidence for prognostic factors

Level of evidence	
Strong	Consistent findings (≥ 80%) in at least two high quality cohorts
Moderate	One high quality cohort and consistent findings (≥ 80%) in one or more low quality cohorts
Limited	Findings in one cohort or consistent findings in one or more low quality cohorts
Inconclusive	Inconsistent findings irrespective of study quality

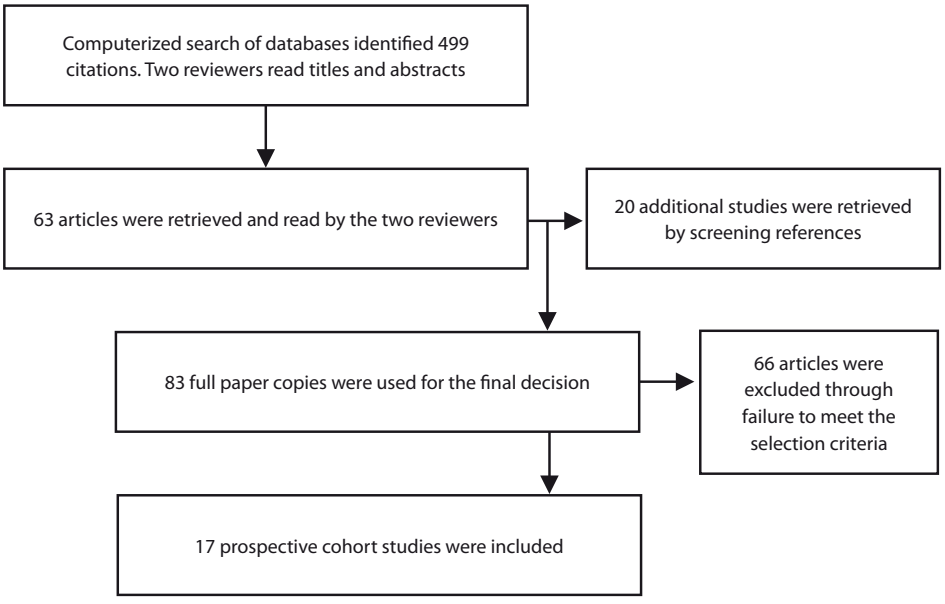

Figure 1 Flow diagram of papers accepted and rejected by the reviewers during the selection procedure

RESULTS

Search strategy

The search of the computerized databases identified a total of 499 citations. Based on title and abstract, 63 papers were selected, and a full copy of each paper was applied for and used for the final decision. Screening of the references of all relevant papers resulted in 20 additional studies, making a total of 83. Of these, 43 papers were excluded because the design was either a case control study, or a case report; 20 were excluded because the study population did not include nursing home residents with dementia or cognitive impairment; and three because they did not describe psychoactive medication as a determinant for falls. In 25 of the 66 excluded papers, falls were not described as an outcome measure. Randomized controlled trials on drug withdrawal as an intervention were not available.

Table 2 Results of the quality assessment, showing numeration of the quality items from the Dutch Cochrane Center checklist[14]

	Methodological items									
Cohort name	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Quality score**
Arfken et al., 2001	1	1	1	1	0	1	?	1	1	7
Avidan et al., 2005	1	1	1	0	?	1	1	1	1	7
Capezuti et al., 1996	1	1	1	1	0	1	1	1	1	8
Cooper et al., 2007	0	1	1	1	0	1	?	1	1	6
van Doorn et al., 2003	1	1	1	1	0	1	?	1	1	7
Hien et al., 2005	1	1	1	1	0	0	1	1	1	7
Kiely et al., 1998	0	1	1	0	?	1	1	1	1	6
Kuchynka et al., 2004	0	1	?	1	0	1	?	1	?	4
Lipsitz et al., 1991	1	1	1	1	0	1	1	1	1	8
Lord et al., 2003	0	1	0	1	0	1	1	1	1	6
Ray et al., 2000	1	1	1	1	0	1	1	1	1	8
Ray et al., 2002	1	1	1	1	0	1	1	1	1	8
Rosendahl et al., 2002	1	1	1	1	0	1	0	1	1	7
Ruthazer and Lipzitz, 1993	1	1	1	1	0	0	1	1	1	7
Thapa et al., 1995	1	1	1	1	0	1	1	1	1	8
Thapa et al., 1996	1	1	1	1	?	1	1	1	1	8
Thapa et al., 1998	1	1	1	1	0	1	1	1	1	8

Quality items: sufficient description study population (item 1); exclusion of selection bias (item 2); sufficient description determinant (item 3); sufficient description outcome (item 4); is the outcome blinded for the determinant? (item 5); sufficiently long follow-up (item 6); information on completers versus loss to follow up (item 7); information on confounders (item 8); validity results (item 9). Items are scored as positive scores (1), negative (0), or unclear (insufficient information) (?).

Table 3 Summary of study characteristics

Cohort	Population	Determinants	Outcome measures
Arfken *et al*., 2001 Q=7	N=368 Memory problems 43.7% Age ± 80 Female ± 70%	Antidepressant (Selective serotonine- reuptake inhibitor and Non- Selective serotonine-reuptake inhibitor) use	Falls (incident reports and fall logs) Injurious falls
Avidan *et al*., 2005 Q=7	N=34163 Moderately -very severely cognitive impaired 77.3% Age 84.2 (7.7) Female 76.5%	Hypnotic use	Falls (The Resident Assessment Instrument/ Minimum Data Set)
Capezuti *et al*., 1996 Q=8	N=322 Severely cognitive impaired 27.6% Age ± 84 (7.3)	Psychoactive drug use	Falls (incidence reports)
Cooper *et al*., 2007 Q=6	N=177 Age 81.8 (10.7) Female 79%	No. Psychotropic drug use	Falls (patient charts)
van Doorn *et al*., 2003 Q=7	N=2015 Demented 48.2% Age 81.4 (7.6) Female 70.4%	Antipsychotic, Antianxiety, Antidepressant medication use	Falls (nursing home charts)
Hien *et al*., 2005 Q=7	N=898 Mean age 85.7 Female 76%	Antidepressant, Sedatives/ anxiolytics, Typical antipsychotic, Olanzapine, Risperidone use	Falls (incidents reports and medical records)
Kiely *et al*., 1998 Q=6	N=18855 Cognitive impaired 82% Median age 87 Female 84%	Antipsychotic and Antianxiety medication use	Falls (The Resident Assessment Instrument/ Minimum Data Set)

Crude estimates and 95% CI	Adjusted estimates and 95% CI	Notes
	Selective serotonine- reuptake inhibitor OR=2.01 (1.23-3.28) Non- Selective serotonine-reuptake inhibitor OR=1.40 (0.65-3.03) Selective serotonine- reuptake inhibitor OR=1.77 (1.0-3.13)	Adjusted for age, number of medications, number of diagnoses, gender, memory problems, restraints.
OR=1.29 (1.13-1.48)	OR=1.13 (0.98-1.30)	Adjusted for age, sex, functional status, cognitive status, intensity of resource utilization, burden of illness, number of medications taken, emergency department visits, and new admission.
OR=1.78 (1.14-2.79)	Not provided	Table provides unadjusted estimates, the text shows the same figures as adjusted estimates.
1 psychotropic RR=1.8 (1.21-2.84) 2 psychotropics RR=3.2 (2.25-4.51) 3 psychotropics RR=6.7 (4.15-8.53) 4 psychotropics RR=10.3 (6.91-12.8)		
Antipsychotics RR=1.83 (1.48-2.26) Antianxiety medication RR=1.32 (1.01-1.72) Antidepressants RR=1.44 (1.08-1.90)	Not provided	
Antidepressants HR=1.56 (1.19-2.04) Sedatives/ anxiolytics HR=1.37 (1.10-1.72) Typical antipsychotic HR=1.48 (0.96-2.26) Olanzapine HR=2.35 (1.43-3.87) Risperidone HR=1.70 (0.75-3.87)	Antidepressants HR=1.45 (1.09-1.93) Sedatives/ anxiolytics HR=1.19 (0.94-1.50) Typical antipsychotic HR=1.35 (0.87-2.09) Olanzapine HR=1.74 (1.04-2.90) Risperidone HR=1.32 (0.57-3.06)	Adjusted for other psychotropics in the model, age, sex, type of residential care facility, length of stay, residential Classification Scale score, Implicit illness severity scale, MMSE-score, Parkinson's disease, previous falls, static balance score.
Antipsychotic OR=1.21 (1.11-1.33) Antianxiety OR=1.22 (1.11-1.33)	Not provided	

Table 3 Summary of study characteristics (continued)

Cohort	Population	Determinants	Outcome measures
Kuchynka *et al*., 2004 Q=4	N=314 Demented 31.8% Age ± 82 Female 67%	Benzodiazepine use	Falls (incidence reports)
Lipsitz *et al*., 1991 Q=8	N=126 Cognitive impaired N=40 Mean age 87 Female 61%	Antidepressant and Sedative medication use	Falls (incidence and computer reports, medical records, and subject interview)
Lord *et al*., 2003 Q=6	N=228 N=demented? Age 85 (7.4) Females 72 %	Sedatives, Antipsychotics, Antidepressants, Any psychotropic, ≥ 2 psychotropics	Falls (incidence reports and medical records)
Thapa *et al*., 1998 Ray *et al*., 2000 Ray *et al*., 2002 Q=8	N=2428 (Ray 2000 N=2510) Mean age 82 Major cognitive impairment 22% Female 75 %	Benzodiazepine Antidepressant (Tricyclic antidepressants, Selective serotonine-reuptake inhibitor, and Trazodone use) Antipsychotic and other sedatives/ hypnotic specific drug use	Falls (incidence reports and medical records)

Crude estimates and 95% CI	Adjusted estimates and 95% CI	Notes
Not provided	Not provided	Prevalence: 27 % of the fallers were benzodiazepine users, 25 % of the non-fallers were benzodiazepine users.
Antidepressant OR=5.67 (1.57-20.48) Sedatives OR=1.95 (0.89-4.30)	Antidepressant OR=7.6 (1.6- 35.3)	Adjusted for Medication variables: cardiovascular, neuroleptic, sedative, non-steroidal anti-inflammatory; Physical examination variables: visual acuity, impaired hearing, impaired vibration sensation, impaired position sensation, impaired touch sensation, lower extremity muscle weakness, increased muscle tone, apraxia combing hair, dysmetria, orthopedic deformity, orthostatic dizziness, orthostatic hypotension; Functional examination variables: unsteady (eyes open/closed), unsteady (sternal push), intermittent turning, unsteady turning, chair stand, broad stance, hesitant gait initiation, reduced step height, reduced step length, step asymmetry, step discontinuity, path deviation, trunkal instability; Continuous functional gait variables: chair stand, > 25 steps/ 20 foot walk, > 18.8 sec/20 foot walk, > 9.1 sec to turn 360, > 12 steps to turn.
Sedatives IRR=1.27 (1.01-1.60) Antipsychotics IRR=1.27 (0.92-1.75) Antidepressants IRR=1.34 (1.05-1.72) Any psychotropic IRR=1.47 (1.20-1.81) ≥ 2 psychotropics IRR=1.30 (1.00-1.69)	Any psychotropic IRR=1.36 (1.05-1.76)	Adjusted for age, sex, resident classification score, Implicit illness severity score, SMMSE, Parkinson's disease, stroke, day incontinence, night incontinence, osteoarthritis in either/both knees, fall in previous year, walking aid, ≥4 medications, visual contrast sensitivity, proprioception, quadriceps strength, reaction time, sway-on floor, sway-on foam, static balance, sit-to-stand ability.
Tricyclic antidepressant RR=2.4 (2.1-2.6) Nortriptyline RR=2.3 (2.0-2.5) Amitriptyline RR=2.2 (2.0-2.5) Doxepin RR=2.4 (2.1-2.8) Imipramine RR=2.6 (2.2-3.1) Other RR=3.1 (2.5-3.9)	Tricyclic antidepressant RR=2.0 (1.8-2.2) Nortriptyline RR=2.0 (1.8-2.3) Amitriptyline RR=1.9 (1.7-2.1) Doxepin RR=2.0 (1.7-2.3) Imipramine RR=2.2 (1.8-2.6) Other RR=2.4 (1.9-3.0)	Adjusted for age, gender, race, time since Admission to facility and since cohort entry, body mass index, ambulatory status, number of activities of daily living with total dependency, incontinence, cognitive impairment, physical restraint use, past falls, use of anticonvulsants, antiparkinson drugs, antidepressants, antipsychotics, and other sedatives.

Table 3 Summary of study characteristics (continued)

Cohort	Population	Determinants	Outcome measures

Crude estimates and 95% CI	Adjusted estimates and 95% CI	Notes
	Selective serotonine-reuptake inhibitors < 20 mg RR=1.5 (1.3-1.7) ≥ 20 mg RR=1.9 (1.7-2.2)	
Selective serotonine-reuptake inhibitors RR=2.4 (2.2-2.6)	Selective serotonine-reuptake inhibitors RR=1.8 (1.6-2.0)	
Paroxetine RR=2.3 (2.1-2.6)	Paroxetine RR=1.7 (1.5-1.9)	
Fluoxetine RR=2.4 (2.1-2.8)	Fluoxetine RR=1.8 (1.6-2.1)	
Sertraline RR=2.6 (2.3-3.0)	Sertraline RR=1.8 (1.5-2.1)	
	Trazodone < 50 mg RR=1.5 (1.2-1.8) ≥ 50 mg RR=1.1 (1.0-1.3)	
Trazodone RR=1.9 (1.7-2.1)	Trazodone RR=1.2 (1.0-1.4)	
	Baseline benzodiazepines RR=1.02 (0.95-1.10) Tricyclic antidepressant ≤ 10 mg RR=1.2 (1.0-1.5) 11-25 mg RR=2.0 (1.8-2.3) 26-50 mg RR=2.1 (1.8-2.3) > 50 mg RR=2.4 (2.1-2.8)	
	Current benzodiazepines RR=1.44 (1.33-1.56) Dose current users ≤ 2 mg RR=1.30 (1.12-1.52) 2.01- 4 mg RR=1.34 (1.20-1.51) 4.01-8 mg RR=1.38 (1.20-1.51) > 8 mg RR=2.21 (1.89-2.60) Days since start of use < 7 RR=2.96 (2.33-3.75) 7-29 RR=2.23 (1.64-3.03) ≥ 30 RR=1.30 (1.17-1.44) Elimination half-life, hours	

Table 3 Summary of study characteristics (continued)

Cohort	Population	Determinants	Outcome measures
			Daytime falls
			Nighttime falls
Rosendahl *et al*., 2003 Q=7	N=78 Demented 47 % Age 81 (6) Female 72%	Tranquilizers/ sedatives, Antidepressant use	Falls (register form and reported to study nurse)
Ruthazer and Lipsitz, 1993 Q=7	N=635 N=demented ? Mean age 88.7 Female 77%	Antidepressant, Antipsychotic, Benzodiazepine use	Falls (computerized documentation systems and chart reviews)
Thapa *et al*., 1995 Q=8	N=282 Moderate – severely cognitive impaired 68.8% Age 80.9 Female 72%	Any psychotropic drug, Antipsychotics, Benzodiazepines, Cyclic antidepressants, Other anxiolytics / hypnotics, Multiple psychotropic drug use	Recurrent falls ≥2 (incidence reports and nursing home charts)

Crude estimates and 95% CI	Adjusted estimates and 95% CI	Notes
	< 12 RR=1.15 (0.94-1.40) 12-23 RR=1.44 (1.33-1.59) ≥ 24 RR=1.73 (1.40-2.14)	
	Current benzodiazepine use RR=1.38 (1.25-1.51) Elimination half-life, hours < 12 RR=0.90 (0.70-1.17) 12-23 RR=1.43 (1.29-1.59) ≥ 24 RR=1.77 (1.38-2.26)	
	Current benzodiazepine use RR=1.83 (1.55-2.15) Elimination half-life, hours < 12 RR=2.19 (1.59-3.03) 12-23 RR=1.68 (1.39-2.02) ≥ 24 RR=1.80 (1.14-2.83)	
Tranquillizers/ sedatives HR=1.66 (0.93-2.96) Antidepressants HR=1.93 (1.05-3.52)	Not provided	
Antidepressants (women) OR=1.95 (1.02-3.70)	Antidepressants (women) OR=1.84 (0.91-3.69)	Stratified for sex. Adjusted for age and fall history
Any psychotropic drug IDR=1.67 (1.10-2.5) Antipsychotics IDR=1.54 (0.88-2.7) Benzodiazepines IDR=1.70 (0.96-2.9) Cyclic antidepressants IDR=1.98 (0.97-4.0) Other anxiolytics / hypnotics IDR=1.26 (0.57-2.7) Multiple psychotropic drugs IDR=1.89 (1.10-3.2)	Any psychotropic drug IDR=1.97 (1.28-3.05) Antipsychotics IDR=1.48 (0.79-2.78) Benzodiazepines IDR=2.10 (1.17-3.76) Cyclic antidepressants IDR=2.92 (1.39-6.16) Other anxiolytics / hypnotics IDR=1.23 (0.55-2.76) Multiple psychotropic drugs IDR=2.57 (1.45-4.57)	Adjusted for age, assisted activities of daily living, balance score, symptoms of dementia and depression, other psychotropic drug use.

Table 3 Summary of study characteristics (continued)

Cohort	Population	Determinants	Outcome measures
Thapa *et al.*, 1996 Q=8	N=503 Moderate and Severe cognitive impaired N N=218 Age 37.2% ≥85 Female 73%	Psychotropic drug use (Antipsychotics, Benzodiazepines, Cyclic antidepressants/ Trazodone, other Hypnotics/ anxiolytics)	Injurious falls (incidents reports and nursing home charts)

Abbreviations: Q=quality score; OR=odds ratio; RR=relative risk; HR=hazard ratio; IRR=incidence rate ratio; IDR=incidence density ratio.

At the end of this selection process, 17 prospective cohort studies were included in this systematic review (see Figure 1).

Quality assessment

The two reviewers were in agreement on 135 out of 153 items. The inter-observer agreement was *k*=0.72. Disagreement occurred mainly because of reading errors and interpretation of the methodological criteria list and was readily resolved. The results of the quality assessment are presented in Table 2.

Most methodological shortcomings concerned the following items: an insufficient description of the study population (item 1); an insufficient description of the determinant (item 3); an insufficient description of the outcome (item 4); is the outcome blinded for the determinant? (item 5); an insufficiently long follow-up (item 6); and no information on completers versus loss to follow-up (item 7). Sixteen studies were considered as high quality; one study was considered as low quality.

Study characteristics

The studies that qualified for inclusion in our review presented their data for total groups of nursing home residents, without a specific sub-group analysis for those with dementia or some cognitive impairment. We therefore analyzed the total groups as this was the nearest possible solution to our initial approach. Table 3 presents a summary of the study characteristics including sample size and population characteristics; determinants of our interest; outcome; crude and adjusted estimates with their 95% confidence intervals. Table 3 also provides information on adjustments for confounding of the final statistical analysis if reported by the authors.

The sample size varied between n=78[19] and n=43163.[20] The shortest follow-up period was one month,[21-22] the longest two years.[11, 23]

Falls

Most studies ascertained falls from medical records or nursing home charts and from incidence reports.[21-22, 24-30] In one study falls were ascertained from a subject interview,[23]

Crude estimates and 95% CI	Adjusted estimates and 95% CI	Notes
Unadjusted incidence rates, per 100 person-years	Adjusted incidence density ratios	Adjusted for age, gender, BMI, cognitive impairment
Psychotropic drugs IDR=23.4	Psychotropic drugs IDR=2.49 (1.43-4.33)	

and in another from the registration form and reported to a study nurse.[19] In six studies falls were ascertained only from incidence reports.[31-32] or nursing home charts.[11, 20, 33-34]

Gait parameters

None of the studies described gait parameters as outcome measure for psychoactive drug use. Some studies described gait parameters as determinants for falls.[11, 19, 23, 30, 32]

Psychoactive drug use

In most studies drug use is the determinant of primary interest.[20-22, 24-29, 34] In other studies psychoactive drugs are studied among other risk factors to develop or to evaluate a fall risk model.[19, 23, 30, 33] One study described the effect of restraint use on falls, with drug use being a confounder in their multiple logistic regression model.[31] In another study, dementia is the factor of primary interest. Other variables, including antipsychotic, anti-anxiety and antidepressant drug use were evaluated as potential confounders.[11]

The Minimum Data Set (MDS)[35] was used by most studies to ascertain psychoactive drug use.[11, 20, 33] Other studies used pharmacy records,[29, 34] medical records,[21, 30] or medication administration records.[22-25, 27-28, 31] Some studies provided information on dose or duration of use.[26-28, 31] In one study, psychoactive drug use was calculated as the proportion of days when psychoactive drugs were used divided by the number of days the resident was present in the nursing home; drug use was categorized by degrees of use as "none," "some" (1–98 days), and "all" (daily use).[31] In two studies, benzodiazepine use was classified for each day of follow-up as "current" (taken that day), "recent", or "none".[27-28] One study considered dose, duration and elimination half-life in relation to falls. Elimination half-life was also considered in relation to daytime and night-time falls.[27] In one study any recent change in medication and the time when medications were taken in relation to the fall were recorded, and a blood sample was obtained to check any relevant drug level. [23] In only one study is it unclear as to how drug use was ascertained.[32]

Table 4 Qualitative summary of the available evidence

Psychoactive drugs	Outcome	Cohort assessed	+ Findings	+ High quality	+ Low quality	- Findings	-High quality	-Low quality	Level of evidence
Any psychoactive drug	Falls	42	28/42 (67%)	28	-	14/42 (33%)	13	1	Inconclusive
	Recurrent falls	1	1/1 (100%)	1	-	-	-	-	Limited yes
	Injurious falls	2	2/2 (100%)	2	-	-	-	-	Strong yes
Benzodiazepines, Hypnotics, Sedatives, or Anti-anxiety drugs	Falls	11	5/11 (45%)	5		6/11 (55%)	5	1	Inconclusive
	Recurrent falls	2	1/2 (50%)	-	-	1/2 (50%)	-	-	Inconclusive
Hypnotics	Falls	2	-	-	-	2/2 (100%)	2	-	Strong no
	Recurrent falls	1	-	-	-	1/1 (100%)	1	-	Limited no
Sedatives	Falls	4	1/4 (25%)	1	-	3/4 (75%)	3	-	Inconclusive
Anti-anxiety drugs	Falls	2	2/2 (100%)	2	-	-	-	-	Strong yes
Benzodiazepines	Falls	3	2/3 (67%)	2	-	1/3 (33%)	-	1	Inconclusive
	Recurrent falls	1	1/1 (100%)	1	-	-	-	-	Limited yes
	Daytime falls	1	1/1 (100%)	1	-	-	-	-	Limited yes
	Nighttime falls	1	1/1 (100%)	1	-	-	-	-	Limited yes
Benzodiazepines elimination half-life < 12 hours	Falls	1	-	-	-	1/1 (100%)	1	-	Limited no
	Daytime falls	1	-	-	-	1/1 (100%)	1	-	Limited no
	Nighttime falls	1	1/1 (100%)	1	-	-	-	-	Limited yes
Benzodiazepines elimination half-life ≥ 12 hours	Falls	1	1/1 (100%)	1	-	-	-	-	Limited yes
	Daytime falls	1	1/1 (100%)	1	-	-	-	-	Limited yes
	Nighttime falls	1	1/1 (100%)	1	-	-	-	-	Limited yes
Antipsychotics	Falls	7	3/7 (43%)	3	-	4/7 (57%)	3	-	Inconclusive
	Recurrent falls	1	-	-	-	1/1 (100%)	1	-	Limited no
Typical antipsychotics	Falls	1	-	-	-	1/1 (100%)	1	-	Limited no
Risperidone	Falls	1	-	-	-	1/1 (100%)	1	-	Limited no

Table 4 Qualitative summary of the available evidence (continued)

Psychoactive drugs	Outcome	Cohort assessed	+ Findings	+ High quality	+ Low quality	- Findings	-High quality	-Low quality	Level of evidence
Olanzapine	Falls	1	1/1 (100%)	1	-	-	-	-	Limited yes
Antidepressants	Falls	12	10/12 (83%)	10	-	2/12 (17%)	2	-	Strong yes
Tricyclic antidepressants	Falls	2	2/2 (100%)	2	-	-	-	-	Strong yes
	Recurrent falls	1	1/1 (100%)	1	-	-	-	-	Limited yes
SSRIs	Falls	2	2/2 (100%)	2	-	-	-	-	Strong yes
	Injurious falls	1	1/1 (100%)	1	-	-	-	-	Limited yes
Non-SSRIs	Falls	1	-	-	-	1/1 (100%)	1	-	Limited no
Trazodone	Falls	1	1/1 (100%)	1	-	-	-	-	Limited yes
Multiple psychotropic drugs	Falls	3	3/3 (100%)	3	-	-	-	-	Strong yes
	Recurrent falls	1	1/1 (100%)	1	-	-	-	-	Limited yes

Positive findings: the association between the use of psychoactive drugs and falls is strong (OR, RR or HRR>2.0 or <0.5 or significant ($p<0.05$).

Associations

Eleven publications presented the associations between psychoactive drug use and falls in adjusted estimates: OR,[20, 22-23, 29] RR,[26-28] incidence density ratio (IDR),[24-25] HR,[21] and incidence rate ratio (IRR).[30] One study stratified for sex.[22] Five publications presented only crude estimates of the associations between psychoactive drug use and falls: OR,[31] RR,[11, 33-34]and HR.[19] One publication only presented the prevalence of fallers among benzodiazepine users and among non-users.[32]

All publications presented their results for residents with and without dementia together. None of the studies provided a sub-group analysis of the estimates in the population of nursing home residents with dementia. In five studies, it was unclear which proportion of the population had dementia.[21-22, 27, 30, 34] In two publications, the estimates for the whole cohort – both those in nursing homes and in intermediate care facilities – were given. In these studies there was no sub-group analysis of the estimates of the proportion of the population in the nursing homes.[21, 30]

Level of evidence

The heterogeneity of the study population and determinants necessitated a qualitative summary of the results. Table 4 presents a summary of the available evidence for the use of psychoactive drugs and its association with falls in nursing home populations including residents with dementia. Three papers classified all psychoactive drugs together, regardless of specific drug class.[25, 31, 34] All other studies presented data by drug class; they are presented both in the psychoactive and in the individual drug summary of the results. The results of studies that presented data on benzodiazepines, hypnotics, sedatives and anti-anxiety drugs were also summarized together and for the individual drug classes. Three papers provided data on the antidepressant class;[24, 26, 29] they are presented in both the antidepressant and the individual antidepressant class summary.

Any psychoactive drug

The overall evidence that the use of any psychoactive drug increases fall risk in nursing home residents with dementia is inconclusive. The reported strength of the associations varied widely (ORs and RRs 0.90–7.6). Positive findings were found in 28 out of 42 (67%) of the studies. The evidence that any psychoactive drug increases recurrent falls is limited. We found only one study in which the use of psychoactive drugs increased the risk of recurrent falls.[24] The evidence for injurious falls is strong. Positive findings were found in two studies (n=503, IDR 2.49 and n=368, OR 1.77).[29, 36]

Benzodiazepines and other hypnotic, sedative or anti-anxiety drugs

For the whole spectrum of benzodiazepines or any other hypnotic, sedative or anti-anxiety drug, we found that the overall evidence that these drugs increase the risk of falls

or recurrent falls is inconclusive. Positive findings for the risk of falls were found in five out of 11 cohorts (45%) (range of ORs and RRs 1.13– 2.4).[11, 24, 26, 30, 33] Positive findings for the risk of recurrent falls were found in one out of two (50%) cohorts.[24] However, when we examined these drugs separately, the evidence for the individual drug classes differed from the overall evidence. Based on only one cohort, we found limited evidence that benzodiazepines increase the risk of recurrent falls,[24] and that intermediate- and long-acting benzodiazepines increase overall fall risk. We also found limited evidence that short-acting benzodiazepines increase fall risk at night-time but not during the day.[27] For the whole spectrum of benzodiazepines, the individual effects described above disappear.

Furthermore, we found strong evidence that the use of anti-anxiety drugs increases fall risk. Positive findings were found in two out of two studies (n=2015, RR 1.32 and n=18,855, OR 1.22).[11, 33]

We found inconclusive evidence for the use of sedatives. Positive findings were found in only one out of four studies.[30]

There is strong evidence that the use of hypnotics does not increase fall risk. In the two studies we included, there were no significant associations found between the use of hypnotics and (recurrent) falls {n=34,163, OR 1.13 (0.98– 1.30)[20] and n=282, IDR=1.23 (0.55–2.76)}.[24]

Antipsychotics

The evidence that antipsychotics increase fall risk is inconclusive. Positive findings were found in three out of seven (43%) cohorts.[11, 21, 33] However, after stratification by type of antipsychotic, there is limited evidence that olanzapine use increases fall risk, and limited evidence that risperidone and typical antipsychotics do not increase fall risk. There is limited evidence that antipsychotics do not increase the risk of recurrent falls.[21]

Antidepressants

There is strong evidence that the use of antidepressants increases fall risk. In 10 out of 12 (83%) cohorts significant associations were found (n=78–2428, range of effect sizes 1.1–7.6).[11, 19, 21, 23-24, 26, 29-30] After stratification by the categories of antidepressants, the evidence that the use of tricyclic antidepressants (2/2 cohorts, n=282, IDR 2.96 and n=2428, RR 2.0)[24, 26] and the use of SSRIs (2/2 cohorts, n=368, OR 2.01 and n=2428, RR 1.8)[26, 29] increase fall risk remains strong. The evidence that the use of trazodone increases fall risk is limited.[26]

Multiple psychoactive drugs

There is strong evidence that multiple psychoactive drug use increases fall risk (3/3 studies, n=177–282, range of RR 1.30–10.3).[24, 30, 34] One study classified multiple drugs as the use two psychotropics (RR 3.2), three psychotropics (RR 6.7) or four psychotropics (RR 10.3).[34] The evidence for recurrent falls is limited.[24]

DISCUSSION

This systematic review has summarized the results of 17 prospective cohort studies concerning the influence of psychoactive drug use on fall risk and the influence of these drugs on gait parameters in nursing home populations with residents who have dementia. Substantial heterogeneity across studies for determinant measures, outcome measures, statistical analysis and data presentation was found. This heterogeneity impeded sensible statistical pooling of results; hence, a qualitative summary was undertaken. Strong evidence was found for the use of multiple psychotropic drugs, antidepressants and anti-anxiety drugs to increase fall risk. Strong evidence was found that hypnotics did not increase fall risk. The reported strength of the associations varied widely in the evidence for multiple psychotropic drugs (RR 1.30–10.3). The strength of the significant association seems to be moderate in one study (RR=1.30),[30] whereas in another study the strength is larger (RR=10.3) for the concurrent use of four psychotropics.[34] The evidence was based on three smaller cohorts.[24, 30, 34] The conclusion of strong evidence that the use of anti-anxiety drugs increases fall risk is based on only two cohorts. Although the strength of the associations in these two cohorts is moderate (RR=1.32, OR=1.22), the two cohorts were large.[11, 33] The strong evidence for the use of antidepressants is based on 10 cohorts,[11, 19, 21, 23-24, 26, 29-30] with the strongest association (OR=7.6) being found in a relatively small cohort (n=126 women).[23] In the largest cohort (n=2428) only a weak association was found (RR=1.1).[26]

For other drug classes, the evidence was limited or inconclusive. Limited evidence was always because the evidence was based on only one cohort.

It is generally recommended to prescribe benzodiazepines with a short elimination half-life to older persons. However, these were found to increase night-time falls,[24] which can be particularly hazardous. Intermediate- and long-acting benzodiazepines were found to increase overall fall risk.[24]

An earlier review on the association between psychoactive drugs and falls found an increased fall risk for all psychoactive drugs.[8] However, the Leipzig review was performed in the general population, not exclusively in nursing home residents. Possible explanations for these inconsistent findings might lie with our different methodology and review criteria, and with our qualitative summary using levels of evidence. We only included papers with a prospective study design because this is considered to be the optimal design to identify the presence of prognostic factors and their associations with the outcome.[37] The Leipzig review also included studies with a cross-sectional and a case control study design.[8]

Limitations of this review

The lack of homogeneity across the studies impeded sensible statistical pooling of data. This is a limitation of our study, as we had to define levels of evidence based on the strength of positive and negative findings across the studies for each medication type or group, and each outcome. A particular limitation of this approach is that the strength of findings is not strengthened or ameliorated depending upon the sample size, which is an important influence when pooled data is incorporated into a meta-analysis. A large study with a moderate positive effect contributes substantially more to a pooled effect size than does a small sample study with the same positive effect.

The fact that none of the studies we included presented a sub-group analysis of the estimates in the population of nursing home residents with dementia could have biased our conclusions. The exact contribution of psychoactive drug use to fall risk in nursing home residents with dementia is not yet known.

Also, the presentation of the different drug classes in the papers could have biased our conclusions. Some papers classified all psychoactive drugs together, regardless of specific drug class. Furthermore, the difference between anti-anxiety, sedative and hypnotic characteristics of psychoactive drugs is often a matter of dose and of elimination half-life. In general, benzodiazepines are prescribed as a hypnotic, anti-anxiety drug or sedative. The overall level of evidence for benzodiazepines is inconclusive, which may be due to the fact that there is strong evidence that anti-anxiety drugs increase fall risk and limited evidence that intermediate- and long-acting benzodiazepines increase fall risk, and that there is strong evidence that hypnotics do not increase fall risk and limited evidence that short-acting benzodiazepines do not increase fall risk.

Levels of evidence in this review were based on positive findings from multivariate or univariate results. The use of univariate results when multivariate results were not available could have biased our conclusions regarding the level of available evidence. Overestimation of the estimates may occur because univariate results are not adjusted for potential confounding.

The possibility of publication bias cannot be excluded. One cohort published three articles.[26-28] Studies with significant results are more likely to lead to multiple publications. Furthermore, relevant studies hidden in unknown databases are difficult to locate and therefore may have been missed.

Validity of the studies in the review

Information bias can result from differential and non-differential misclassification and can influence the estimate of the strength of the association. The incidence reports and medical records from which falls were ascertained may not be complete. On the other hand, a recorded fall may not be a fall according to the definition, as acute medical conditions may have been involved in the population under study.[38]

Misclassification of drug use may result when drug use is ascertained only from medical records and when it is not assured that medications were actually administered. Baseline measurement of drug use can induce substantial misclassification. One study found that this misclassification caused substantial underestimation of the association of benzodiazepine use with fall risk.[28]

Finally, selective loss to follow-up cannot be excluded in all studies. In one cohort, residents were followed through the day of facility exit, defined as discharge, death or transfer or a hospital stay of more than 14 days.[26-28]

Conclusions and recommendations

In summary, we conclude that the studies conducted within the period covered by this review consistently show an increased fall risk for the use of multiple drugs, antidepressants and anti-anxiety drugs in nursing home populations with residents with dementia. The evidence for other psychoactive drug classes is limited or inconclusive. Our initial approach was to analyze the data of nursing home residents with dementia only. However, none of the studies we found used a sub-group analysis for this specific group of residents.

It is generally accepted that falls are an intrinsic component of dementia and living in a nursing home. However, because of the multi-morbidity of this patient group, we do not know which risk factors are (potentially) reversible. The relative contribution of each drug class is not clear from the current literature. Also, little is known about dose and duration of use in relation to fall risk.

It was revealing to discover how little is known about the influence of psychoactive drugs on gait parameters in nursing home residents with dementia. As drug withdrawal has been shown to reduce fall risk[39] and improve mobility tests in community-dwelling older persons without dementia,[40-41] it is important to know the effect of psychoactive drugs on gait in nursing home residents with dementia. Falls due to psychoactive drug use might be caused by impairment of mobility generated by these drugs.[13] If gait can be improved by withdrawal of these drugs, a number of falls might be prevented, even among nursing home residents. Gait measurements may be useful in the clinical follow-up of fallers in whom these drugs are withdrawn. Large prospective studies on the relationship between psychoactive drugs and gait in nursing home residents with dementia are needed, and should focus on the contribution of each drug class and dose and duration of use on fall risk.

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CHAPTER 6

New insights: Dose-response relationship between psychotropic drugs and falls: A study in nursing home residents with dementia

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ABSTRACT

The contribution of specific psychotropic drugs to fall risk in patients with dementia has not been quantified precisely until now. We evaluated the dose-response relationship between psychotropic drugs and falls in nursing home residents with dementia. Daily drug use and daily falls were recorded in 248 nursing home residents with dementia from January 1, 2006, to January 1, 2008. For each day of the study period, data on drug use were abstracted from the prescription database, and falls were retrieved from a standardized incident report system, resulting in a data set of 85,074 person-days. We found significant dose-response relationships for the use of antipsychotics (hazard ratio [HR] 2.78, 95% confidence interval [CI] 1.49-5.17), anxiolytics (HR 1.60, 95% CI 1.20-2.14), hypnotics and sedatives (HR 2.58, 95% CI 1.42-4.68), and antidepressants (HR 2.84, 95% CI 1.93-4.16). Fall risk increased significantly with 28% at 0.25 of the Defined Daily Dose (DDD) of an antipsychotic or antidepressant, with 8% at 0.2 of the DDD of an anxiolytic, and with 56% at 0.5 of the DDD of a hypnotic or sedative; it increased further with dose increments and with combinations of psychotropics. Even at low dosages, psychotropic drugs are associated with increased fall risk in nursing home residents with dementia.

INTRODUCTION

Approximately 30% to 70% of nursing home residents fall at least once a year, with 1.5 falls per bed per year occurring in somatic (nonpsychogeriatric) nursing homes and more than two falls per bed per year in psychogeriatric nursing homes.[1,2] Dementia is an independent risk factor for falls,[3] as is psychotropic drug use.[4] A high proportion of nursing home residents with dementia are treated with psychotropic drugs because of behavioral and neuropsychiatric symptoms.[5] The general message that psychotropic drugs increase fall risk is already well accepted. However, the contribution of specific

psychotropic drugs to fall risk in nursing home residents with dementia has not been quantified precisely until now. The magnitude of the associations between specific psychotropic drugs and fall risk within this group is not known, and so far, a dose-response relationship has not been reported.[6]

In the setting of psychogeriatric nursing homes the fall risk profile of each individual resident should be periodically evaluated to take tailor-made preventive measures in time. A systematic evaluation of fall risk should include an assessment of all major contributing components, including the use and dosage of psychotropic drugs. However, it is not yet known at which dosages specific psychotropic drugs, as well as combinations of these drugs, could lead to an increased fall risk.

Therefore, we addressed the following questions:

1. What is the magnitude of the associations between specific psychotropic drugs and fall risk in nursing home residents with dementia?
2. Are there dose-response relationships between (combinations of) specific psychotropic drugs and fall risk in nursing home residents with dementia?

METHODS

Design and setting

For this observational cohort study, we built a database in which we analyzed daily drug use and daily falls in a population of nursing home residents with dementia living in the psychogeriatric nursing home Smeetsland (De StromenOpmaatGroep), Rotterdam, The Netherlands, between January 1, 2006, and January 1, 2008. We collected data of residents, who were resident for at least six weeks and who were able to walk independently, with or without a walking aid. Information on the ambulatory status (i.e. able/unable to walk independently) was retrieved from the medical records and nursing home charts. Reasons to end data collection were immobility, death or discharge.

The Medical Ethics Committee of the Erasmus University Medical Center approved the study.

Dementia diagnosis and severity

All residents in the nursing home met the criteria for the diagnosis of dementia from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR).[7] Severity of dementia was defined as stage 5 or 6 on the Global Deterioration Scale (GDS)[8] and was based on the regular multidisciplinary team assessment by the nursing home staff, including the nursing home physician. A GDS stage 5 corresponds with a Mini-Mental State Examination (MMSE)[9] score of 10.0±1.9 points and a GDS stage 6 corresponds with a MMSE score of 6.4±3.2 points.[10]

Data collection

Psychotropic drug use

For each resident and for each day of the study period, we extracted the use and dose of antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants from the prescription database in the medical records.

Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification system, and doses were recorded and expressed as a proportion of the defined daily dose (DDD), that is, the average dosage of a drug taken by adults for the main indication as indicated by the World Health Organization.[11]

Psychotropic drugs were categorized as: antipsychotics (ATC code N05A), anxiolytics (ATC code N05B), hypnotics and sedatives (ATC code N05C), and antidepressants (ATC code N06A).

Patient characteristics

Data collected from the medical records and nursing home charts were: age, gender, and co-morbid conditions that are considered potentially causative of falls (i.e. visual impairment, urinary incontinence, Parkinson's disease, arthritis and other joint diseases, depression, and cardiovascular diseases).[12,13] The use and dose of other fall risk increasing drugs (FRIDs) were extracted from the prescription database in the medical records (i.e., drugs used in diabetes, cardiovascular drugs, beta-blocker eye drops, analgesics, anticholinergic drugs, antihistamines, and antivertigo drugs).[4,14-16]

Falls

A fall was defined as unintentionally coming to rest on the ground or another lower level.[17] Falls were recorded on a standardized incidence registration form,[18] which is part of the national incidence registration system for monitoring the quality of care in nursing homes in the Netherlands.[19] The staff are trained to complete the forms immediately after a fall takes place or after a resident is found on the floor or any other lower level. A committee collects and processes the forms in the computer and provides incidence reports. For each day of the study period, falls were obtained from these computerized reports.

Falls history

Because a positive falls history is a known risk factor for further falls, we also collected data on falls in the year preceding the start of the study from this computer system from January 1, 2005, to January 1, 2006.

Statistical analysis

Drug use was first defined as a categorical dichotomous variable (use/no-use) on a daily basis. To assess the dose-response relationship, we defined drug use as a continuous variable, expressed as a proportion of the DDD on a daily basis.

To analyze the relation between drug use and falls, we used generalized multilevel regression with days per resident as the unit of analysis and resident as the cluster variable. We assumed the number of falls per day to have a Poisson distribution. Hazard ratio's (HRs) and 95% confidence intervals (CIs) were calculated for all variables.

All variables (i.e., psychotropic drugs, other FRIDs, co-morbidities, age, and gender) that were significant in the univariate analysis were included in the multivariate model. The initial multivariate model included variables associated with falls ($p \leq 0.05$). The model was then reduced by backward elimination to exclude factors that did not reach significance (at $p \leq 0.05$). To examine significant interactions between the variables in the final multivariate model, interaction terms were calculated and added to the model.

All statistical analyses were performed using SPSS software (version 16.0, SPSS INC., Chicago, IL, USA), and R: A language and Environment for Statistical Computing[20] (package lme4: linear mixed-effects models using S4 classes. R package version 0.999375-28,[21] R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

During the study period, a total of 443 persons resided in the psychogeriatric nursing home Smeetsland. The data of 248 residents were included in the study. Seventy-four persons were excluded because they were resident for less than six weeks, 121 persons were excluded because they were not able to walk independently at the start of the data collection. The data collection resulted in a dataset of 85,074 person-days. Mean time spent in the database was 350 days. The mean age of the participants was 82±8 years. During 85,074 person-days, 152 (61.5%) residents sustained 683 falls, which corresponds to a fall incidence of 2.9 falls/person-year. Thirty-eight residents (15.4%) were single fallers, and 114 (46.2%) were frequent fallers. Characteristics of the study population and falls incidence are presented in Table 1.

Prevalence of psychotropic drug use

During a total of 38,662 (45.4%) person-days, an antipsychotic (N05A) was used (Table 1). The most common antipsychotic drugs used were haloperidol (13.3% of person-time) and pipamperone (17.0% of person-time). Mostly a dose less than 1 DDD was prescribed (44.4% of person-time), with a mean (SD) DDD of 0.24 (0.27). Antipsychotics were prescribed in dosages varying between 0.02 and 2.25 of the DDD.

During a total of 17,781 (20.9%) person-days, an anxiolytic (N05B) was used. The most prevalent anxiolytic drug used was oxazepam (19.3% of person-time). Ninety-nine percent of the prescriptions of oxazepam were less than 1 DDD (50 mg), with a mean (SD) DDD of 0.36 (0.20). The most used dose was 0.2 DDD (10 mg) in 32.8% of all prescriptions.

During a total of 11,538 (13.6%) person-days, a hypnotic or sedative (N05C) was used. Temazepam was the most prescribed hypnotic drug (13.0% of person-time). Seventeen percent of the prescriptions of temazepam were 1 DDD (20 mg), with a mean (SD) DDD of 0.59 (0.20). The most used dose was 0.5 DDD (10 mg) in 81.3% of the prescriptions.

During a total of 13,729 (16.1%) person-days, an antidepressant (N06A) was used. Selective serotonin reuptake inhibitors (SSRIs) were the most prescribed antidepressants (13.1% of person-time). Citalopram was the most prescribed SSRI (8.2% of person-time). Seventy-six percent of the prescriptions of SSRIs were 1 DDD, with a mean (SD) DDD of 0.95 (0.28).

The combinations of psychotropic drugs registered during the study period are described in Table 1.

Fall risk

Table 1 presents the univariate HRs for falls. The results of the multivariate analysis are presented in Table 2. Fall risk was increased with age (HR 1.05, 95% CI 1.02 to 1.08). Fall risk was also increased with the use of antipsychotics (HR 1.53, 95% CI 1.17 to 2.00), anxiolytics (HR 1.60, 95% CI 1.19 to 2.16), hypnotics and sedatives (HR 1.50, 95% CI 1.04 to 2.16), and antidepressants (HR 2.28, 95% CI 1.58 to 3.29).

Analysis of subgroups of antipsychotics showed that the use of zuclopenthixol (HR 2.18, 95% CI 1.18 to 4.03) and clozapine, olanzapine, and quetiapine (HR 2.24, 95% CI 1.20 to 4.15) remained significant. Analysis of subgroups of antidepressants showed that the use of tricyclic antidepressants (HR 3.13, 95% CI 1.09 to 8.98) and SSRIs (HR 2.04, 95% CI 1.39 to 2.99) remained significant.

Dose-response relationships

Significant dose-response relationships were found for the use of antipsychotics (HR 2.78, 95% CI 1.49 to 5.17), anxiolytics (HR 1.60, 95% CI 1.20-2.14), hypnotics and sedatives (HR 2.58, 95% CI 1.42-4.68), and antidepressants (HR 2.84, 95% CI 1.93-4.16). Analysis of subgroups of antipsychotics showed that the dose-response relationship for the use of zuclopenthixol (HR 4.97, 95% CI 1.42-17.41) and clozapine, olanzapine, and quetiapine (HR 3.71, 95% CI 1.06-13.03) remained significant. Analysis of subgroups of antidepressants showed that the dose-response relationship for the use of SSRIs (HR 2.15, 95% CI 1.57-2.93) remained significant.

The interaction term for the use antipsychotics and antidepressants was found significant (p=0.02).

Table 1 Characteristics of the study population and risk of falling

Characteristic	All person-days (N=85,074) N (% of total)	Person-days with fall (N=643) N	Person-days without fall (N=84,455) N	Univariate HR falls (95% CI)
Demographic data				
Gender				
Male	34,282 (40·3)	283	33,999	1.12 (0.72- 1.73)
Female	50,792 (59·7)	360	50,432	Reference
Mean (SD) age,[a] 82 (8) years				1.04 (1.01-1.07)[b]
Falls history in previous year	45,982 (54·0)	518	45,464	1.76 (0.95-3.23)
Visual impairment	18,139 (21·3)	121	18,018	0.99 (0.58-1.68)
Urinary incontinence	44,310 (52·1)	367	43,943	1.40 (0.90-2.16)
Parkinson's disease	1,151 (1·4)	13	1,138	1.68 (0.53-5.33)
Arthritis and other joint diseases	23,074 (27·1)	214	22,860	1.46 (0.89-2.38)
Depression	7,161 (8·4)	72	7,089	1.90 (0.94-3.83)
Cardiovascular diseases	61,123 (71·8)	467	60,656	0.95 (0.58-1.58)
Use of psychotropic drugs				
Antipsychotics (ATC code N05A)	38,662 (45·4)	370	38,292	1.61 (1.23-2.10)[b]
Haloperidol and pipamperone (ATC code N05AD)	25,346 (29·8)	227	25,119	1.23 (0.93-1.63)
Zuclopenthixol (ATC code N05AF)	2,572 (3·0)	34	2,538	2.39 (1.28-4.45)[b]
Penfluridol (ATC code N05AG)	1,350 (1·6)	28	1,322	2.06 (0.38-11.2)
Clozapine, olanzapine, and quetiapine (ATC code N05AH)	3,683 (4·3)	57	3,626	2.36 (1.26-4.40)[b]
Risperidone (ATC code N05AX)	7,499 (8·8)	42	7,457	1.04 (0.61-1.77)
Anxiolytics (ATC code N05B)	17,781 (20·9)	190	17,591	1.65 (1.22-2.23)[b]
Hypnotics and sedatives (ATC code N05C)	11,538 (13·6)	127	11,411	1.61 (1.12-2.33)[b]
Antidepressants (ATC code N06A)	13,729 (16·1)	173	13,556	2.49 (1.72-3.62)[b]
Amitriptyline and nortriptyline (ATC code N06AA)	1,141 (1·3)	12	1,129	3.27 (1.10-9.72)[b]

Table 1 Characteristics of the study population and risk of falling (continued)

Characteristic	All person-days (N=85,074) N (% of total)	Person-days with fall (N=643) N	Person-days without fall (N=84,455) N	Univariate HR falls (95% CI)
Citalopram, paroxetine, sertraline, and fluvoxamine (ATC code N06AB)	11,105 (13·1)	148	10,957	2.24 (1.52-3.31)[b]
Trazodone and mirtazapine (ATC code N06AX)	1,739 (2·0)	14	1,725	1.11 (0.49-2.53)
Combinations of psychotropic drugs				
Antipsychotics and anxiolytics	11,144 (13·1)	137	11,007	
Antipsychotics and hypnotics/sedatives	7,108 (8·4)	94	7,014	
Antipsychotics and antidepressants	8,085 (9·5)	118	7,967	
Antidepressants and anxiolytics	4,922 (5·8)	73	4,849	
Antidepressants and hypnotics/sedatives	3,119 (3·7)	40	3,079	
Antipsychotics, antidepressants, and anxiolytics	3,491 (4·1)	56	3,435	
Antipsychotics, antidepressants, and hypnotics/sedatives	2,337 (2·7)	38	2,299	
Use of other drug classes				
Antihypertensives	12,081 (14·2)	100	11,981	1.12 (0.73-1.72)
Antiarrythmics	8,069 (9·5)	58	8,011	0.89 (0.51-1.57)
Nitrates and other vasodilators	2,830 (3·3)	36	2,794	1.41 (0.55-3.56)
Digoxin	2,865 (3·4)	19	2,846	0.65 (0.20-2.07)
Beta-blocker eye drops	798 (0·9)	12	786	2.24 (0.43-11.73)
Analgesics	1,684 (2·0)	14	1,670	1.94 (0.99-3.77)
Anticholinergic drugs	138 (0·2)	2	136	1.70 (0.32-9.01)
Antihistamines	2,538 (3·0)	21	2,517	0.80 (0.44-1.43)
Antivertigo drugs	202 (0·2)	3	199	1.98 (0.17-22.76)
Drugs used in diabetes	5,172 (6·1)	30	5,142	0.72 (0.32-1.66)

Abbreviations: ATC, Anatomical Therapeutic Chemical classification system; CI, confidence interval; HR, hazard ratio.
[a]HR for age (continuous variable) HR per year.
[b]Significant parameters

Table 2 Multivariate hazard ratios for falls

Characteristic	HR Falls (95% CI)	p-value	HR Falls[a] (95% CI)	p-value
Gender				
Male	1.37 (0.89-2.11), (NS)	.15		
Female	Reference			
Age (continuous variable)[b]	1.05 (1.02-1.08)	.00		
Drug use	Use/no-use (95% CI)		Dose-response (95% CI)	
Antipsychotics (ATC code N05A)	1.53 (1.17-2.00)	.00	2.78 (1.49-5.17)	.00
Zuclopenthixol (ATC code N05AF)	2.18 (1.18-4.03)	.01	4.97 (1.42-17.41)	.01
Clozapine, olanzapine, and quetiapine (ATC code N05AH)	2.24 (1.20-4.15)	.01	3.71 (1.06-13.03)	.04
Anxiolytics (ATC code N05B)	1.60 (1.19-2.16)	.00	1.60 (1.20-2.14)	.00
Hypnotics and sedatives (ATC code N05C)	1.50 (1.04-2.16)	.03	2.58 (1.42-4.68)	.00
Antidepressants (ATC code N06A)	2.28 (1.58-3.29)	.00	2.84 (1.93-4.16)	.00
Amitriptyline and nortriptyline (ATC code N06AA)	3.13 (1.09-8.98)	.03		
Citalopram, paroxetine, sertraline, and fluvoxamine (ATC code N06AB)	2.04 (1.39-2.99)	.00	2.15 (1.57-2.93)	.00

Abbreviations: CI, confidence interval; HR, hazard ratio; NS, not significant.
[a]HR for increase with 1 defined daily dose.
[b]HR per year.

Table 3 shows the probability of a fall in percentages per day (i.e., absolute risk) and 95% CIs. Increases in absolute fall risk for various combinations of doses of antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants were found for both men and women, for different ages (see Table 3). An example of a patient in Table 3 is shown in Box 1.

DISCUSSION

The main finding of this study is that we have quantified the dose-response relationship between specific (combinations of) psychotropic drugs and fall risk in nursing home residents with dementia. Fall risk was already increased at low doses (0.25 DDD). Furthermore, we found that fall risk increased with increasing doses of antipsychotics, anxiolytics, hypnotics or sedatives, and antidepressants and with the combined use of these drugs.

We expressed drug use as a proportion of the DDD. We found that psychotropics already increased fall risk at a low DDD. The DDD is a statistical measure of drug consumption and is used to standardize the comparative usage of various drugs between

Table 3 Dose-response relationship with fall risk for the use of psychotropics

Fall probability	0 DDD antipsychotics 0 DDD antidepressants	0.25 DDD antipsychotics 0 DDD antidepressants	0 DDD antipsychotics 0.25 DDD antidepressants	0.25 DDD antipsychotics 0.25 DDD antidepressants	0.25 DDD antipsychotics 1 DDD antidepressants	1 DDD antipsychotics 1 DDD antidepressants
No benzodiazepines						
p(f,80) (95%CI)	0.25% (0.18-0.34)	0.32% (0.23-0.44)	0.32% (0.23-0.44)	0.38% (0.28-0.52)	0.64% (0.43-0.94)	0.49% (0.19-1.27)
p(m,80) (95%CI)	0.34% (0.24-0.47)	0.44% (0.31-0.60)	0.44% (0.31-0.61)	0.52% (0.38-0.72)	0.88% (0.58-1.32)	0.68% (0.26-1.73)
p(f,85) (95%CI)	0.31% (0.23-0.42)	0.40% (0.03-0.55)	0.40% (0.30-0.54)	0.48% (0.36-0.64)	0.81% (0.55-1.18)	0.62% (0.24-1.61)
p(m,85) (95%CI)	0.43% (0.30-0.61)	0.55% (0.38-0.79)	0.55% (0.39-0.79)	0.66% (0.46-0.94)	1.11% (0.72-1.72)	0.86% (0.33-2.23)
0.2 DDD anxiolytics						
p(f,80) (95%CI)	0.27% (0.19-0.37)	0.35% (0.25-0.48)	0.35% (0.26-0.48)	0.41% (0.30-0.57)	0.70% (0.48-1.03)	0.54% (0.21-1.39)
p(m,80) (95%CI)	0.37% (0.26-0.52)	0.48% (0.35-0.66)	0.48% (0.35-0.67	0.57% (0.41-0.78)	0.96% (0.64-1.44)	0.74% (0.29-1.89)
p(f,85) (95%CI)	0.34% (0.25-0.46)	0.44% (0.32-0.60)	0.44% (0.33-0.59)	0.52% (0.39-0.70)	0.89% (0.61-1.29)	0.69% (0.27-1.76)
p(m,85) (95%CI)	0.47% (0.32-0.68)	0.60% (0.42-0.87)	0.61% (0.42-0.87)	0.72% (0.51-1.03)	1.21% (0.79-1.88)	0.94% (0.36-2.44)
0.4 DDD anxiolytics						
p(f,80) (95%CI)	0.30% (0.21-0.41)	0.38% (0.28-0.53)	0.38% (0.28-0.53)	0.45% (0.33-0.62)	0.77% (0.52-1.14)	0.59% (0.23-1.52)
p(m,80) (95%CI)	0.41% (0.29-0.57)	0.52% (0.38-0.73)	0.53% (0.38-0.74)	0.63% (0.45-0.86)	1.05% (0.71-1.59)	0.82% (0.32-2.07)
p(f,85) (95%CI)	0.37% (0.27-0.52)	0.48% (0.35-0.66)	0.49% (0.36-0.66)	0.57% (0.43-0.78)	0.98% (0.67-1.43)	0.75% (0.29-1.93)
p(m,85) (95%CI)	0.51% (0.35-0.75)	0.66% (0.46-0.96)	0.67% (0.46-0.97)	0.79% (0.55-1.14)	1.33% (0.86-2.08)	1.03% (0.40-2.68)
0.6 DDD anxiolytics						
p(f,80) (95%CI)	0.32% (0.23-0.46)	0.42% (0.30-0.59)	0.42% (0.30-0.59)	0.50% (0.36-0.70)	0.84% (0.57-1.26)	0.65% (0.25-1.67)
p(m,80) (95%CI)	0.45% (0.31-0.64)	0.57% (0.41-0.81)	0.57% (0.41-0.82)	0.68% (0.49-0.96)	1.15% (0.77-1.76)	0.90% (0.35-2.28)
p(f,85) (95%CI)	0.41% (0.29-0.58)	0.53% (0.38-0.74)	0.53% (0.39-0.74)	0.63% (0.46-0.88)	1.07% (0.72-1.59)	0.82% (0.32-2.13)
p(m,85) (95%CI)	0.56% (0.38-0.84)	0.73% (0.50-1.07)	0.73% (0.50-1.08)	0.87% (0.60-1.27)	1.46% (0.94-2.30)	1.13% (0.44-2.96)
0.5 DDD hypnotics or sedatives						
p(f,80) (95%CI)	0.39% (0.26-0.59)	0.51% (0.34-0.76)	0.51% (0.34-0.76)	0.60% (0.41-0.90)	1.02% (0.65-1.62)	0.79% (0.30-2.06)
p(m,80) (95%CI)	0.54% (0.36-0.81)	0.70% (0.47-1.04)	0.70% (0.47-1.05)	0.83% (0.56-1.23)	1.40% (0.88-2.25)	1.08% (0.42-2.80)
p(f,85) (95%CI)	0.50% (0.34-0.73)	0.64% (0.44-0.95)	0.65% (0.44-0.94)	0.76% (0.53-1.12)	1.29% (0.83-2.03)	1.00% (0.38-2.61)
p(m,85) (95%CI)	0.68% (0.45-1.05)	0.88% (0.58-1.35)	0.88% (0.58-1.36)	1.05% (0.69-1.60)	1.77% (1.09-2.91)	1.37% (0.52-3.61)

Abbreviations: DDD, defined daily dose; p(f,80)=probability to fall in percentages per day for women aged 80; p(m,80)=probability to fall in percentages per day for men aged 80; p(f,85)=probability to fall in percentages per day for women aged 85; p(m,85)=probability to fall in percentages per day for men aged 85.

Box 1

A female resident aged 80, who used no anxiolytic, hypnotic or sedative, antipsychotic, or antidepressant had an absolute fall risk of 0.25%. Compared with nonuse, a dosage of 0.25 defined daily dose (DDD) of an antipsychotic or an antidepressant increased her absolute fall risk with 28% (fall probability per day from p=0.25% to p=0.32%). A dosage of 0.2 DDD of an anxiolytic increased the absolute fall risk with 8% (fall probability per day from p=0.25% to p=0.27%). A dosage of 0.5 DDD of a hypnotic or sedative increased the absolute fall risk with 56% (fall probability per day from p=0.25% to p=0.39%). A combination of an antipsychotic and an antidepressant in a dosage of 0.25 DDD in the same female resident increased the absolute fall risk with 52% (fall probability per day from p=0.25% to p=0.38%) (see Table 3). A combination of 0.25 DDD of an antipsychotic or an antidepressant and 0.50 DDD of a hypnotic increased absolute fall risk with 104% (fall probability per day from p=0.25% to p=0.51%). In the same female resident, a further increase in absolute fall risk was seen with increasing doses of antipsychotics, anxiolytics, hypnotics or sedatives, and antidepressants, as well as combinations of these drugs. With the use of 0.25 DDD of an antipsychotic and 1.00 DDD of an antidepressant, absolute fall risk increased with 156% (fall probability per day from p=0.25% to p=0.64%).

themselves or between different health care environments.[11] Modifications in pharmacokinetics of psychotropic drugs have been noticed in older subjects. A prolongation of the half-life of drugs metabolized by oxidation has been reported in the older age group. As a result, psychotropic drugs metabolized by oxidation should be prescribed with caution in older patients because higher plasma concentrations for a given drug dosage and consequently enhanced clinical effects are to be expected.[22,23] Other important and frequently seen age-related changes that may influence metabolism of psychotropic drugs include decreased liver blood flow, plasma albumin, and lean body mass.[24]

Modifications in pharmacodynamics may also occur as a consequence of increased sensitivity of the receptors, which implies a greater effect for a given plasma concentration. Different investigators report that older subjects require both a lower dose and a lower plasma concentration to cause a constant level of desired clinical effect.[25,26]

Strengths and limitations of this study

The main strength of this study is the fact that because of the large and detailed data set, we were able to identify the dose-response relationship between psychotropic drugs and fall risk in this high risk population. Data on medication use were collected for each day of the study period. Therefore, no misclassification was induced by the use of baseline measurement of drug use. This type of misclassification has been shown to increase with length of study period.[27]

A second strength of this study is the fact that there was no selection bias. All eligible residents participated in the study. Furthermore, all falls were recorded on a standard-

ized form by the nursing staff regardless of the type of drugs a resident might have taken, so there was no registration bias.

A third strength of this study is the relatively homogenous population of residents with dementia stage 5 or 6 on the GDS[8] because it reduces confounding by indication.

A potential limitation of this study is that behavioral and neuropsychiatric symptoms may themselves lead to an increased fall risk and may result in higher drug doses. We were not able to control for this type of confounding by indication because there was no standard procedure in place to quantify and record neuropsychiatric symptoms and behavioral disturbances in the medical charts. However, recent studies have shown that behavioural and neuropsychiatric symptoms as measured with the Neuropsychiatric Inventory – Nursing Home (NPI–NH)[28,29] version are very common in nursing home patients with dementia stage 5 or 6 on the GDS[8]. One study found that more than 80% of the study population had at least one clinically relevant symptom, whereas the majority of the patients had multiple symptoms.[30] In another study the prevalence of specific behavioural and neuropsychiatric symptoms in nursing home patients with dementia was quantified by the GDS score.[31] This study found a prevalence of 62.0% of physically nonaggressive behaviour in GDS stage 5 and a prevalence of 69.5% in GDS stage 6, as well as a prevalence of 66.7% of verbally agitated behaviour in GDS stage 5 and a prevalence of 65.3 % in GDS stage 6; other neuropsychiatric symptoms like disinhibition, irritability, delusions, and depression were more common in patients in GDS stage 5 or 6 than in other GDS stages.[31]

Because all residents in our study population were nursing home residents with dementia stage 5 or 6 on the GDS,[8] they were all likely to have neuropsychiatric symptoms and behavioral disturbances fitting with these stages.

Furthermore, we cannot rule out possible confounding by indication regarding the increased risk we found for the use of clozapine, olanzapine, and quetiapine because it concerned either residents who used these drugs already when admitted to the nursing home or users who had been switched from either haloperidol or pipamperone.

Another potential limitation might be that our study is from a single institution. However, we think that our results could be generalized because the high prevalence of antipsychotics and antidepressant prescriptions in our study is comparable with both Dutch and international studies in nursing home settings.[5,32]

Finally, underascertainment of falls events could have biased our results. Probably, not all falls have been witnessed by the staff. However, this type of information bias is likely to be nondifferential (i.e., the underascertainment of falls is equal for the users and for nonusers of all drug classes), so this would not influence the HRs we found.

To the best of our knowledge, this is the first study specifying the dose-response relationship between psychotropic drugs and fall risk in nursing home residents with dementia.

The study demonstrates clearly the excessive risk of falls due to psychotropic drug use in nursing home residents with dementia and lends support to the current opinion that implementation of effective nonpharmacological interventions should be tried before psychotropic drugs are prescribed to nursing home residents with dementia.[33] If psychotropic drugs still need to be prescribed, their use should be restricted to the lowest possible dose, and the need for continuation should be reassessed on a regular basis.

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CHAPTER 7

Dose-response relationship between Selective Serotonin Reuptake Inhibitors and injurious falls: A study in nursing home residents with dementia

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ABSTRACT

Aim The contribution of selective serotonin reuptake inhibitors (SSRIs) to injurious fall risk in patients with dementia has not been quantified precisely until now. Our objective was to determine whether a dose-response relationship exists for the use of SSRIs and injurious falls in a population of nursing home residents with dementia.

Methods Daily drug use and daily falls were recorded in 248 nursing home residents with dementia from 1 January 2006 until 1 January 2008. For each resident and for each day of the study period, data on drug use were abstracted from the prescription database, and information on falls and subsequent injuries was retrieved from a standardized incident report system, resulting in a dataset of 85,074 person-days.

Results We found a significant dose-response relationship between injurious falls and the use of SSRIs. The risk of an injurious fall increased significantly by 31% at 0.25 of the Defined Daily Dose (DDD) of a SSRI, 73% at 0.50 DDD, and 198% at 1.00 DDD (Hazard Rate=2.98; 95% confidence interval 1.94-4.57). The risk increased further in combination with a hypnotic or sedative.

Conclusions Even at low doses, SSRIs are associated with increased risk of an injurious fall in nursing home residents with dementia. Higher doses increase the risk further with a threefold risk at 1.00 DDD. New treatment protocols might be needed that take into account the dose-response relationship between SSRIs and injurious falls.

INTRODUCTION

Falls are a major health problem among the elderly, particularly in nursing homes.[1-2] In nursing homes one-third of all falls results in an injury.[3] Nursing home residents with dementia are at particular risk of falling, with an average of more than 2 falls per bed per year.[4]

In order to take tailor-made preventive measures in time, the fall risk profile of each individual nursing home resident should be periodically evaluated. A systematic evaluation of fall risk should include an assessment of all major contributing components, including the use of medication.[5-6] Depressive symptoms are common in patients with dementia.[7] Therefore, a high proportion of nursing home residents with dementia are treated with antidepressants,[8-10] including selective serotonin reuptake inhibitors (SSRIs), which are generally considered the treatment of choice for depression in dementia.[11] However, recent research has shown that use of SSRIs is associated with an increased risk of injurious falls and fractures,[12-14] and that there is a dose-dependent relationship between the use of SSRIs and fracture risk in the general population.[15]

So far, data on the association between use of SSRIs and injurious fall risk in the specific population of nursing home residents with dementia are lacking.[16] Therefore we addressed the question:

Is there a dose-response relationship between the use of SSRIs and injurious falls in a population of nursing home residents with dementia?

METHODS

Design and setting

For this retrospective study we included all eligible participants of nursing home residents with dementia living in the psychogeriatric nursing home Smeetsland (De StromenOpmaatGroep), in Rotterdam, The Netherlands. We analysed daily drug use and daily falls over a two year period, i.e., from 1 January 2006 until 1 January 2008. We collected data of residents, who were resident for at least six weeks, and who were able to walk independently, with or without a walking aid. Information on the ambulatory status (able/unable to walk independently) was retrieved from the medical records and nursing home charts. Reasons to end data collection were immobility, death or discharge. The Medical Ethics Committee of the Erasmus University Medical Center approved the study.

Dementia diagnosis and severity

All residents in the nursing home met the criteria for the diagnosis of dementia from the Diagnostic and Statistical Manual of mental disorders (DSM-IV-TR).[17] Severity of demen-

tia was defined as stage 5 or 6 on the Global Deterioration Scale (GDS),[18] and was based on the regular multidisciplinary team assessment by the nursing home staff, including the nursing home physician.

Drug use

For each resident and for each day of the study period, we extracted the use and dose of SSRIs and other fall-risk-increasing drugs (FRIDs) from the prescription database in the medical records. These drugs included antipsychotic drugs, anxiolytics, hypnotics or sedatives, other antidepressants, drugs used in diabetes, cardiovascular drugs, beta-blocker eye drops, analgesics, anticholinergic drugs, antihistamines, and antivertigo drugs.[19-22]

Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification system and doses were recorded and expressed as a proportion of the Defined Daily Dose (DDD), i.e. the average of a dosage of a drug taken by adults for the main indication as indicated by the World Health Organization.[23] As an example from the ATC classification system, 1 DDD citalopram is a dosage of 20mg.[23] We expressed 10mg citalopram as 0.5 DDD.

We accessed the P450 Drug Interaction Table to retrieve information about cytochrome P450 enzymes that metabolize the prescribed SSRIs in our dataset.[24] We then explored our dataset to check for the combined use of a SSRI and a cytochrome P450 (1A2, 2C9, 2C19, and 2D6 pathways) inhibitor. Because SSRIs may become long-acting, when co-administered with an inhibitor, thereby increasing the risk further. We considered strong, moderate, and weak inhibitors.[24]

Patient characteristics

Baseline data collected from medical records and nursing home charts were: age, gender, and comorbid conditions that are considered potentially causative of falls. These comorbid conditions included: visual impairment, urinary incontinence, Parkinson's disease, arthritis and other joint diseases, depression and cardiovascular diseases.[25-26]

Injurious falls

A fall was defined as unintentionally coming to rest on the ground or any other lower level.[27] Falls were recorded on a standardized incidence registration form.[28] This incidence registration form is part of the incidence registration system. This standard procedure is a national instrument to monitor the quality of care in nursing homes in the Netherlands.[29] The staff are trained to complete the forms immediately after a fall took place, or after a resident is found on the floor or any other lower level. A committee collected, and processed the forms in the computer, and provided incidence reports. For each day of the study period falls and information on subsequent injuries were obtained from these computerised reports. Injurious falls were categorised as falls resulting in fractures, grazes, open wounds, sprains, bruises, and swellings.

Falls history

Because a positive falls history is a known risk factor for further falls, we also collected data on falls in the year before the start of the study from this computer system, i.e. from 1 January 2005 until 1 January 2006.

Statistical analysis

To assess the dose-response relationship we defined SSRI use, and all other FRID use as a continuous variable, expressed as a proportion of the DDD on a daily basis. To analyse the relation between drug use and the incidence of injurious falls we used multilevel logistic regression with "days-per-resident" as unit of analysis and "resident" as cluster variable. We had observations about many days for each patient. The outcome variable was whether a patient had experienced an injurious fall on any given day; we assumed the number of injurious falls per day to have a binominal distribution. For every day observed we registered the type and amount of drugs administered to that patient. We expected every patient to have a personal expected probability of injurious falls, so a random intercept per person was added to the model. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for all variables (i.e., psychotropic drugs, other FRIDs, co-morbidities, age and gender). All variables that were significant in the univariate analysis were included in the multivariate model. The initial multivariate model included variables associated with falls ($p \leq 0.05$). The model was then reduced by backward elimination to exclude factors that did not reach significance (at $p \leq 0.05$). To examine significant interactions between the variables in the final multivariate model, interaction terms were calculated and added to the model.

All statistical analyses were performed using SPSS software (version 16.0, SPSS INC., Chicago, IL, USA), and R (package lme4, R Foundation for Statistical Computing, Vienna, Austria).[30-31]

RESULTS

During the study period, a total of 443 persons were residents in the psychogeriatric nursing home Smeetsland. Seventy-four persons were excluded because they were residents for less than six weeks. One hundred twenty-one residents were excluded because they were not able to walk independently at the start of the data collection. The data of 248 residents were included in the study. The data collection resulted in a dataset of 85,074 person-days. Mean time spent in the database was 350 days. The mean age (sd) of the participants was 82 (8) years. During 85,074 person-days, 152 (61.5%) of the residents sustained 683 falls, which corresponds to a fall incidence of 2.9 falls/person-year. Thirty-eight residents (15.4%) were single fallers, and 114 (46.2%) were frequent fallers.

Two hundred twenty (32.2%) falls resulted in an injury. One person died, 21 (3.1%) falls resulted in a fracture, of which 10 (1.5%) were hip fractures, and 11 (1.6%) other fractures. One hundred ninety-eight (30.0%) falls resulted in injuries other than fractures,

Table 1 Characteristics of the study population, and person-days with and without injurious falls

Characteristic	All person-days (N=85,074) N (% of total)	Person-days with injurious fall (N=220) N	Person-days without injurious fall (N=84,854) N
Demographic data			
Gender			
male	34,282(40.3)	92(41.8%)	34,190(40.3%)
female	50,792(59.7)	128(58.2%)	50,664(59.7%)
Falls history	45,982(54.0)	168(19.1%)	45,814(20.5%)
Visual impairment	18,139(21.3)	38(17.3%)	18,101(21.3%)
Urinary incontinence	44,310(52.1)	124(56.4%)	44,310(52.0%)
Parkinson's disease	1,151(1.4)	3(1.4%)	1,151(1.4%)
Arthritis and other joint diseases	23,074(27.1)	75(34.1%)	22,999(27.1%)
Depression	7,161(8.4)	26(11.8%)	7,135(8.4%)
Cardiovascular diseases	61,123(71.8)	165(75.0%)	60,958(71.8%)
Drug use			
Antipsychotics (ATC-code N05A)	38,662(45.4)	126(57.3%)	38,536(45.4%)
Anxiolytics (ATC-code N05B)	17,781(20.9)	58(26.4%)	17,723(20.9%)
Hypnotics or sedatives (ATC-code N05C)	11,538(13.6)	44(20.0%)	11,494(13.5%)
Antidepressants (ATC-code N06A)	13,729(16.1)	62(28.2%)	13,667(16.1%)
Tricyclic antidepressants (ATC-code N06AA)	1,141(1.3)	2(0.9%)	1,139(1.3%)
Selective serotonin reuptake inhibitors (ATC-code N06AB)	11,105(13.1)	55 (25.0%)	11,050(13.0%)
Other antidepressants (ATC-code N06AX)	1,739(2.0)	5(2.3%)	1,734(2.0%)
Antihypertensives (ATC-codes C02, C03, C07, C08, C09)	12,081(14.2)	41(18.6%)	12,040(14.2%)
Anti-arrythmics (ATC code C01B)	8,069(9.5)	24(10.9%)	8,045(9.5%)
Nitrates and other vasodilators (ATC code C01D)	2,830(3.3)	7(3.2%)	2,823(3.3%)
Digoxin (ATC code C01AA05)	2,865(3.4)	7(3.2%)	2,858(3.4%)
Beta-blocker eye drops (ATC code S01ED)	798(0.9)	3(1.4%)	795(0.9%)
Analgesics (ATC code N02)	1,684(2.0)	5(2.3%)	1,679(2.0%)
Anticholinergic drugs (ATC codes R03BB01, G04BD07)	138(0.2)	0(0.0%)	138(0.2%)
Antihistamines (ATC code R06)	2,538(3.0)	4(1.8%)	2,534(3.0%)
Antivertigo drugs (ATC code N07C)	202(0.2)	0(0.0%)	202(0.2%)
Drugs used in diabetes (ATC code A10)	5,172(6.1)	13(5.9%)	5,159(6.1%)

such as grazes, open wounds, sprains, bruises, and swellings. Characteristics of the study population and incidence of injurious falls are presented in Table 1.

Prevalence of antidepressant use

During a total of 13,729 (16.1%) person-days an antidepressant was used, of which 11,105 (13.1%) person-days concerned the use of a SSRI (mean DDD=0.95, sd=0.28). The SSRIs used were citalopram (6,969 person-days, mean DDD=0.96, sd=0.28), paroxetine (4,199 person-days, mean DDD=0.89, sd=0.25), sertraline (116 person-days, DDD=1.00), and fluvoxamine (43 person-days, DDD=0.40). Tricyclic antidepressants used were amitriptyline (75 person-days, mean DDD=0.20, sd=0.07), and nortriptyline (1,066 person-days, mean DDD=0.62, sd=0.36). Other antidepressants used were trazodone (847 person-days, mean DDD=0.37, sd=0.18), and mirtazapine (892 person-days, mean DDD=0.80, sd=0.25). We found no person-days of SSRIs co-administered with a cytochrome P450 (1A2, 2C9, 2C19, and 2D6 pathways) inhibitor.[24]

Risk of an injurious fall

Table 2 presents the univariate HRs for injurious falls. The results of the multivariate analysis are presented in Table 3. The risk of an injurious fall increased with age (HR 1.05, 95% CI 1.01 to 1.09). The risk of an injurious fall also increased with the use of antipsychotics (HR 1.76, 95% CI 1.18-2.63), and antidepressants (HR 2.58, 95% CI 1.57 to 4.24). Analysis of subgroups of antidepressants showed that only the use of SSRIs (HR 2.50, 95% CI 1.50 to 4.19) remained significant.

Dose-response relationships with injurious fall risk

Significant dose-response relationships were found for the use of hypnotics or sedatives (HR 2.55, 95% CI 1.03 to 6.30), and antidepressants (HR 2.97, 95% CI 1.95 to 4.53). Analysis of subgroups of antidepressants showed that only the dose-response relationship for the use of SSRIs (HR 2.98, 95% CI 1.94 to 4.57) remained significant.

Table 4 shows the probability of an injurious fall in percentages per day for various doses of SSRIs and hypnotics or sedatives, and for various combinations of SSRIs with hypnotics or sedatives. The figures in Table 4 stand for absolute risk. A priori we do not know which patient it concerns. Therefore, we predicted the probability to experience an injurious fall for a person with average characteristics, except for age and gender. Absolute risks are stratified at age 80 and 85 for a male and a female resident. Increases in the absolute risk of an injurious fall for various combinations of doses of a SSRI with a hypnotic or sedative were found for both males and females, for different ages. An example of a patient in Table 4, which shows the increase in absolute risk of an injurious fall, is shown in Figure 1.

Table 2 Univariate hazard ratios for injurious falls

Characteristic	HR Injurious falls (95% CI)	p-value		p-value
Demographic data				
Gender				
male	0.93(0.55-1.56)	0.77		
female	ref			
Age(continuous variable)[b]	[a]1.04(1.01-1.08)	0.02		
Falls history	0.97(0.48-1.95)	0.93		
Visual impairment	0.86(0.45-1.63)	0.64		
Urinary incontinence	1.16(0.69-1.94)	0.58		
Parkinson's disease	0.96(0.17-5.50)	0.96		
Arthritis and other joint diseases	1.42(0.81-2.51)	0.22		
Depression	1.95(0.88-4.32)	0.10		
Cardiovascular diseases	1.34(0.73-2.44)	0.35		
Drug use	Use/no-use (95% CI)		Dose-response[c] (95% CI)	
Antipsychotics	[a]1.86(1.24-2.78)	0.00	2.21(0.89-5.48)	0.09
Anxiolytics	1.28(0.78-2.10)	0.33	1.40(0.85-2.33)	0.19
Hypnotics or sedatives	[a]2.10(1.19-3.68)	0.01	[a]2.79(1.13-6.91)	0.03
Antidepressants	[a]2.77(1.68-4.57)	0.00	[a]2.96(1.94-4.53)	0.00
Tricyclic antidepressants	1.35(0.19-9.65)	0.77	0.23(0.00-70.38)	0.62
Selective serotonin reuptake inhibitors	[a]2.74(1.63-4.62)	0.00	[a]3.00(1.95-4.62)	0.00
Other antidepressants	1.35(0.39-4.73)	0.64	1.10(0.49-2.49)	0.81
Antihypertensives	1.39(0.79-2.47)	0.26	1.15(0.91-1.46)	0.25
Anti-arrythmics	1.22(0.59-2.55)	0.59	1.23(0.51-2.98)	0.65
Nitrates and other vasodilators	0.84(0.22-3.22)	0.80	1.31(0.54-3.15)	0.55
Digoxin	0.87(0.21-3.58)	0.84	0.77(0.02-28.58)	0.89
Beta-blocker eye drops	1.68(0.23-12.30)	0.61	1.17(0.03-39.71)	0.93
Analgesics	1.45(0.48-4.36)	0.50	1.17(0.96-1.43)	0.11
Antihistamines	0.63(0.19-2.12)	0.46	0.91(0.43-1.92)	0.80
Drugs used in diabetes	0.95(0.34-2.65)	0.92	1.00(0.56-1.78)	1.00

Abbreviations: CI, confidence interval; HR, hazard ratio. All estimates are adjusted for gender and age.

[a]Significant parameters.

[b]HR per year.

[c]HR for increase with 1 DDD.

Table 3 Multivariate hazard ratios for injurious falls

Characteristic	HR Injurious falls (95% CI)	p-value		p-value
Gender				
male	(ns) 1.20(0.71-2.04)	0.50		
female	ref			
Age[a]	1.05(1.01-1.09)	0.01		
Drug use	Use/no-use (95% CI)		Dose-response[b] (95% CI)	
Antipsychotics	1.76(1.18-2.63)	0.01		
Hypnotics or sedatives	(ns) 1.69(0.96-2.98)	0.07	2.55(1.03-6.30)	0.04
Antidepressants	2.58(1.57-4.24)	0.00	2.97(1.95-4.53)	0.00
Selective serotonin reuptake inhibitors	2.50(1.50-4.19)	0.00	2.98(1.94-4.57)	0.00

Abbreviations: CI, confidence interval; HR, hazard ratio; ns, not significant.

[a]HR for age (continuous variable) HR per year.

[b]HR for increase with 1 DDD.

DISCUSSION

The main finding of this study in nursing home residents with dementia is that there is a dose-response relationship between the use of a SSRIs and a fall with a subsequent injury. The risk of an injurious fall increased with increasing doses of SSRIs. The combination of a SSRI with a hypnotic or sedative increased the risk even further.

Strength and limitations of this study

The main strength of this study is that data on medication use were collected for each day of the study period. Therefore, no misclassification was induced by the use of baseline measurement of drug use. This type of misclassification has been shown to increase with the length of a study period.[32] Another strength of this study is the fact that there was no selection bias. All eligible residents participated in the study. Furthermore, all falls were recorded by the nursing staff regardless of the type of drugs a resident might have taken. So there was no registration bias. However, as the outcome measure was injurious falls rather than falls, it might be possible that residents with depression were more likely to have their falls recorded as injurious (e.g. appear to be more distressed, take longer to get up etc.) and were also more likely to use a SSRI. This might have led to an overestimation of our results.

Confounding by indication may be a limitation to our study. The differences in patient characteristics, which are related to the use of a SSRI and the occurrence of an injurious fall, are probably difficult to adjust for.[33] First, the underlying depression rather than the use of a SSRI might have caused the fall.[34] However, in a study which was adequately

Table 4 Absolute risk of an injurious fall per day for the use of SSRIs and hypnotics or sedatives

	No SSRIs	0.25 DDD SSRIs	0.50 DDD SSRIs	1.00 DDD SSRIs
Absolute risk of an injurious fall		**No co-prescribed hypnotics or sedatives**		
p(f,80) (95%CI)	0.09 (0.06-0.14)	0.12 (0.09-0.18)	0.16 (0.11-0.24)	0.28 (0.17-0.45)
p(m,80) (95%CI)	0.13 (0.07-0.17)	0.17 (0.10-0.22)	0.22 (0.13-0.29)	0.38 (0.20-0.55)
p(f,85) (95%CI)	0.12 (0.08-0.17)	0.15 (0.11-0.22)	0.20 (0.14-0.29)	0.35 (0.22-0.56)
p(m,85) (95%CI)	0.16 (0.09-0.22)	0.21 (0.12-0.28)	0.28 (0.15-0.38)	0.48 (0.24-0.72)
Increase in absolute risk of an injurious fall[a]	ref	31%	73%	198%
	No SSRIs	**0.25 DDD SSRIs**	**0.50 DDD SSRIs**	**1.00 DDD SSRIs**
Absolute risk of an injurious fall		**0.50 DDD hypnotics or sedatives**		
p(f,80) (95%CI)	0.15 (0.09-0.25)	0.20 (0.12-0.33)	0.26 (0.15-0.43)	0.44 (0.25-0.80)
p(m,80) (95%CI)	0.20 (0.10-0.30)	0.27 (0.14-0.39)	0.35 (0.18-0.51)	0.61 (0.29-0.96)
p(f,85) (95%CI)	0.19 (0.11-0.31)	0.25 (0.15-0.40)	0.32 (0.20-0.53)	0.56 (0.31-0.99)
p(m,85) (95%CI)	0.26 (0.13-0.38)	0.34 (0.17-0.50)	0.44 (0.22-0.66)	0.76 (0.35-1.23)
Increase in absolute risk of an injurious fall[a]	59%	109%	174%	373%
	No SSRIs	**0.25 DDD SSRIs**	**0.50 DDD SSRIs**	**1 DDD SSRIs**
Absolute risk of an injurious fall		**1.00 DDD hypnotics or sedatives**		
p(f,80) (95%CI)	0.24 (0.10-0.58)	0.31 (0.13-0.76)	0.41 (0.17-1.00)	0.71 (0.28-1.80)
p(m,80) (95%CI)	0.33 (0.12-0.68)	0.43 (0.15-0.89)	0.56 (0.20-1.17)	0.97 (0.33-2.11)
p(f,85) (95%CI)	0.30 (0.12-0.72)	0.39 (0.16-0.94)	0.51 (0.21-1.23)	0.88 (0.35-2.22)
p(m,85) (95%CI)	0.41 (0.14-0.86)	0.53 (0.19-1.13)	0.70 (0.25-1.49)	1.21 (0.41-2.69)
Increase in absolute risk of an injurious fall[a]	152%	232%	336%	651%

Abbreviations: DDD=Defined Daily Dose; p(f,80)=absolute risk of an injurious fall in percentages per day for females aged 80; p(m,80)=absolute risk of an injurious fall in percentages per day for males aged 80; p(f,85)=absolute risk of an injurious fall in percentages per day for females aged 85; p(m,85)=absolute risk of an injurious fall in percentages per day for males aged 85. Hypnotics or sedatives (N05C); SSRIs (N05AB).

[a]The increase in absolute risk of an injurious fall is relative to a person of any age taking no SSRIs and no sedatives or hypnotics.

controlled for confounding by indication by restricting the analysis to antidepressant users, SSRI users still had an increased risk of a fracture.[14]

Another potential limitation concerns the possible cytochrome P450 interactions. Some SSRIs are moderate to strong inhibitors of certain cytochrome P450 enzymes – notably paroxetine (strong inhibitor of CYP2D6), fluvoxamine (strong inhibitor of CYP1A2 and weaker inhibitor of CYP2C9 and CYP3A4), sertraline (moderate inhibitor

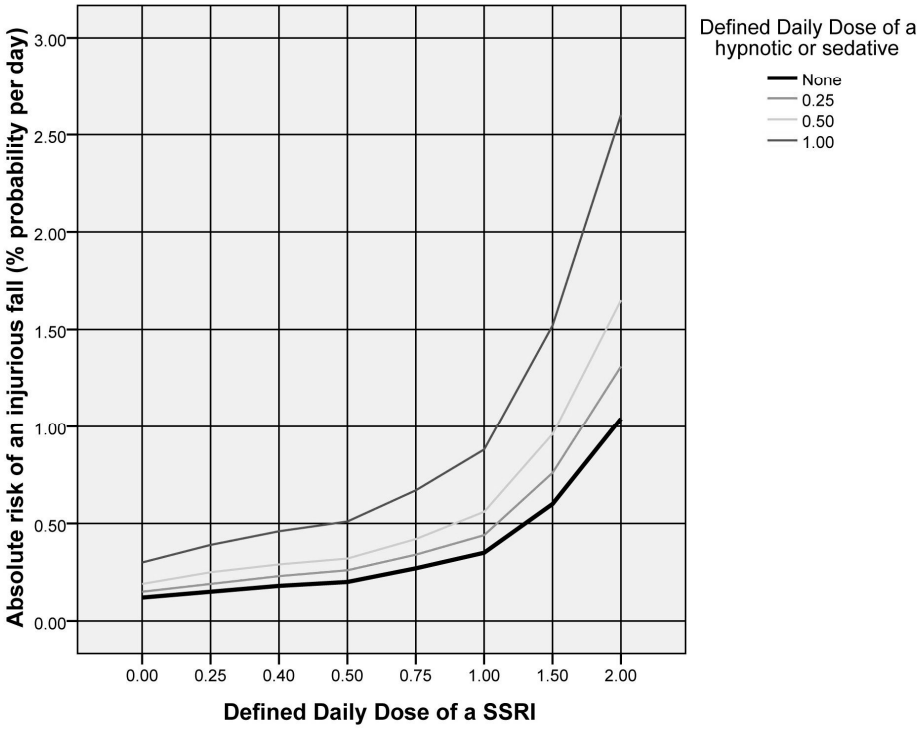

Figure 1 Absolute risk of an injurious fall (% per day) for a female resident aged 85 by SSRI defined daily dose and co-prescribed hypnotic or sedative defined daily dose

of CYP2D6), and citalopram (weak inhibitor of CYP2D6). Thus it is certainly a possibility that the presence of SSRIs causes pharmacokinetic inhibition of the metabolism of other co-prescribed drugs. Therefore co-prescribed fall risk increasing drugs such as benzodiazepines (CYP 3A4 substrates), antihypertensives (CYP2D6 and 3A4 substrates), and antipsychotics (CYP2D6, 3A4, 1A2 substrates and others) might have had higher plasma concentrations than in the absence of SSRIs.[24] Previous research in old age psychiatry inpatients has shown that CYP2D6 and CYP3A4 interactions involving a SSRI as an inhibitor are common in old age psychiatry inpatients.[35] These interactions may have been present in our study population, but were not the focus of the current study.

Third, neuropsychiatric symptoms and behavioural disturbances, like agitation and aggressive behaviour, for which SSRIs are recommended in dementia patients,[36] may themselves lead to an increased fall risk and may result in higher drug doses. We were not able to control for this type of confounding by indication since there was no standard procedure in place to quantify and record neuropsychiatric symptoms and behavioural disturbances in the medical charts. However, recent studies have shown that behavioural and neuropsychiatric symptoms as measured with the Neuropsychiat-

ric Inventory – Nursing Home version (NPI–NH)[37-38] are very common in nursing home patients with dementia stage 5 or 6 on the GDS,[18] with more than 80% showing at least one clinically relevant symptom.[39-40] Because all residents in the study population were nursing home residents with dementia stage 5 or 6 on the GDS,[18] they were all likely to have neuropsychiatric symptoms and behavioural disturbances fitting with these stages of dementia, which may reduce confounding by indication.

Another potential limitation might be that our study is from a single institution. In our study there were no users of fluoxetine or escitalopram, which are widely prescribed in many countries.[41] However, we think that our results are generalizable, because the high prevalence of antidepressant prescriptions in our study is comparable with both Dutch and international studies in nursing home settings.[8-9]

Our findings are consistent with earlier studies on the use of SSRIs and injurious falls.[12, 15, 42] However, one of these earlier studies was done in a mixed nursing home population (residents with dementia, and residents without dementia), and did not investigate the dose-response relationship.[12] To the best of our knowledge, ours is the first study which assessed the dose-response relationship between SSRIs and injurious fall risk in nursing home residents with dementia. Another study on the risk of fractures with SSRI use found a significant dose-response relationship for the risk of a fracture, but it was done in the general population (mean age 43.4 years; sd 27.4).[15, 42] We found an increased dose-dependent risk for injurious falls, but not for fractures. However, it is possible that with a larger sample or longer observations, we might have found a dose-dependent relationship for fractures. For, the increased fracture risk of SSRIs that was found in other studies may be linked to their effect on the serotonin transporter system.[15]

It has been shown that users of SSRIs have a 2.35-fold (95% CI 1.23-3.50) increased risk of a fracture, which further increased with prolonged use.[14] Moreover, in general, it has not been shown that higher doses are more effective in the treatment of depressive symptoms.[43] Furthermore, there is a paucity of studies on the efficacy of SSRIs in the treatment of depression in patients with dementia, and on the correlation between SSRI dose and effect in this specific population. Available evidence offers only weak support to the contention that SSRIs are an effective treatment for patients with depression and dementia.[44] Further studies in patients with dementia and depression are needed. Given that they may produce serious side effects clinicians should prescribe SSRIs with due caution to nursing home residents with dementia and depression.

Conclusion

Even at low doses, SSRIs are associated with increased risk of an injurious fall in nursing home residents with dementia. Higher doses, which were most prevalent in our study population, increased the risk further, with a threefold risk at 1.00 DDD. The use of a SSRI

in combination with a hypnotic or sedative further increased the risk. The results of this study lend support to the consideration that new treatment protocols might be needed that take into account the dose-response relationship between SSRIs and injurious falls.

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CHAPTER 8

General discussion

1. INTRODUCTION

The objective of this thesis was to gain more knowledge about the assessment of balance and gait with regard to fall risk, and about the contribution of psychotropic drugs to fall risk in a population of nursing home residents with dementia. This thesis is divided in two parts. In part one we analyse balance and gait parameters; in part two the contribution of psychotropic drug use to fall risk in nursing home residents with dementia.

Part one

- Two prospective cohort studies of balance and gait as predictors for falls, in which we evaluated the feasibility and validity of a clinical measurement, the POMA, and an electronic walkway system, the GAITRite® to predict fall risk in nursing home residents with dementia.

Part two

- First, a systematic review of the literature on the influence of psychotropic drug use on fall risk in nursing home residents with dementia. Second, a retrospective database analysis of psychotropic drug use and falls; and of psychotropic drug use and injurious falls in nursing home residents with dementia. During a two-year period, data on psychotropic drug use and falls were collected for each day of the study period.

In this general discussion, we will start to answer our research questions one by one. Then we consider the methodological and theoretical issues regarding the studies that

were conducted. Finally, we will give recommendations for clinical practice and for future research.

2. MAIN FINDINGS

Fall risk and balance and gait impairments

We conducted two prospective cohort studies of balance and gait as predictors for falls to answer the three research questions in part one of this thesis:

1. Is the Tinetti Performance Oriented Mobility Assessment (POMA) a feasible and valid instrument to predict short-term fall risk in ambulatory nursing home residents with dementia?
2. Is an electronic walkway system a feasible and valid instrument to predict short-term fall risk in ambulatory nursing home residents with dementia?
3. Which of the gait parameters has the best predictive value with regard to fall risk in this specific population?

In our study population the POMA showed several feasibility problems, with 41% of patients having problems in understanding one or more instructions. Nevertheless, we found that the predictive validity of the POMA was acceptable. After adjustment for potential confounders in a multivariate model, we found that the POMA was significant in predicting a fall. Per point lower, the risk of a fall increased with 8%.

We found that the electronic walkway system was a feasible instrument for the prediction of fall risk in nursing home residents with dementia. The test procedure took on average only 5 minutes per resident, and only some physical cueing or assistance was needed. We also found that the electronic walkway system had an acceptable validity to predict a fall. After adjustment for potential confounders in a multivariate model, we found that the gait parameters velocity and mean stride length were the best significant gait predictors of a fall within three months. With a decrease in gait velocity of 10 cm/s the risk of a fall increased with 22%. Per 10 centimetre decrease in mean stride length the risk of a fall increased with 19%.

We conclude that both the POMA and an electronic walkway system are valid instruments to predict short-term fall risk in nursing home residents with dementia. With regard to feasibility, the electronic walkway system is preferable because this instrument saves time and is not hampered by information losses as met with the application of the POMA.

Fall risk and psychotropic drug use

We formulated three research questions to be answered in part two of this thesis:

1. Which psychotropic drugs increase fall risk and what is known about the influence of these drugs on gait in nursing home residents with dementia?
2. What is the magnitude of the associations between specific psychotropic drugs and fall risk in nursing home residents with dementia?
3. Are there dose-response relationships between specific psychotropic drugs and fall risk in nursing home residents with dementia; and are there dose-response relationships between specific psychotropic drugs and the risk of an injurious fall?

We found in a systematic review of the literature that there is a paucity of data on the relation between psychotropic drug use and fall risk in nursing home residents with dementia. We summarized the results of 17 prospective cohort studies. However, none of these 17 studies conducted a sub-group analysis for the specific group of nursing home residents with dementia. Furthermore, we found that the relative contribution to fall risk of each drug class was not clear from the current literature. Also little was found about dose and duration of use in relation to fall risk in nursing home residents with dementia. We found no studies that described gait parameters as outcome measure for psychotropic drug use. Thus we found no evidence for the influence of psychotropic drugs on gait parameters in nursing home residents with dementia.

The main finding of our retrospective database analysis is that we have quantified the contribution of specific psychotropic drugs to fall risk in nursing home residents with dementia. It is generally accepted that falls are an intrinsic component of dementia and living in a nursing home. However, we found an additive contribution of psychotropic drugs to fall risk. After adjustment for potential confounders (i.e., drugs, co-morbidities, falls history, age and gender) in a multivariate model, we found that the use of antipsychotics (HR 1.53, 95% CI 1.17 to 2.00), anxiolytics (HR 1.60, 95% CI 1.19 to 2.16), hypnotics and sedatives (HR 1.50 95% CI 1.04 to 2.16), and antidepressants (HR 2.28, 95% CI 1.58 to 3.29) increased fall risk.

With regard to the dose-response relationships between specific psychotropic drugs and fall risk we found significant dose-response relationships for the use of antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants. Fall risk increased significantly with 28% at 0.25 of the Defined Daily Dose (DDD) of an antipsychotic or antidepressant, with 8% at 0.2 of the DDD of an anxiolytic, and with 56% at 0.5 of the DDD of a hypnotic or sedative; it increased further with dose increments, and with combinations of psychotropics.

With regard to the dose-response relationships between specific psychotropic drugs and the risk of an injurious fall we found a significant dose-response relationship for the use of selective serotonin reuptake inhibitors (SSRIs). The risk of an injurious fall increased significantly with 31% at 0.25 of the DDD of a SSRI. Higher doses increased

the risk further with a threefold risk at 1.00 DDD (HR 2.98, 95% CI 1.94-4.57). The risk increased further with the use of a SSRI in combination with a hypnotic or sedative.

We conclude that the use and higher dosages of psychotropics are associated with an increased fall risk in nursing home residents with dementia, and that the use and higher dosages of SSRIs are associated with an increased risk of an injurious fall in this population.

3. METHODOLOGICAL AND THEORETICAL ISSUES

Before we can give recommendations for clinical practice and future research, some methodological issues need to be considered. As some of these have already been discussed in the previous chapters, in this section we will review more general methodological issues with regard to our prospective cohort study, and our retrospective database analysis.

Prospective cohort study on fall risk and balance and gait impairments

Regarding the prospective cohort study, there are some methodological points that need consideration. A strength of this study is the relatively homogeneous population of residents with dementia stage 5 or 6 on the Global Deterioration Scale (GDS).[1] However, a potential limitation concerns the relatively small samples in our studies, which may hamper the generalizability of our results.

A second potential limitation concerns the fact that selection bias and selective loss to follow-up could have influenced our results. The true relationship between the balance and gait measurements and falls, might be distorted if consent was lower among legal guardians of residents in more severe stages of dementia, and if more severely impaired residents were lost to follow-up. Gait disturbances have been shown to vary according to the stage of the disease,[2-3] but it has also been shown that residents with more severe cognitive impairment are no more likely to fall than residents with moderate cognitive impairment,[4] Therefore, the predictive validity of the POMA and the electronic walkway system may have been overestimated. However, we think this potential overestimation would have been relatively small because all residents of this nursing home (both participants and nonparticipants) were in stage 5 or 6 on the GDS.[1]

A third point that needs to be considered is the fact that baseline data, that were considered as potential confounders, were abstracted from medical records and nursing home charts on the day the balance and gait measurements took place. When a fall occurred during the follow-up period, residents were not examined again for new co-morbidities. We registered no data on symptoms of disease or changes in medical

conditions which could be precipitating factors associated with a fall. Due to this limitation we may have overestimated the predictive validity of the POMA and the electronic walkway system.

Retrospective database analysis on fall risk and psychotropic drug use

The main strength of our study on drugs and (injurious) falls is our large and detailed dataset of 85,074 person-days in which all eligible residents were included. For each day of the study period, data on drug use were abstracted from the prescription database, and falls were retrieved from a standardized incident report system. Therefore, no misclassification was induced by the use of baseline measurement of drug use.[5] Because of our large and detailed dataset we were able to identify the dose-response relationship between psychotropic drugs and (injurious) fall risk. Another strength of this study is the relatively homogeneous population of residents with dementia stage 5 or 6 on the GDS.[1] As far as we are aware, we were the first to study the contribution of psychotropic drugs to falls in this population. For, it appeared from our systematic review as described in chapter 5 that there were no previous studies that conducted a sub-group analysis for this specific group of nursing home residents with dementia.

A potential limitation that has to be considered is that our study was performed in a single institution. However, the high prevalence of psychotropic drug use in our study is comparable with both Dutch and international studies in nursing home settings.[6-9] Moreover, also the prevalence of falls,[10] and of injurious falls[11] in our study is comparable with other studies in nursing homes. Therefore, we think that the results of our studies on psychotropic drugs and (injurious) falls will be generalizable to other nursing homes with residents with dementia, but this has to be demonstrated in multicenter studies in different countries.

The retrospective study design of our studies on drugs and (injurious) falls also necessitates some consideration. Retrospective studies have the advantage of being relatively quick and inexpensive to implement. A disadvantage is that the gathered data was limited to the information available in the medical charts. Therefore, not all potentially relevant variables were included in the study like measures of the drugs' indications. Many indications for the study drugs (e.g. depression, sleep disorder, agitation)[12-14] are also fall risk determinants and indications for higher doses. We were not able to control for this type of confounding by indication since there was no standard procedure in place to quantify and record neuropsychiatric symptoms and behavioral disturbances in the medical charts. If we assume that residents with more severe neuropsychiatric symptoms received higher doses of psychotropic drugs, then this might have led to an overestimation of the dose-response relationship.

4. RECOMMENDATIONS FOR CLINICAL PRACTICE

Balance and gait assessment

Mobility, i.e., the ability to get around in one's environment, is a complicated function composed of multiple component manoeuvres. The assessment of mobility problems related to fall risk includes direct observation of the items of the POMA-Balance test, and the POMA-Gait test.[15] By observing balance and gait components, underlying abnormalities can be screened, and possible restorative, preventive, or adaptive measures can be identified.[15]

For clinical practice, we recommend to use the POMA for those residents who understand the instructions, especially since the POMA has a balance component besides a gait component. Impairments in balance could be important targets for interventions. However, for residents who have problems to understand the instructions of the POMA, an electronic walkway system is preferable because this instrument saves time and is not hampered by feasibility problems and information losses as seen with the application of the POMA. Furthermore, the resident is not confronted with tasks that are too difficult. If the use of an electronic walkway system in practice is hindered because of cost constraints, we believe that velocity, which was the best predictive parameter for a fall, can alternatively be measured in a standardized way for example using a stopwatch, such as in the 4-meter walking test.[16]

Psychotropic drugs and falls

The results of our study have important clinical implications. The study lends support to the current opinion that implementation of effective nonpharmacological interventions should be tried before psychotropic drugs are prescribed to nursing home residents with dementia.[17] Our findings demonstrate the necessity of investing in professionals in nursing homes to be able to cope with the complex problems they are faced with. The Dutch guideline on diagnosis and management of dementia recommends psychosocial interventions as first-line treatment of neuropsychiatric symptoms.[18] Also bright light, education of the staff about sleep hygiene, aromatherapy, activity and exercise have been shown to be effective for the management of neuropsychiatric symptoms and behavioral disturbances which frequently occur in persons with dementia.[19-20]

With regard to the use of antipsychotics, there is growing evidence that discontinuation of antipsychotics is possible without an increase in problem behaviours,[21] and that the most promising treatments are individually tailored behavioural interventions.[22] Regarding the limited effectiveness of antipsychotics,[17, 23-26] the risk of stroke and increased mortality,[27-29] and the nonpharmacological alternatives,[19-20] the question arises whether these drugs should be prescribed at all to patients with dementia. If antipsychotics need

to be prescribed, their use should be restricted to the lowest possible dose and the need for continuation should be re-assessed on a regular basis.

Concerning the use of antidepressants, in current practice SSRIs are considered the best choice because of the less serious side effects in dementia[17, 30] compared with other types of antidepressants.[31-32] However, evidence is increasing that SSRIs are associated with falls and fractures.[33-35] In our study we found a strong dose-response relationship between SSRIs and injurious falls. So, physicians should be cautious in prescribing SSRIs, even at low doses. Preference should be given to nonpharmacological interventions for depressive symptoms in persons with dementia. It has been shown that depression in nursing home residents with dementia can be reduced if well-trained nursing assistants help residents to undertake pleasant activities and to worry less.[36]

5. RECOMMENDATIONS FOR FUTURE RESEARCH

We have three recommendations for further research. First, to refine our findings, large prospective studies on the predictive validity of balance and gait measurements for falls in a population with moderate to severe dementia are needed, and should focus on the differences in test and assessment methods, including more sophisticated technology such as an electronic walkway system. In addition, we recommend future research to determine whether fall risk profiles that consist of multiple fall predictors achieve better prediction of short-term fall risk than balance and gait measurements only.

Our second recommendation for future research concerns gait training in physical therapy. In physical therapy, gait training may focus on increasing gait velocity and mean stride length. We imagine that a retained ability to increased velocity and mean stride length, may be ideal candidates for interventions aimed at preventing falls. The question that will have to be addressed in future research is whether velocity and mean stride length are useful as outcome measures to evaluate the effect of interventions.

Third, our analysis of psychotropic drugs and falls was a retrospective study in a single institution. Multicenter prospective studies in similar populations are needed to confirm our findings. In addition, forthcoming research should analyse the temporal relationship between a fall and the initiation of a particular drug, as it is important to know when the risk of falling is highest in the days following the start or the increase of a certain drug.

Finally, our study experiences point to one last ethical consideration regarding research with nursing home residents with dementia. As mentioned above, more research within this specific population is needed. However, studies on patients with dementia are difficult to conduct because these patients may have limited capacity to give informed consent to participate in clinical research. Moreover, regulations have formulated that

potential research subjects who are incompetent "must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden".[37] Our studies have shown that research within this population can be carefully conducted by experienced caregivers, primarily using existing data sources and thereby minimising the burden to the participants. Since this type of research may lead to important knowledge gains and potential health benefits to nursing home residents with dementia, it should be continued and expanded in the future.

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CHAPTER 9

Summary/Samenvatting

Falls are a major health problem among older people, particularly in nursing homes, and are associated with considerable morbidity and mortality. In nursing homes one-third of all falls results in an injury. Falls in nursing homes are usually multifactorial in origin. Among others, dementia, balance and gait impairments, and psychotropic drug use (antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants) have been associated with an increased fall risk. In this thesis we focus on these three fall risk factors.

In part one of this thesis (**chapter 3 and 4**) we evaluate the feasibility and predictive validity of two assessment methods for balance and gait impairments in this population with a specific view to predicting falls in the short term, i.e., three months. There, we address the questions: 1) Is the Tinetti Performance Oriented Mobility Assessment (POMA) a feasible and valid instrument to predict short-term fall risk in ambulatory nursing home residents with dementia? 2) Is an electronic walkway system a feasible and valid instrument to predict short-term fall risk in ambulatory nursing home residents with dementia? 3) Which of the gait parameters has the best predictive value with regard to fall risk in this specific population?

In part two of this thesis (**chapter 5,6 and 7**) we quantify the contribution of specific (combinations of) psychotropic drugs to fall risk in nursing home residents with dementia. We address three specific research questions: 1) Which psychotropic drugs increase fall risk and what is known about the influence of these drugs on gait in nursing home residents with dementia? 2) What is the magnitude of the associations between specific psychotropic drugs and fall risk in nursing home residents with dementia? 3) Are there dose-response relationships between specific psychotropic drugs and fall risk in nursing home residents with dementia; and are there dose-response relationships between specific psychotropic drugs and the risk of an injurious fall?

Chapter 1 gives a general introduction of this thesis. In **chapter 2** we describe the rationale for starting this study, and we formulate the research questions of this thesis.

Chapter 3 presents the results of a prospective cohort study in which we evaluated the clinimetric properties of the POMA with a specific view to predicting falls in the short-term. In this study, the POMA showed several feasibility problems, with 41% of the residents having problems in understanding the instructions of one or more items of the test. Hence it was not possible to score these items. The inter-rater reliability of the instrument was good. The predictive validity was acceptable, and the POMA was significant in predicting a fall. **Chapter 4** presents the results of a prospective cohort study in which we evaluate the feasibility and validity of gait parameters measured with an electronic walkway system in predicting short-term fall risk. Our results showed that gait parameters as measured with an electronic walkway system can be used for the prediction of short-term fall risk, and that velocity and mean stride length were the best significant gait predictors. The test procedure took only five minutes per resident, and for its conduction only some physical cueing or assistance was needed.

Chapter 5 presents a systematic review of the literature. We investigated which psychotropic drugs increased fall risk and what was known about the influence of these drugs on gait in nursing home residents with dementia. We summarised the results of 17 prospective cohort studies. These studies consistently showed an increased fall risk for the use of multiple psychotropic drugs, anxiolytics, and antidepressants. The evidence for other psychotropic drug classes was limited or inconclusive. Our initial approach was to analyse the data of nursing home residents with dementia only. However, none of the studies we found used a sub-group analysis for this specific group of residents. We also found that little was known about the influence of psychoactive drugs on gait parameters.

Chapter 6 presents our analysis of the magnitude of the associations between specific psychotropic drugs and fall risk. We found that the use of antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants significantly increased fall risk. We also found significant dose-response relationships for the use of antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants. Fall risk was already increased significantly at low dosages of these drugs; it increased further with dose increments, and with combinations of psychotropics. **Chapter 7** describes our analysis of the dose-response relationship between the use of the most used an preferred antidepressants {i.e., selective serotonin reuptake inhibitors (SSRIs)} and injurious falls. We found a significant dose-response relationship for the use of SSRIs. The risk of an injurious fall was already increased significantly at low dosages; it increased further with dose increments, and in combination with a hypnotic or sedative.

In the general discussion, **chapter 8**, the main findings of this thesis are summarised, and some methodological issues are discussed. In addition, recommendations for clinical practice and for future research are discussed.

SAMENVATTING

Valincidenten komen veel voor bij oudere mensen en vormen een belangrijk gezondheidsprobleem, vooral in verpleeghuizen. De gevolgen kunnen ernstig zijn. In verpleeghuizen leidt één derde van alle valpartijen tot een letsel. Een val wordt vaak veroorzaakt door een combinatie van verschillende factoren. Onder andere, het hebben van een dementie, problemen met het evenwicht en met het lopen en het gebruik van zogenaamde psychotrope medicijnen (antipsychotica, middelen tegen angst en depressie, en slaap-en kalmeringsmiddelen) verhogen de kans op een val. In dit proefschrift richten we ons op deze drie risicofactoren voor vallen.

In het eerste deel van dit proefschrift (**hoofdstuk 3 en 4**) evalueren we de bruikbaarheid en de validiteit van twee verschillende meetinstrumenten voor het evenwicht en het looppatroon in deze populatie. Waarbij we vooral onderzoeken of we met deze meetinstrumenten kunnen voorspellen of een bewoner op korte termijn gaat vallen, dat wil zeggen, binnen drie maanden. De twee onderzoeksvragen in het eerste deel luiden: 1) Is de Tinetti Performance Oriented Mobility Assessment (POMA) een bruikbaar en valide instrument om de kans op een val binnen drie maanden te voorspellen bij zelfstandig lopende verpleeghuisbewoners met dementie? 2) Is een elektronische loopmat een bruikbaar en valide instrument om de kans op een val binnen drie maanden te voorspellen bij zelfstandig lopende verpleeghuisbewoners met dementie? 3) Zo ja, welke facetten van het looppatroon hebben de beste voorspellende waarde in deze doelgroep?

In het tweede deel van dit proefschrift (**hoofdstuk 5,6 en 7**) brengen we in kaart hoe groot de bijdrage is van specifieke psychotrope medicijnen, en van combinaties van deze medicijnen, aan het valrisico van dementerende verpleeghuisbewoners. De drie onderzoeksvragen in het tweede deel luiden: 1) Welke psychotrope medicijnen verhogen het valrisico en wat is er bekend over de invloed van deze medicijnen op het looppatroon bij verpleeghuisbewoners met dementie? 2) Hoe sterk is het verband tussen specifieke psychotrope middelen en de kans op een val bij verpleeghuisbewoners met dementie? 3) Zijn er dosis-respons relaties tussen specifieke psychotrope middelen en de kans op een val bij verpleeghuisbewoners met dementie; zijn er dosis-respons relaties tussen specifieke psychotrope middelen en de kans op een val met letsel bij verpleeghuisbewoners met dementie?

Hoofdstuk 1 geeft een algemene inleiding over de onderwerpen beschreven in dit proefschrift. **Hoofdstuk 2** beschrijft de motivatie om deze studie te starten. Tevens worden in dit hoofdstuk de onderzoeksvragen van dit proefschrift geformuleerd.

In **Hoofdstuk 3** wordt een prospectief cohortonderzoek beschreven naar de klinimetrische eigenschappen van de POMA. Hierin werd nadrukkelijk gekeken naar de bruikbaarheid van de POMA en of deze test een val op de korte termijn (binnen drie maanden) kan voorspellen. In deze studie bleek dat 41% van de bewoners problemen

had met het begrijpen van de instructies van één of meer items van de test, waardoor het niet mogelijk was om deze items te scoren. Verder bleek dat de interbeoordelaarsbetrouwbaarheid van de test goed was, dat de predictieve validiteit acceptabel was, en dat de POMA significant was bij het voorspellen van een val. **Hoofdstuk 4** presenteert de resultaten van een prospectief cohortonderzoek met een elektronische loopmat. Er werd onderzocht in welke mate deze elektronische loopmat bruikbaar is en of de verschillende facetten van het looppatroon een val op korte termijn kunnen voorspellen. Onze resultaten toonden aan dat een elektronische loopmat gebruikt kan worden voor de voorspelling van valrisico op korte termijn. Verder bleek dat de loopsnelheid en de gemiddelde paslengte de beste voorspellers waren voor een val. De testprocedure duurde slechts vijf minuten per bewoner. Voor de uitvoering waren slechts enige fysieke aanwijzingen of hulp noodzakelijk.

In **Hoofdstuk 5** worden de resultaten gepresenteerd van een literatuuronderzoek (systematic review) naar de invloed van psychotrope geneesmiddelen op het valrisico en op het looppatroon van demente verpleeghuisbewoners. In de review zijn 17 prospectieve cohortstudies opgenomen. Deze studies toonden aan dat er een verhoogd valrisico was wanneer meerdere psychotrope middelen tegelijk gebruikt werden, en bij het gebruik van middelen tegen angst en depressie. Het bewijs voor andere psychotrope middelen was beperkt of niet overtuigend. Het was in eerste instantie onze bedoeling om alleen gegevens van verpleeghuisbewoners met dementie te analyseren. Echter, in geen van de studies was een subgroepanalyse gedaan voor deze specifieke groep bewoners. Verder vonden we dat er weinig bekend was over de invloed van psychotrope geneesmiddelen op het looppatroon bij deze doelgroep.

Hoofdstuk 6 beschrijft onze analyse van de sterkte van het verband tussen het gebruik van specifieke psychotrope medicijnen en het valrisico. We vonden dat het gebruik van antipsychotica, middelen tegen angst en depressie, en slaap- en kalmeringsmiddelen het valrisico significant verhoogden. Tevens vonden we significante dosis-respons relaties voor het gebruik van antipsychotica, middelen tegen angst en depressie, en slaap- en kalmeringsmiddelen. Een lage dosering gaf al een verhoogd valrisico. Het valrisico nam verder toe bij een verhoging van de dosis en bij combinaties van psychotrope medicijnen. **Hoofdstuk 7** beschrijft onze analyse van de dosis-respons relatie tussen het gebruik van de meest gebruikte en geprefereerde antidepressiva {selectieve serotonine heropname remmers (SSRI's)} en een val met letsel. We vonden een significante dosis-respons relatie voor het gebruik van SSRI's. Het risico op een val met letsel nam al toe bij een lage dosering. Het risico nam verder toe bij een verhoging van de dosis en in combinatie met een slaap- of kalmeringsmiddel.

In de algemene discussie, **hoofdstuk 8** worden de belangrijkste bevindingen van dit proefschrift samengevat. Tevens wordt een aantal methodologische aspecten besproken. Tot slot worden aanbevelingen voor de klinische praktijk en voor toekomstig onderzoek besproken.

DANKWOORD

Dit proefschrift is tot stand gekomen dankzij de hulp, de inbreng en de ondersteuning van vele anderen. Allereerst wil ik de deelnemers en hun zorginhoudelijk vertegenwoordigers bedanken. Zonder hun toestemming was dit onderzoek niet mogelijk geweest.

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CURRICULUM VITAE

Shanty Sterke werd op 18 september 1964 geboren te Spijkenisse. In 1983 behaalde zij haar VWO diploma aan de Openbare Scholengemeenschap "de Ring van Putten" te Spijkenisse. In 1984 begon zij met haar opleiding fysiotherapie aan de Hogeschool Rotterdam. In 1988 behaalde zij haar Bachelor's degree (eindexamenscriptie *cum laude*). Na de studie werkte zij in 1989 en 1990 als assistent-onderzoeker in het anatomisch laboratorium van het Erasmus Medisch Centrum, hierna Erasmus MC, in Rotterdam. In 1991 begon zij als praktiserend fysiotherapeut in psychogeriatrisch verpleeghuis Smeetsland te Rotterdam. Daarnaast studeerde zij Bewegingswetenschappen aan de Vrije Universiteit te Amsterdam (propedeuse *cum laude*). In december 2002 behaalde zij haar Master's degree. Dankzij de steun van de directie en management van verpleeghuis Smeetsland, het bestuur van de StromenOpmaatGroep, en de Sector Geriatrie van de afdeling Inwendige Geneeskunde van het Erasmus MC, kon in 2006 een aanvang gemaakt worden met een wetenschappelijk onderzoek naar valincidenten bij verpleeghuisbewoners in psychogeriatrisch verpleeghuis Smeetsland, in samenwerking met de Sector Geriatrie, afdeling Inwendige Geneeskunde, Erasmus MC (Dr. Tischa J.M. van der Cammen) en de afdeling Maatschappelijke Gezondheidszorg, Erasmus MC (Dr. Ed F. van Beeck). De resultaten van dit onderzoek worden beschreven in dit proefschrift. Sinds september 2010 is Shanty parttime aangesteld als projectleider valpreventie in verpleeg- en verzorgingshuis Meerweide. De auteur woont in Rotterdam met haar twee kinderen, Aron (1993) en Maria (1997).

PHD PORTFOLIO

Name PhD student: Shanty Sterke
Erasmus MC Department: Section of Geriatrics, Department of Internal Medicine
Research School: Nihes
PhD period: 2006-2011
Promotor: Prof. dr. ir. A Burdorf
Supervisors: Dr. TJM van der Cammen and Dr. EF van Beeck

1. PhD training

	Year	Workload (Hours/ECTS)
General academic skills		
- CPO mini cursus - Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen	2010	0.3 ECTS
- De Basiscursus Regelgeving en Organisatie van Klinische trials (BROK)	2010	1 ECTS
- Biomedical writing	2010-2011	2 ECTS
Research skills		
- Course Gait analysis using the GAITRite® walkway system	2006	1 ECTS
- Nihes course Study design	2006	4.3 ECTS
- Nihes course Classical Methods for Data-analysis	2006	5.7 ECTS
- Introduction for the statistical language R	2010	0.1 ECTS
Presentations		
- Poster presentation International Congress on Gait and Mental Function, Madrid, February 3-5	2006	1 ECTS
- Oral presentation Wiener Internationaler Geriatriekongress, Alter Mensch – neue Technologien, Vienna, May 8	2009	1 ECTS
- Oral presentation Congres Nederlandse Vereniging Verpleeghuis Artsen, Utrecht, November 27	2009	1 ECTS

- Three oral presentations falls prevention group Section of Geriatrics, ErasmusMC	2007-2008	1 ECTS
- Oral presentation (refereeravond) Section of Geriatrics, ErasmusMC, Valincidenten in het verpleeghuis: de invloed van medicatie, November 5	2009	1 ECTS
- Oral presentation Kwaliteitsbijeenkomst fysiotherapeuten, bruikbaarheid en validiteit van de Tinettitest, Rotterdam, November 9	2009	1 ECTS
- Poster presentation Congres over patiëntveiligheid Inspectie voor de Gezondheidszorg, Rotterdam, June 15	2010	1 ECTS
- Poster presentation The 6th Congress of the European Union Geriatric Medicine Society, Dublin, September 29-October 1	2010	1 ECTS
(Inter)national conferences		
- International Congress on Gait and Mental Function, Madrid, February 3-5	2006	1 ECTS
- 3rd International Gaitrite meeting, Kuopio, Finland, August 4-5	2006	1 ECTS
- *5e* Erasmus Geriatrie Symposium 'Delier, dementie en depressie', Rotterdam, November 9	2006	0.2 ECTS
- The 2nd International Congress on GAIT & Mental Function, Amsterdam, February 1-3	2008	1 ECTS
Seminars and workshops		
- PhD Days Erasmus MC	2008-2010	0.5 ECTS
- Erasmus MC Consultation Center for Patient Oriented Research Autumn Symposium	2009	0.1 ECTS
- NWO-Talent Class Successful Presentations	2010	0.3 ECTS
- Kickoff meeting Postdoc Network ErasmusMC	2011	0.1 ECTC
Didactic skills		
- Training for Project leader "Blijf Staan"	2010	0.2 ECTS

Other attended meetings

- Research meetings of the Falls Prevention Group, Section of Geriatrics, ErasmusMC	2007-2008	1 ECTS
- Verenso specialisten in ouderengeneeskunde Zuid-Holland-Zuid, June 1	2010	0.1 ECTS
- Kennisnetwerk Valpreventie Senioren	2010-2011	0.4 ECTS

2. Teaching activities

	Year	Workload (Hours/ECTS)
Lecturing		
- Lecturing to nursing home physicians, Department of Public Health and Primary Care, Leiden University Medical Center	2006-2010	1.5 ECTS
Supervising practicals and excursions		
- Supervising physiotherapy students in their 3th and 4th year	2006-2010	10 ECTS
Supervising Master's theses		
- MSc student Medicine, VU University, Amsterdam	2008	4 ECTS
- MSc student Health Sciences, VU University, Amsterdam	2011	4 ECTS
Other		
- Project leader and lecturer, information sessions on falls prevention	2006-2011	6 ECTS
- Lecturer on falls prevention in courses for healthcare workers	2010	1 ECTS

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ABSTRACTS

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Sterke CS. Mobiliteits- en balansproblemen en het gebruik van psychofarmaca in relatie tot vallen. Congres Nederlandse Vereniging Verpleeghuis Artsen. November 2009. Utrecht (abstract p 20).

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