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REVIEW

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

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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,

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however, that multiple drugs, antidepressants and anti-anxiety drugs increase fall risk in nursing home populations with residents with dementia.

Key words: falls, gait, psychoactive drugs, dementia, nursing homes

Introduction

Falls are a major health problem among the elderly, particularly in nursing homes (Bueno-Cavanillas *et al.*, 2001; Krueger *et al.*, 2001; Jensen *et al.*, 2002; Heinze *et al.*, 2007). Abnormalities of balance and gait (Tinetti *et al.*, 1988; Speechley and Tinetti, 1990; Studenski *et al.*, 1994), psychoactive drug use (Tinetti *et al.*, 1988; Leipzig *et al.*, 1999; Ensrud *et al.*, 2002), and dementia (Morris *et al.*, 1987; van Doorn *et al.*, 2003) have been shown to contribute to fall risk. Gait and balance problems usually occur in the more advanced stages of dementia (Nakamura *et al.*, 1996), and might be due to the use of psychoactive drugs such as antipsychotics, antidepressants and sedatives (Lord *et al.*, 1995).

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 of 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 Center website. 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 on 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 Center website. 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 $\kappa = 0.60–0.80$ represents a good agreement. An inter-observer agreement of $\kappa = 0.80–1.00$ represents a very good agreement (Landis and Koch, 1977).

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

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 (Ariens *et al.*, 2000; Sackett *et al.*, 2000). In the case of dichotomous outcomes, positive clinical relevant findings were considered relative risks (RRs), odds ratios (ORs) or hazard ratios (HRRs) > 2.0 or < 0.5 or else significant associations ($p < 0.05$) (van der Windt *et al.*, 2000). 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.

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.

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 $\kappa = 0.72$. Disagreement occurred mainly because of

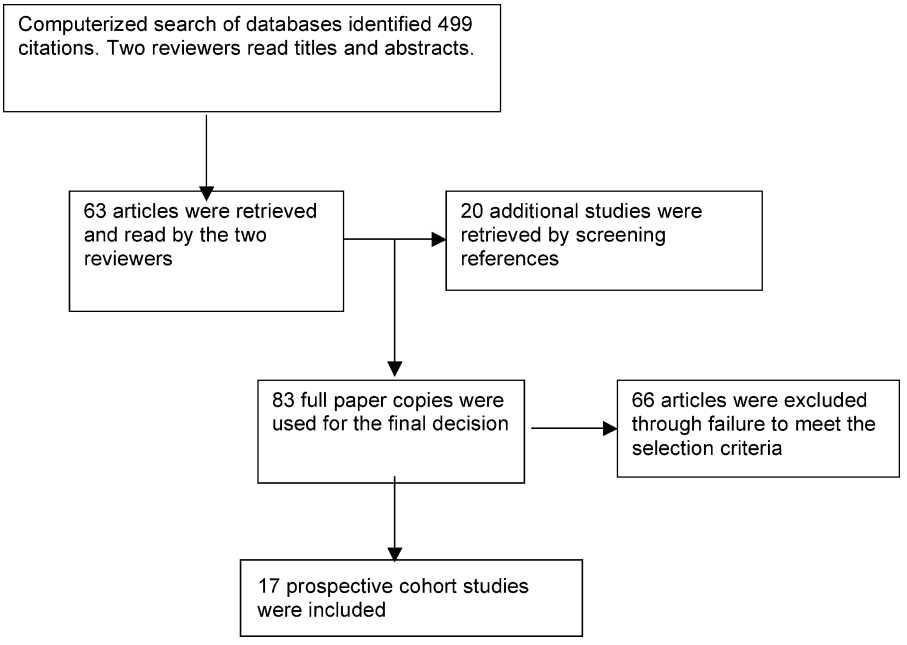

Figure 1. Flow diagram of papers accepted and rejected by the reviewers during the selection procedure

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 (Rosendahl *et al.*, 2003) and n = 43,163 (Avidan *et al.*, 2005). The shortest follow-up period was one month

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

	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
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
van Doorn *et al.*, 2003	1	1	1	1	0	1	?	1	1	7

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 (?).

(Ruthazer and Lipsitz, 1993; Hien *et al.*, 2005), and the longest was two years (Lipsitz *et al.*, 1991; van Doorn *et al.*, 2003).

Falls

Most studies ascertained falls from medical records or nursing home charts and from incidence reports (Ruthazer and Lipsitz, 1993; Thapa *et al.*, 1995; 1996; 1998; Ray *et al.*, 2000; 2002; Arfken *et al.*, 2001; Lord *et al.*, 2003; Hien *et al.*, 2005). In one study falls were ascertained from a subject interview (Lipsitz *et al.*, 1991), and in another from the registration form and reported to a study nurse (Rosendahl *et al.*, 2003). In four studies falls were ascertained only from incidence reports (Capezuti *et al.*, 1996; Kuchynka *et al.*, 2004) or nursing home charts (Kiely *et al.*, 1998; van Doorn *et al.*, 2003; Avidan *et al.*, 2005; Cooper *et al.*, 2007).

Gait parameters

None of the studies described gait parameters as outcome measure for psychoactive drug use. Some studies described gait parameters as determinants

Table 3. Summary of study characteristics

COHORT	POPULATION	DETERMINANTS	OUTCOME MEASURES	CRUDE ESTIMATES AND 95% CI	ADJUSTED ESTIMATES AND 95% CI	NOTES
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)		Selective serotonine-reuptake inhibitor OR = 2.01 (1.23–3.28) Non- Selective serotonine-reuptake inhibitor OR = 1.40 (0.65–3.03)	Adjusted for age, number of medications, number of diagnoses, gender, memory problems, restraints
			Injurious falls		Selective serotonine-reuptake inhibitor OR = 1.77 (1.0–3.13)	
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)	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
Capezuti *et al.*, 1996 Q = 8	N = 322 Severe cognitive impaired 27.6% Age ± 84 (7.3)	Psychoactive drug use	Falls (incidence reports)	OR = 1.78 (1.14–2.79)	Not provided	Table provides unadjusted estimates, the text shows the same figures as adjusted estimates
Cooper *et al.*, 2007 Q = 6	N = 177 Age 81.8 (10.7) Female 79%	No. Psychotropic drug use	Falls (patient charts)	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)		
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)	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	

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)	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
Kiely *et al.*, 1998 Q = 6	N = 18855 Cognitive impaired 82% Median age 87 Female 84%	Antipsychotic Antianxiety medication use	Falls (The Resident Assessment Instrument/ Minimum Data Set)	Antipsychotic OR = 1.21 (1.11–1.33) Antianxiety OR = 1.22 (1.11–1.33)	Not provided	
Kuchynka *et al.*, 2004 Q = 4	N = 314 Demented 31.8% Age ± 82 Female 67%	Benzodiazepine use	Falls (incidence reports)	Not provided	Not provided	Prevalence: 27% of the fallers were benzodiazepine users, 25% of the non-fallers were benzodiazepine users
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)	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

Table 3. Continued

COHORT	POPULATION	DETERMINANTS	OUTCOME MEASURES	CRUDE ESTIMATES AND 95% CI	ADJUSTED ESTIMATES AND 95% CI	NOTES
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)	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
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)	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) Selective serotonine-reuptake inhibitors RR = 2.4 (2.2–2.6) Paroxetine RR = 2.3 (2.1–2.6) Fluoxetine RR = 2.4 (2.1–2.8) Sertraline RR = 2.6 (2.3–3.0)	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) 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 = 1.8 (1.6–2.0) Paroxetine RR = 1.7 (1.5–1.9) Fluoxetine RR = 1.8 (1.6–2.1) 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)	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

		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 < 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)
	Daytime falls		Current benzodiazepine use RR = 1.38 (1.25–1.51) Elimination half-life, hours < 12 RR = 0.90 (0.70–1.17) 12–23

Table 3. Continued

COHORT	POPULATION	DETERMINANTS	OUTCOME MEASURES	CRUDE ESTIMATES AND 95% CI	ADJUSTED ESTIMATES AND 95% CI	NOTES
			Nighttime falls		RR = 1.43 (1.29–1.59) ≥ 24 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)	
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)	Tranquillizers/ sedatives HR = 1.66 (0.93–2.96) Antidepressants HR = 1.93 (1.05–3.52)	Not provided	
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)	Antidepressants (women) OR = 1.95 (1.02–3.70)	Adjusted estimate Antidepressants (women) OR = 1.84 (0.91–3.69)	Stratified for sex. Adjusted for age and fall history
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)	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)	Adjusted incidence density ratios 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.
Thapa *et al.*, 1996 Q = 8	N = 503 Moderate and Severe cognitive impaired 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)	Unadjusted incidence rates, per 100 person years Psychotropic drugs IDR = 23.4	Adjusted incidence density ratios Psychotropic drugs IDR = 2.49 (1.43–4.33)	Adjusted for age, gender, BMI, cognitive impairment

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

for falls (Lipsitz *et al.*, 1991; Lord *et al.*, 2003; Rosendahl *et al.*, 2003; van Doorn *et al.*, 2003; Kuchynka *et al.*, 2004).

Psychoactive drug use

In most studies drug use is the determinant of primary interest (Ruthazer and Lipsitz, 1993; Thapa *et al.*, 1995; 1996; 1998; Ray *et al.*, 2000; 2002; Arfken *et al.*, 2001; Avidan *et al.*, 2005; Hien *et al.*, 2005; Cooper *et al.*, 2007). In other studies psychoactive drugs are studied among other risk factors to develop or to evaluate a fall risk model (Lipsitz *et al* 1991; Kiely *et al.*, 1998; Lord *et al.*, 2003; Rosendahl *et al.*, 2003). One study described the effect of restraint use on falls, with drug use being a confounder in their multiple logistic regression model (Capezuti *et al.*, 1996). 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 (van Doorn *et al.*, 2003).

The Minimum Data Set (MDS; Morris *et al.*, 1990) was used by most studies to ascertain psychoactive drug use (Kiely *et al.*, 1998; van Doorn *et al.*, 2003; Avidan *et al.*, 2005). Other studies used pharmacy records (Arfken *et al.*, 2001; Cooper *et al.*, 2007), medical records (Lord *et al.*, 2003; Hien *et al.*, 2005), or medication administration records (Lipsitz *et al* 1991; Ruthazer and Lipsitz, 1993; Thapa *et al.*, 1995; 1996; Capezuti *et al.*, 1996; Ray *et al.*, 2000; 2002). Some studies provided information on dose or duration of use (Capezuti *et al.*, 1996; Thapa *et al.*, 1998; Ray *et al.*, 2000; 2002). 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) (Capezuti *et al.*, 1996). In two studies, benzodiazepine use was classified for each day of follow-up as "current" (taken that day), "recent", or "none" (Ray *et al.*, 2000; 2002). 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 (Ray *et al.*, 2000). 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 (Lipsitz *et al.*, 1991). In only one study is it unclear as to how drug use was ascertained (Kuchynka *et al.*, 2004).

Associations

Eleven publications presented the associations between psychoactive drug use and falls in adjusted estimates: OR (Lipsitz *et al.*, 1991; Ruthazer and Lipsitz, 1993; Arfken *et al.*, 2001; Avidan *et al.*, 2005); RR (Thapa *et al.*, 1998; Ray *et al.*, 2000; 2002); incidence density ratio (IDR; Thapa *et al.*, 1995; 1996), HR (Hien *et al.*, 2005), and incidence rate ratio (IRR; Lord *et al.*, 2003). One study stratified for sex (Ruthazer and Lipsitz, 1993). Five publications presented only crude estimates of the associations between psychoactive drug use and falls: OR (Capezuti *et al.*, 1996), RR (Kiely *et al.*, 1998; van Doorn *et al.*, 2003; Cooper *et al.*, 2007), and HR (Rosendahl *et al.*, 2003). One publication only presented

the prevalence of fallers among benzodiazepine users and among non-users (Kuchynka *et al.*, 2004).

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 (Ruthazer and Lipsitz, 1993; Ray *et al.*, 2000; Lord *et al.*, 2003; Hien *et al.*, 2005; Cooper *et al.*, 2007). 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 (Lord *et al.*, 2003; Hien *et al.*, 2005).

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 (Capezuti *et al.*, 1996; Thapa *et al.*, 1996; Cooper *et al.*, 2007). 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 (Thapa *et al.*, 1995; 1998; Arfken *et al.*, 2001); 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 (Thapa *et al.*, 1995). 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) (Thapa *et al.*, 1996; Arfken *et al.*, 2001).

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) (Thapa *et al.*, 1995; 1998; Kiely *et al.*, 1998; van Doorn *et al.*, 2003; Lord

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
Hypnotics	Falls	11	5/11 (45%)	5		6/11 (55%)	5	1	Inconclusive
Sedatives	Recurrent falls	2	1/2 (50%)	–	–	1/2 (50%)	–	–	Inconclusive
Anti-anxiety Benzodiazepines									
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	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
	Night-time falls	1	1/1 (100%)	1	–	–	–	–	Limited yes
Benzodiazepine use elimination half-life < 12 hours	Falls	1	–	–	–	1/1 (100%)	1	–	Limited no
	Daytime falls	1	–	–	–	1/1 (100%)	1	–	Limited no
	Night-time falls	1	1/1 (100%)	1	–	–	–	–	Limited yes
Benzodiazepine use elimination half-life ≥ 12 hours	Falls	1	1/1 (100%)	1	–	–	–	–	Limited yes
	Daytime falls	1	1/1 (100%)	1	–	–	–	–	Limited yes
	Night-time 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
Olanzapine	Falls	1	1/1 (100%)	1	–	–	–	–	Limited yes
Antidepressant	Falls	12	10/12 (83%)	10	–	2/12 (17%)	2	–	Strong yes
Tricyclic antidepressant	Falls	2	2/2 (100%)	2	–	–	–	–	Strong yes
	Recurrent falls	1	1/1 (100%)	1	–	–	–	–	Limited yes
SSRI	Falls	2	2/2 (100%)	2	–	–	–	–	Strong yes
	Injurious falls	1	1/1 (100%)	1	–	–	–	–	Limited yes
Non-SSRI	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).

et al., 2003). Positive findings for the risk of recurrent falls were found in one out of two (50%) cohorts (Thapa *et al.*, 1995). 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 (Thapa *et al.*, 1995), 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 (Ray *et al.*, 2000). 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) (van Doorn *et al.*, 2003; Kiely *et al.*, 1998).

We found inconclusive evidence for the use of sedatives. Positive findings were found in only one out of four studies (Lord *et al.*, 2003).

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) and n = 282, IDR = 1.23 (0.55–2.76) (Avidan *et al.*, 2005 and Thapa *et al.*, 1995, respectively).

Antipsychotics

The evidence that antipsychotics increase fall risk is inconclusive. Positive findings were found in three out of seven (43%) cohorts (Kiely *et al.*, 1998; van Doorn *et al.*, 2003; Hien *et al.*, 2005). 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 (Hien *et al.*, 2005).

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) (Lipsitz *et al.*, 1991; Thapa *et al.*, 1995; 1998; Arfken *et al.*, 2001; van Doorn *et al.*, 2003; Lord *et al.*, 2003; Rosendahl *et al.*, 2003; Hien *et al.*, 2005). 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) (Thapa *et al.*, 1995; 1998) and the use of SSRIs (2/2 cohorts, n = 368, OR 2.01 and n = 2428, RR 1.8) (Arfken *et al.*, 2001; Thapa *et al.*, 1998) increase fall risk remains strong. The evidence that the use of trazodone increases fall risk is limited (Thapa *et al.*, 1998).

Multiple psychotropic 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) (Thapa *et al.*, 1995; Lord *et al.*, 2003; Cooper *et al.*, 2007). One study classified multiple drugs as the use of

two psychotropics (RR 3.2), three psychotropics (RR 6.7) or four psychotropics (RR 10.3) (Cooper *et al.*, 2007). The evidence for recurrent falls is limited (Thapa *et al.*, 1995).

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) (Lord *et al.*, 2003), whereas in another study the strength is larger (RR = 10.3) for the concurrent use of four psychotropics (Cooper *et al.*, 2007). The evidence was based on three smaller cohorts (Thapa *et al.*, 1995; Lord *et al.*, 2003; Cooper *et al.*, 2007). 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 (Kiely *et al.*, 1998; van Doorn *et al.*, 2003). The strong evidence for the use of antidepressants is based on 10 cohorts (Lipsitz *et al.*, 1991; Thapa *et al.*, 1995; 1998; Arfken *et al.*, 2001; van Doorn *et al.*, 2003; Lord *et al.*, 2003; Rosendahl *et al.*, 2003; Hien *et al.*, 2005), with the strongest association (OR = 7.6) being found in a relatively small cohort (n = 126 women) (Lipsitz *et al.*, 1991). In the largest cohort (n = 2428) only a weak association was found (RR = 1.1) (Thapa *et al.*, 1998).

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 (Thapa *et al.*, 1995), which can be particularly hazardous. Intermediate- and long-acting benzodiazepines were found to increase overall fall risk (Thapa *et al.*, 1995).

An earlier review on the association between psychoactive drugs and falls found an increased fall risk for all psychoactive drugs (Leipzig *et al.*, 1999). 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 (Altman, 2001). The Leipzig review also included studies with a cross-sectional and a case control study design (Leipzig *et al.*, 1999).

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 (Thapa *et al.*, 1998; Ray *et al.*, 2000; 2002). 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 (Kellogg International Work Group, 1987).

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 (Ray *et al.*, 2002).

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 (Thapa *et al.*, 1998; Ray *et al.*, 2000; 2002).

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 (Campbell *et al.*, 1999) and improve mobility tests in community-dwelling older persons without dementia (van der Velde *et al.*, 2007a; 2007b), 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 (Lord *et al.*, 1995). 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.

Conflict of interest

None.

Description of authors' roles

Carolyn Sterke, Arianne Verhagen and Tischa van der Cammen were responsible for the design of the study and performed the literature search. Carolyn Sterke and Tischa van der Cammen selected the articles and assessed their quality, and Carolyn Sterke extracted and analyzed the data and wrote the manuscript. Arianne Verhagen extracted the data and helped with the resolution of disagreements between reviewers. Ed van Beeck advised on the study and participated in the writing of the manuscript. Tischa van der Cammen initiated and developed the study, participated in and supervised the writing of the manuscript.

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