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Review Article

Medication as a Risk Factor for Falls: Critical Systematic Review

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Background. Falls in older people are associated with poor prognosis. Medication use is a potential cause of falls. Our aim was to systemically review all original articles examining medication use as a risk factor for falls or fall-related fractures in people aged ≥ 60 years.

Methods. We searched English articles in Medline (1996–2004) indexed under “falls” or “accidental falls” and “pharmaceutical preparations” or specific groups of drugs. We excluded studies not meeting the age criterion, not controlled with nonusers of target medicines or nonfallers, or with no clear definition of target medication.

Results. Twenty-eight observational studies and one randomized controlled trial met the inclusion criteria. The number of participants ranged from 70 to 132,873. The outcome measure was a fall in 22 studies and a fracture in 7 studies. The main group of drugs associated with an increased risk of falling was psychotropics: benzodiazepines, antidepressants, and antipsychotics. Antiepileptics and drugs that lower blood pressure were weakly associated with falls.

Conclusions. Central nervous system drugs, especially psychotropics, seem to be associated with an increased risk of falls. The quality of observational studies needs to be improved, for many appear to lack even a clear definition of a fall, target medicines, or prospective follow-up. Many drugs commonly used by older persons are not systematically studied as risk factors for falls.

THE incidence of falls and the severity of fall-related complications increase with age (1,2). Each year, 8% of people 70 years old or older seek care for fall-related injuries in accident and emergency departments (3). Falls are associated with a poor prognosis, including excess mortality and premature institutionalization (4). The majority of falls have a multifactorial etiology. Risk factors for falling can be categorized as environmental (e.g., poor lighting, loose carpets, slippery flooring, lack of handrails), intrinsic (e.g., weak muscle strength or impairment in balance, gait, vision, or cognition), and extrinsic such as use of certain medicines or polypharmacy (5,6).

Leipzig and colleagues (7,8) conducted two meta-analyses that evaluated an association between medication use and falls in older people. None of the studies were randomized controlled trials (RCT), so the evidence between medication use and falls was based on observational data from 69 English articles published from 1966 through March 1996. The use of psychotropic drugs (antidepressants, mainly tricyclic, antipsychotics, long- and short-acting benzodiazepines) was associated with an increase in the risk of falls (7). With respect to cardiovascular drugs, a weak association was reported between falls and use of any diuretic, digoxin, or type IA antiarrhythmic medicine (8). However, no statistically significant associations were found between falls and use of thiazides, loop diuretics, angiotensin-converting enzyme (ACE) inhib-

itors, or calcium channel blockers. Analgesics were not significantly associated with falls. Older adults taking more than three or four medicines were at increased risk of recurrent falls. The studies included in the meta-analyses had minimal adjustment for confounding factors such as an underlying indication for drug use, dosage, or duration of pharmacotherapy.

New pharmaceutical preparations, such as selective serotonin reuptake inhibitors (SSRIs), new atypical antipsychotics, benzodiazepine-like sleeping pills, and angiotensin II antagonists, have come on the market since the mid-1990s, and the use of medications as well as polypharmacy have increased among elderly persons (9,10). Our focus was to detect medicines that could potentially increase the risk of falling. Thus, we excluded those articles concerning the withdrawal of drugs or the protective effects of drugs on falling or fractures. The purpose of this article is to systematically review studies that were published in 1996–2004 and reported an association between the use of medicines and a risk of falls or fall-related fractures in people 60 years old or older.

METHODS

Literature Search

We searched Medline for original English articles published from January 1996 through December 2004 using the

Medical Subject Headings (MeSH) terms “accidental falls” and “pharmaceutical preparations.” This search yielded only 20 hits. Combinations of the terms “falls” and “medication” or “medicines” or specific groups of medications (benzodiazepines, antidepressants, antiepileptics, analgesics, antihypertensive agents, statins, cholinesterase inhibitors) gave altogether 673 hits. We also searched the Cochrane library and examined the reference lists of the retrieved articles.

Study Selection

The abstracts of the articles found in the literature search were read. Full-text copies of potentially includable articles were retrieved, and 48 original articles (11–58) that reported on an association between medication use and falls or fall-related fractures in older people were found. Of the 48 studies, 19 (11–29) were excluded for the following reasons:

1. Not controlled with nonfallers or nonusers of the target medications (11–14);
2. Persons younger than 60 years were included, and results for older persons were not reported separately (15–18);
3. Definition of target medications was missing (19–22);
4. The time between medication ascertainment and outcome of falls or fall-related fractures was > 1 year (23–28); and
5. The participation rate was < 70% (29).

The remaining 29 studies (30–58) were included in this review.

Definition and Classification of Medicines

In this review, we classify medicines according to the Anatomical Therapeutic Chemical (ATC) classification system recommended by the World Health Organization (WHO) (59). The classification divides medicines into 14 main groups according to the organ or system on which they act and into five different levels on the basis of their chemical, therapeutic, and pharmacological properties. For example, citalopram is coded N06AB04 (N = nervous system, N0 = antidepressants and psychostimulants, N06A = antidepressants, N06AB = SSRIs, N06AB04 = citalopram). Based on the ATC, central nervous system (CNS) medicines are defined as including psychotropics (hypnotics, sedatives, anxiolytics, antipsychotics, and antidepressants), antiepileptics, drugs for Parkinson's disease and Alzheimer's disease, and opioids.

Statistical Methods

The strength of the association between medication use and falls was evaluated using odds ratios (OR) and 95% confidence intervals (CI) if they were reported in the original articles. The results were categorized by medication groups or by specific medicines reflecting the level at which they were reported in the original articles.

RESULTS

Description of Included Studies

Table 1 presents a summary of the 29 studies (30–58) included in this systematic review. Only one study was an RCT (31), whereas the others were based on observations of

prospective cohorts (30,32,35,38–40,44,52,53,56–58), retrospective cohorts (33,36,45,46,49,50,55), or cases and controls (34,37,41–43,47,48,51,54).

Of the 29 studies, 8 were population-based (33,37,41–43,51,55,57), 7 concerned community-dwellers (30,34–36,38,44,50), 12 were performed in residential care settings (31,39,40,45–47,49,52–54,56,58), 1 consisted of community-dwellers and nursing home residents (48), and 1 was performed in four different types of geriatric care settings (32). The number of participants ranged from 70 persons in residential care to 132,873 persons in a register database study.

Medication use as a risk factor for falls or fall-related fractures was the main objective in 20 studies (31,32,34–37,39,41–43,45–51,54,55,57), whereas the others focused on multiple risk factors for falls (30,33,38,40,44,52,53,56,58). The outcome measure was a fall (single or recurrent) (31–33,35,36,38–40,44–46,49,50,52,53,55,56), an injurious fall (30,34,54,57,58), a hip fracture (37,41–43,48,51), or a femur fracture (47). The term “fall” was not defined in eight studies (31,33,45,48–50,52,55).

The data on falls were based on recall (33,36,50,55), or the participants filled in fall calendars and/or were contacted by phone or by postcard (30,35,38,44,56). Falls were recorded by staff in 10 institutional care studies (31,32,39,40,45,46,49,52,53,58), whereas hospital registers were the principal sources of information in 10 surveys concerning injurious falls or fall-related fractures (34,37,41–43,47,48,51,54,57).

The data on medication use in the 28 observational studies were obtained by interviewing the participants (30,33,35,36,38,44,50,55,56), from prescription databases (34,37,41,42,51,57), from nursing home records (32,39,40,45–47,49,52–54,58), or through blood tests (43,48). Six studies classified medicines according to the ATC system (30,36,39,44,53,56), five used other classifications (33–35,54,55), and 18 studies did not report the use of any classification (31,33,37,38,40–43,45–52,57,58).

The effects of duration of drug use were evaluated in eight studies (37,39,41,46,49,51,54,57). The effects of dosing were assessed in six studies by the following methods: Patients were randomized on fixed doses (31), the doses of different benzodiazepines were converted to diazepam equivalents (41,46), and the doses used were compared with the defined daily doses (DDD) (47,49,51).

In the RCT, the baseline characteristics of the groups randomized for different treatment were homogenous, and the indication for pharmacotherapy was defined. The trial was also controlled for the degree of wandering behavior and use of other psychotropic drugs.

All nine case-control studies were controlled for age and sex (34,37,41–43,47,48,51,54). Of the 19 observational studies without a case-control framework, 14 were controlled for age (30,32,33,35,39,40,45,46,49,50,53,56–58), 10 for sex (32,39,45,46,49,50,53,56–58), and four included only women (30,33,35,36). At least one chronic condition was considered as a potential confounder in relation to the reported association between medication use and falls in all the case-control studies (34,37,41–43,47,48,51,54), and in 12 of 19 other observational studies (32,33,35,36,39,40,46,49,50,53,55,58). Cognitive status was the most often

Table 1. Summary of the 29 Studies Included in the Systematic Review

Reference	Study Type Setting/Study Population	Number and Age of Participants	Target Medication	Outcome Measure Association Between Medication Use and Falls
Bergland and Wyller, 2004 (30)	P CD	<i>N</i> = 307 women Age ≥ 75	All	Injurious falls: ↑ antihypertensives No association: other medication groups
Katz et al., 2004 (31)	RCT RC	<i>N</i> = 537 persons Mean age = 83	Risperidone	Falls among residents with dementia: ↓ risperidone 1 mg/d ↑ risperidone 2 mg/d
Kallin et al., 2004 (32)	P, CS RC, NH Re, H	<i>N</i> = 3669 persons Age ≥ 65	All	Falls: ↑ antidepressants, antipsychotics
Lawlor et al., 2003 (33)	R, CS PB	<i>N</i> = 4050 women Age ≥ 60	All	Any falls: ↑ hypnotics/anxiolytics, antidepressants No association: analgesics, cardiovascular/endocrine/respiratory system drugs
Kelly et al., 2003 (34)	CC CD	<i>N</i> = 11,390 persons Age ≥ 66	All	Injurious falls: ↑ opioids, anticonvulsants, antidepressants No association: other medication groups
Ensrud et al., 2002 (35)	P CD	<i>N</i> = 8127 women Age ≥ 65	CNS drugs	Falls/recurrent falls: ↑ BZDs, antidepressants, anticonvulsants No association: opioids
Rozenfeld et al., 2003 (36)	R, CS CD	<i>N</i> = 634 women Age ≥ 60	All	Falls/recurrent falls: ↑ Diuretics, beta-blockers, anxiolytics/sedatives
Hubbard et al., 2003 (37)	CC, R PB	<i>N</i> = 46,230 persons Mean age = 79	SSRIs TCAs	Hip fracture: ↑ TCAs, SSRIs
Heitterachi et al., 2002 (38)	P CD	<i>N</i> = 70 persons Age ≥ 62	All	Falls: No association: antihypertensives, antidepressants
Neutel et al., 2002 (39)	P NH	<i>N</i> = 227 persons Age ≥ 65	All	Falls: ↑ five or more medicines ↑ a new prescription of BZDs or antipsychotics No association: other medication groups
Kallin et al., 2002 (40)	P RC	<i>N</i> = 83 persons Mean age = 80	All	Falls: ↑ antidepressants (SSRIs)
Wang et al., 2001 (41)	CC, R PB	<i>N</i> = 6110 persons Age ≥ 65	BZDs	Hip fracture: No association: BZD < 3 mg/d in diazepam equivalents ↑ BZD ≥ 3 mg/d in long- and short-term use
Wang et al., 2001 (42)	CC, R PB	<i>N</i> = 6110 persons Age ≥ 65	Psychotropics	Hip fracture: ↑ zolpidem, BZDs, antipsychotics, antidepressants
Pierfitte et al., 2001 (43)	CC PB	<i>N</i> = 1062 persons Age ≥ 65	BZDs	Hip fracture: No association: exposure to BZD ↑ lorazepam in plasma, reported use of ≥ 2 BZDs
Tromp et al., 2001 (44)	P CD	<i>N</i> = 1285 persons Mean age = 75	All	Falls: ↑ use of ≥ 4 drugs, BZDs, antiepileptics
Arfken et al., 2001 (45)	R NH	<i>N</i> = 368 persons Age ≥ 60	Antidepressants	Falls: ↑ SSRIs
Ray et al., 2000 (46)	R NH	<i>N</i> = 2510 persons Age ≥ 65	BZDs	Falls: ↑ BZDs ≤ 2 mg/d in diazepam equivalents ↑ BZDs > 8 mg/d in diazepam equivalents ↑ BZD, BZD started within 1 wk, BZD use > 30 d No association: elimination half-life < 12 h ↑ nightly falls when half-life < 12 h ↑ elimination half-life ≥ 12 h
Sgadari et al., 2000 (47)	CC NH	<i>N</i> = 46,803 persons Age ≥ 65	BZDs	Hip fracture: ↑ nonoxidative BZDs No association: BZDs as a group, oxidative BZDs
Schwab et al., 2000 (48)	CC CD NH	<i>N</i> = 187 persons Mean age = 80.0	TCA Barbiturates BZD	Hip fracture: No association: BZD use based on history/prescription data ↑ BZD use based on serum analysis
Thapa et al., 1998 (49)	R NH	<i>N</i> = 2428 persons Age ≥ 65	Antidepressants	Falls: ↑ TCAs, SSRIs, trazodone
Chaimowicz et al., 2000 (50)	R CD	<i>N</i> = 161 persons Age ≥ 65	Psychoactive drugs	Falls: ↑ BZDs, BZDs, and/or antidepressants
Liu et al., 1998 (51)	CC, R PB	<i>N</i> = 49,648 persons Age ≥ 66	Antidepressants	Hip fracture: ↑ SSRIs, TCAs

Table 1. Summary of the 29 Studies Included in the Systematic Review (Continued)

Reference	Study Type Setting/Study Population	Number and Age of Participants	Target Medication	Outcome Measure Association Between Medication Use and Falls
Kiely et al., 1998 (52)	P NH	N = 18,855 persons Age ≥65	Psychotropics	Falls: ↑ antipsychotics, anxiolytics
Nygaard, 1998 (53)	P LTC	N = 118 persons Median age = 85	All	Falls: No association with any group of drugs ↑ psychotropics in mentally impaired patients
Mustard and Mayer, 1997 (54)	CC, R NH	N = 2972 persons Age = 83	12 categories of medications	Injurious falls: ↑ antipsychotics, anxiolytics/sedatives/hypnotics ↓ inotropic agents
Ebly et al., 1997 (55)	R PB	N = 2034 persons Age ≥65	CNS drugs	Falls in cognitively normal persons: ↑ BDZs, antidepressants
Graafmans et al., 1996 (56)	P RC	N = 354 persons Age ≥70	A few classes of medication	Falls: ↑ nitrates, peripheral vasodilators
Neutel et al., 1996 (57)	P PB	N = 132,873 persons Age ≥60	BZDs	Injurious falls: ↑ within 4 weeks after a new prescription: triazolam, flurazepam, diazepam, lorazepam, oxazepam
Thapa et al., 1996 (58)	P NH	N = 1228 persons Age ≥65	Psychotropics	Injurious falls: ↑ psychotropics among ambulatory users

Note: CC = case control; CS = cross-sectional; P = prospective; R = retrospective; RCT = randomized controlled trial; PB = population-based; CD = community-dwelling; H = hospital; LTC = long-term care; NH = nursing home; Re = rehabilitation; RC = residential care; BZD = benzodiazepine; CNS = central nervous system; TCA = tricyclic antidepressants; SSRI = serotonin reuptake inhibitor. ↑ = increase; ↓ = decrease.

addressed confounder (32,34,35,39,40,46–49,51,53–55,58). Physical performance (activities of daily living, ambulatory status) was considered as a confounder in 10 studies (32,35,43,46,47,49,53,54,56,58), and the use of other medicines was considered as a confounder in 14 studies (34,37,39,40–43,46,47,49–51,57,58).

Psychotropic and Other CNS Drugs

Twenty-seven studies reported results from CNS drugs, and all of them included at least one psychotropic drug or drug group. Benzodiazepines as a group or by certain preparations were associated with falls or fall-related fractures in 17 studies (33,35,36,39,41–44,46–48,50,52–55,57) (Figure 1). The risk of falling increased after a new prescription (39,41,46,54,57), in long-term use (41,46), and regardless of the preparation's half-life (35,41,46,57). Only one benzodiazepine-like sleeping pill (zolpidem) was studied, and it proved to be as risky as traditional benzodiazepines (42). Concomitant use of two or more benzodiazepines increased the risk of hip fracture 2-fold (43). In contrast, three studies found no association between the use of benzodiazepines and falls (30,40,56).

Antidepressants, including tricyclic antidepressant (TCA) preparations and SSRIs, were associated with falls or fractures in 12 studies (32–35,37,40,42,45,49–51,55) (Figure 2). The risks varied from 1.20- to 6-fold. Within 2 weeks after a new prescription for SSRIs (fluoxetine or paroxetine), the OR for hip fracture was 6.30 (95% CI, 2.65–14.97), and for TCAs it was 4.76 (95% CI, 3.06–7.41) (35). The risk of falls remained elevated in long-term use of antidepressants, and it was dose-dependent (49). An increased risk of falls or injurious falls was not found in five studies (30,39,44,54,56).

Antipsychotic drugs were associated with increased risk of falls or fractures (31,32,39,42,52,54) (Figure 3). Only two studies gave results for new atypical antipsychotics (31,32). Risperidone (OR 1.26; 95% CI, 0.81–1.95) and

olanzapine (OR 1.89; 95% CI, 0.99–3.62) were not significantly associated with falls in the Swedish study, though antipsychotics as a group were found to increase the risk of falls (32). The risk was dose dependent in the RCT, with risperidone 2 mg/d increasing the risk of falls in demented persons with low levels of wandering, although 1 mg/d did not (31). No association between antipsychotics and falls was found in three studies (30,40,55).

Use of antiepileptics was related to an increased risk of falls in three studies (34,35,44), the OR values ranged from 1.5 to 3.5 (34,35,44), whereas one study showed no elevated risk (OR 1.07; 95% CI, 0.65–1.76) (32). Cholinesterase inhibitors for Alzheimer's disease were included in only one study (32), which found no association between this group of drugs and falls. Opioids were associated with falls in one study (OR 1.68; 95% CI, 1.39–2.03) (34), but not in another (OR 1.02; 95% CI, 0.79–1.31) (35).

Other Medications and Polypharmacy

Data on the use of medicines other than CNS drugs were collected in 12 surveys (30,32–34,36,38–40,44,53,54,56). Three of these studies (30,36,56) reported an association between cardiovascular drug use and an increased risk of falling. Use of antihypertensives increased risk for injurious falls (OR 2.4; 95% CI, 1.1–6.5) (30), use of beta-blockers (OR 2.2; 95% CI, 1.2–4.0) (36) and peripheral vasodilators (OR 3.8; 95% CI, 1.4–10.2) (56) for recurrent falls, and nitrates (OR 2.2; 95% CI, 1.3–3.9) for any falls. Cardiovascular drugs, as a whole or by examined group, were not associated with falls in nine studies (32–34,38–40,44,53,54). The definitions and groupings of these drugs varied considerably, and the results of risk calculations were not reported in three of these studies (40,44,53).

Three studies (33,39,44) reported that the risk of falling increased with the number of drugs taken. In a nursing home population, use of 5–9 drugs increased the risk 4-fold (OR 4.0; 95% CI, 1.6–9.9), and use of ≥10 drugs carried an even

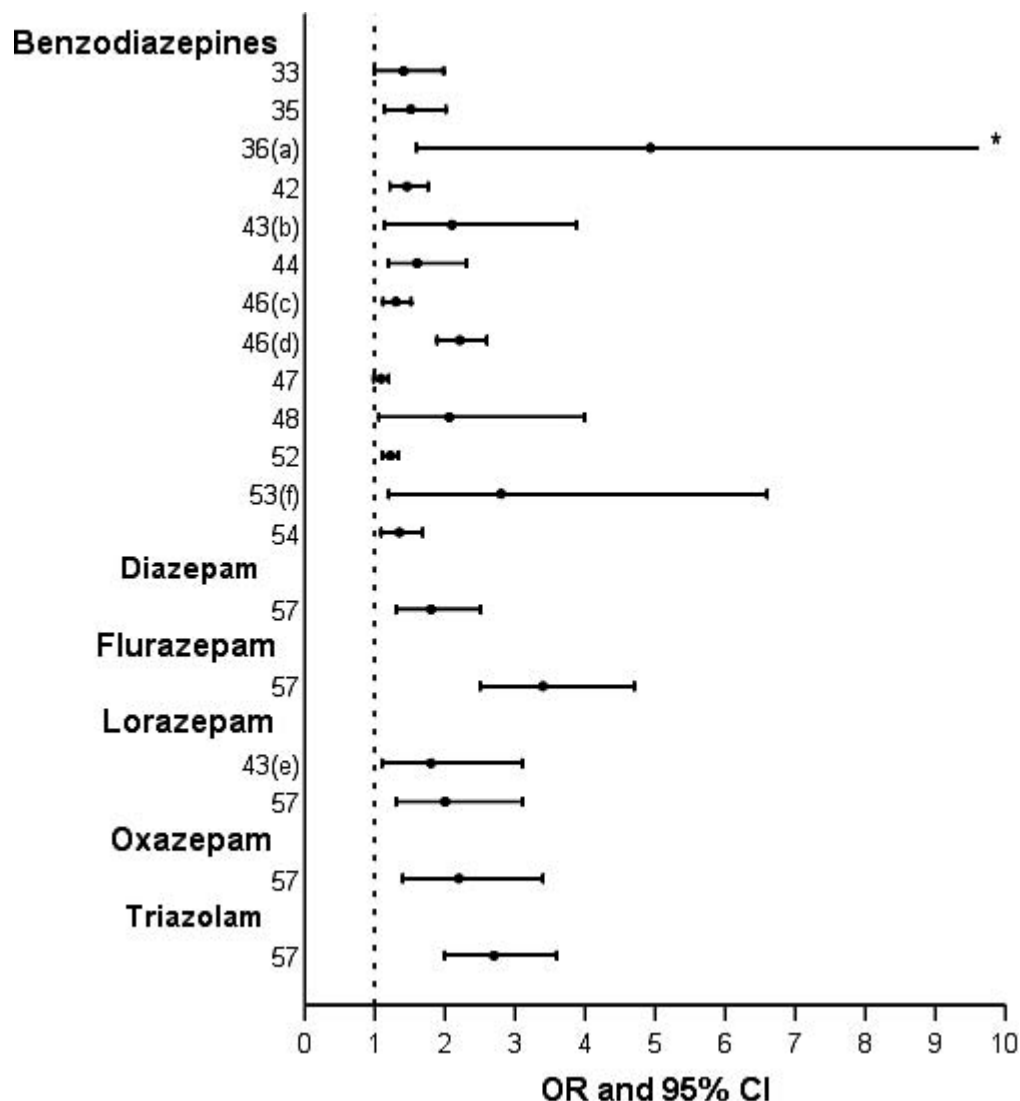


Figure 1. Benzodiazepines and risk of falls. Medication classes or medicines and reference numbers of studies are on vertical axis. a, in persons with postural hypotension; b, use of ≥ 2 benzodiazepines; c, dose ≤ 2 mg/d in diazepam equivalents; d, dose > 8 mg/d in diazepam equivalents; e, in plasma sample; f, in mentally impaired persons. *Upper bound = 15.28. OR = odds ratio; CI = confidence interval.

higher risk (OR 5.5; 95% CI, 1.9–15.9) than that associated with the use of ≤ 4 drugs (39). Among community-dwellers, use of ≥ 4 drugs increased the risk of falling by 30% (OR 1.3; 95% CI, 1.0–1.7) (44). However, among older women, the association with falls was stronger for multiple pathologies than for polypharmacy (33).

DISCUSSION

Benzodiazepines are one of the main risk factors for falls and fractures in older people. They seem to be associated with an increased risk of falls, not only in long-term use but also after a new prescription. Similar findings were reported in a recent meta-analysis of 24 studies (60). Benzodiazepines have negative effects on cognition, gait, and balance, and the pharmacodynamic responses of benzodiazepines tend to change with advancing age; the concentration that produces half of a full response (EC_{50}) for sedation is

reduced by 50% in elderly persons (61–63). Most studies included in this review and in the previous meta-analysis (7) overlooked the active metabolites of benzodiazepines or the effect of age on half-life.

Antidepressants, particularly TCAs and SSRIs, seem to be associated with a high risk for falling. The previous meta-analysis (7) included only one study of SSRIs, and it was hoped that they would be safer (in terms of falling) than TCAs. However, as shown by the studies in this review, SSRIs might carry even higher risks for falling than do traditional antidepressants. Whether antidepressants that inhibit both serotonin and noradrenalin reuptake (SNRI) are safer than TCAs or SSRIs has yet to be studied.

Differences between the risk profiles of TCAs and SSRIs are not as marked as we clinicians hoped. Both affect the serotonergic system and can cause serotonin syndrome when used in higher doses or concomitantly with other

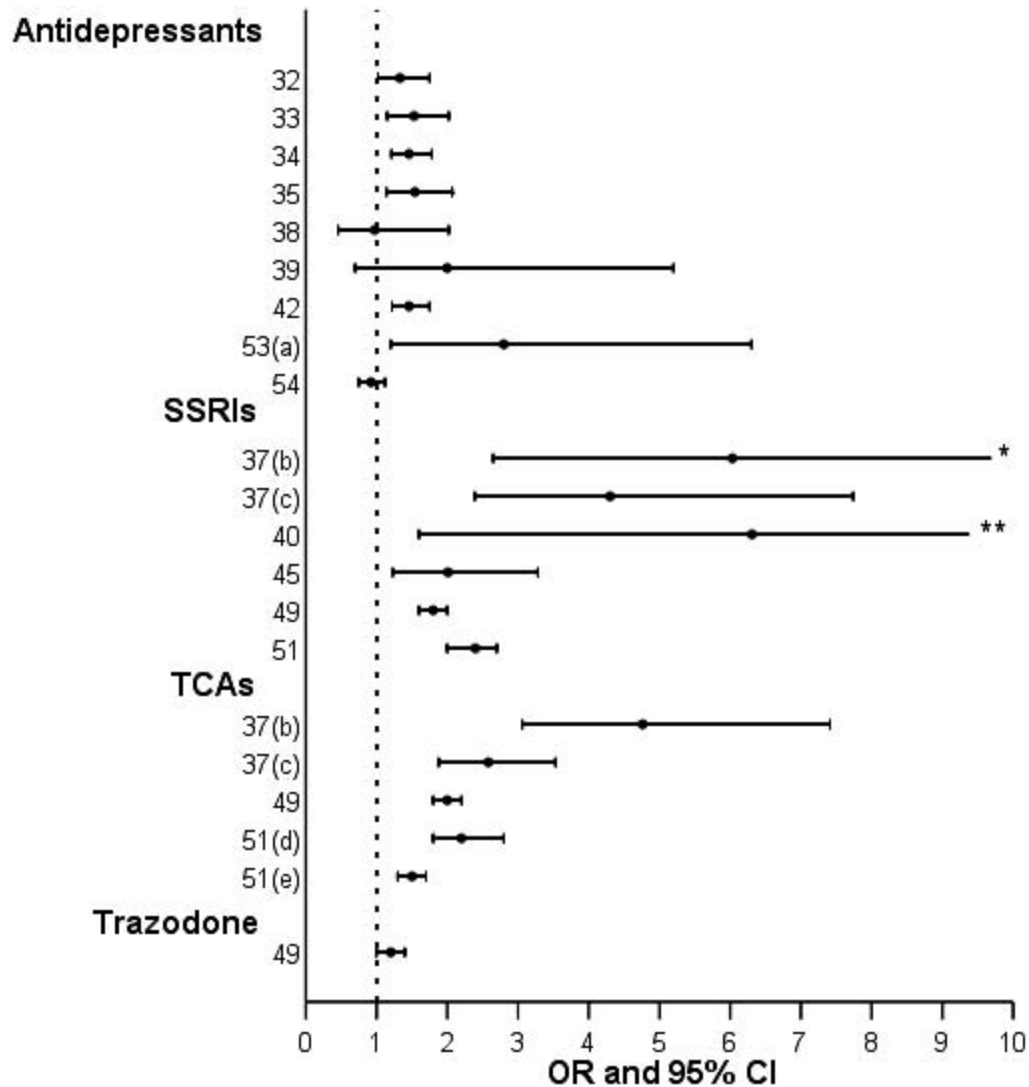


Figure 2. Antidepressants and risk of falls. Medication classes or medicines and reference numbers of studies are on vertical axis. a, in mentally impaired persons; b, exposed for ≤ 14 days; c, exposed for 15–42 days; d, secondary amine tricyclic antidepressant (TCA); e, tertiary amine TCA; *Upper bound = 14.97; **upper bound = 24.93. SSRIs = selective serotonin reuptake inhibitors; OR = odds ratio; CI = confidence interval.

serotonergic drugs. Both TCAs and SSRIs can promote inappropriate antidiuretic hormone secretion (SIADH) and hyponatremia (64,65) and can cause cardiovascular depressant effects by inhibiting cardiac Na^+ and Ca^{2+} channels (66).

Antipsychotic drugs as a group seem to be associated with an increased risk of falling. This association was stronger than that found in the meta-analysis of Leipzig and colleagues (7). In this review, the relative risk of falls ranged between 1.21 and 11.4, whereas in the meta-analysis, the pooled OR was 0.41 for psychiatric inpatients and 1.66 for other participants. More evidence is needed to show whether the new atypical antipsychotic drugs are safer than the traditional ones in terms of the risk of falling. Only two studies reported on them; one study found no significant association, whereas the other showed that the risk was dose-dependent (31,32). The extrapyramidal adverse effects of antipsychotic drugs are one explanation for the increased risk of falls, but also the

anticholinergic properties and effects on alpha-adrenergic receptors may contribute to the risk of falling (67,68).

In addition, other CNS drugs, like antiepileptics, may also increase risk for falls. As clinicians, we need to adhere to well-grounded indications and carefully weigh risks and benefits of treatment. Polypharmacy (the use of five or more drugs) multiplies the risk for falling. The reason for this might not be just the number but also the type of preparations included in the medication. After adjustment for comorbid conditions, polypharmacy remained a risk factor for falls only when the medication included at least one drug known to pose a risk for falling (69). Especially concomitant use of several CNS drugs should be avoided.

Although cardiovascular drugs are the most commonly used drugs among elderly persons (10,70), few studies reported results on the use of them. Preparations that lower blood pressure were associated with an increased risk of

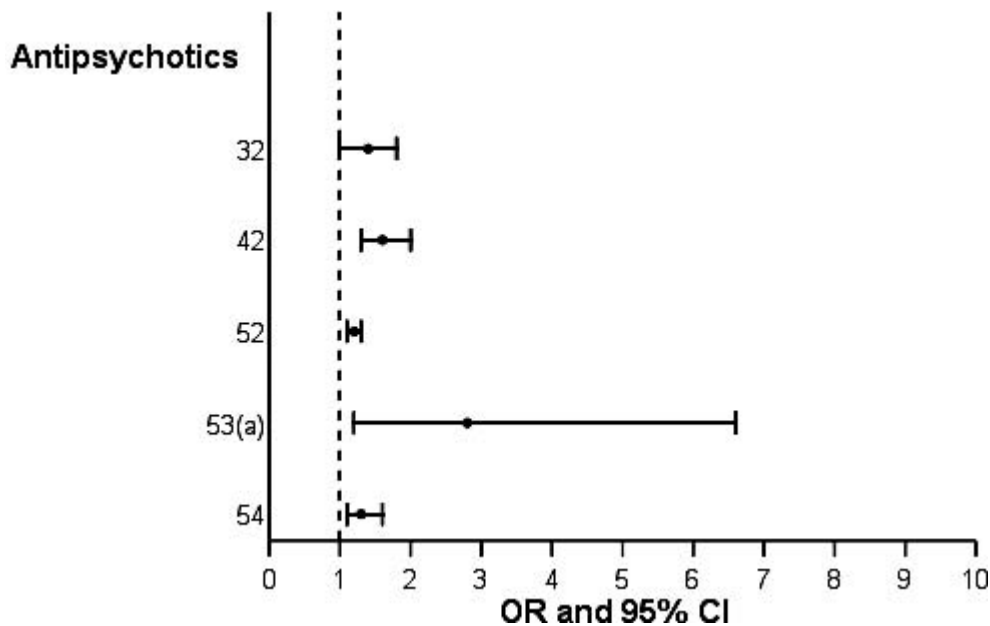


Figure 3. Antipsychotic drugs and risk of falls. Reference numbers of studies are on vertical axis. a, in mentally impaired persons. OR = odds ratio; CI = confidence interval.

falling (30,36,56). Different groups of cardiovascular medications act differently and on different receptors, thus necessitating their study by medication group and by specific preparation. We need to know which preparations and doses are the safest for patients who often have other significant risk factors for falls, like weak muscular strength. Drugs may get new indications as well. For example, alpha-blockers used for hypertension are now indicated for prostatic hyperplasia, and orthostatic hypotension related to this group of drugs may increase the risk of falling (71,72).

Design and Methodology of Studies

An important issue in any epidemiological study is to define outcome measures. In this review, one in every four of the studies failed to define the term "fall." This failure seems to be common even in RCTs (31,73). Moreover, the target medication was often inadequately defined, with more than half of the studies not using any systematic classification of medicines. These omissions significantly decrease the quality, consistency, and comparability of these studies, not to mention their clinical implementation.

Recruiting appropriate controls is critical for case-control studies. In hospital-based case-control studies, controls often consist of hospitalized patients. It is appropriate to get hip-fracture patients from hospitals, but how can we ensure that drug use in controls represents the average drug use among older persons in the general population (74)?

Only one study was an RCT (31), thus indicating that they are still as absent today as they were in the mid-1990s. An indication for drug use is defined in an RCT, whereas indications are not accurately known in observational studies, especially in retrospective or register database studies. Nor is it known whether the indications are current

anymore. Observational studies are also confounded by different doses and durations of drug use. Dosage was only taken into account in every fifth study, and the duration of pharmacotherapy in every fourth study. Anyhow, this is an improvement compared with the previous meta-analyses (7,8). The incidence of falls and fall-related fractures is known to increase with age and to some extent with female gender; therefore, age and gender need to be considered as potential confounders in the studies examining the association between medication use and falls.

Many studies included in this review were controlled for at least some chronic condition. However, when adjusting the final models for diseases like hypertension or coronary heart disease, essential findings can be easily overlooked. A drug can increase the risk of falling regardless of the appropriateness of the indication. In observational studies, it is not known what aspects were considered when a certain preparation was prescribed. Thus, there is a possibility of selection bias regarding the use of target medication; therefore, observational studies might either underestimate or overestimate the harmful effects of drugs in terms of falling.

Exposure to a medicine is often difficult to determine, and the source of information used has an effect on the results. In most studies, the information on medicine use was based on self-reports or medical records. When data obtained from medical records or self-reports were supplemented with plasma concentrations, more users of target medicines were found (48,74). This finding may indicate that studies tend to underestimate the strength of the association between use of benzodiazepines and falls or fractures. Such underreporting may also be common with other CNS drugs. In contrast, the drug can still be active in tissues and on receptors, even though it remains undetectable in the plasma. This is

Table 2. How to Improve the Quality of Observational Studies Examining Medication Use as a Risk Factor for Falling

Study Population
• Representative sample in relation to occurrence of falls or fall-related fractures • Representative sample/proportion of users of target medication • Carefully matched controls or controls who represent general elderly population
Outcome Measures
• Proper definition of falls or fall-related fractures • Prospective and regular follow-up of falls
Medication
• Use medication classification system • Describe all medications used by study population • Define target medicines drug by drug • Evaluate and compare effect of different doses • Define exposure to medication and duration of use
Confounding Factors
• Careful selection, measuring, and modeling of clinically important confounders • Age • Sex • Other medications • Indication/comorbidity • Physical performance
Clinical Implementation
• To improve clinical implementation report results • By diagnostic groups (e.g., persons with dementia or depression) • By living conditions (e.g., residential care, home-dwellers)

especially true with liposoluble drugs like benzodiazepines with active metabolites.

A problem in observational studies is that medication is supposed to remain unchanged throughout the follow-up period, and conclusions are made on that basis. Another suggestion is that participants use only one potentially risky medicine. The medicines in use can be changed many times a year, and the same person may concomitantly use several drugs that can potentially increase the risk of falls. Excessive polypharmacy and the use of psychotropics increase with advancing age (9,10,70). Even concomitant use of several psychotropic drugs is not rare (10). Thus, the current temporal relationship between drug use and falls, the effect of risky drug combinations, as well as the confounding effects of other drugs should be assessed in these studies.

Suggestions for Forthcoming Trials

The drugs on the market and those used by elderly persons are not systematically studied as potential risk factors for falls. Studies with a large number of participants are needed to determine whether new drugs are associated with an increased risk of falls. Falls as harmful side effects should also be included in the protocols of clinical trials of pharmaceutical preparations applying for a license for the market. We are awaiting studies regarding new CNS drugs, like new antiepileptics, new medicines for Parkinson's disease, cholinesterase inhibitors and memantine for Alzheimer's disease, SNRI antidepressants, and new atyp-

ical antipsychotics. Moreover, other medicines commonly used by elderly persons need to be studied as risk factors for falls, including serum lipid-modifying agents, dipyridamole, nonsteroidal analgesics, coxibs, alpha-receptor inhibitors for prostatic hyperplasia, and cardiovascular medicines like ACE inhibitors and angiotensin II antagonists. Suggestions for improving the quality of observational studies are listed in Table 2.

Conclusion

CNS medicines, especially psychotropic drugs, seem to be associated with an increased risk of falling. Yet, many observational studies still fail to provide proper definitions of falls and target medications as well as prospective follow-up of falls and drug use. These problems significantly decrease the quality, consistency, and comparability of studies, not to mention clinical implementation. More RCTs are needed, and falls as an adverse effect should be included in the protocols of the clinical trials of medicines intended for elderly persons.

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REFERENCES

1. Rubenstein LZ, Josephson KR, Robbins AS. Falls in the nursing home. *Ann Intern Med.* 1994;121:442–451.
2. van Weel C, Vermeulen H, van den Bosch W. Falls: a community care perspective. *Lancet.* 1995;345:1549–1551.
3. Sattin RW, Lambert Huber DA, DeVito C, et al. The incidence of fall injury events among the elderly in a defined population. *Am J Epidemiol.* 1990;131:1028–1037.
4. Donald IP, Bulpitt CJ. The prognosis of falls in elderly people living at home. *Age Ageing.* 1999;28:121–125.
5. Tinetti ME, Speechley M. Prevention of falls among the elderly. *N Engl J Med.* 1989;320:1055–1059.
6. Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopedic Surgeons Panel on Falls Prevention. *J Am Geriatr Soc.* 2001;49:664–672.
7. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc.* 1999;47:30–39.
8. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc.* 1999;47:40–50.
9. Hartikainen S, Rahkonen T, Kautiainen H, et al. Kuopio 75+ study: does advanced age predict more common use of psychotropics among the elderly? *Int Clin Psychopharmacol.* 2003;18:163–167.

10. Linjakumpu T, Hartikainen S, Klaukka T, et al. Use of medications and polypharmacy are increasing among the elderly. *J Clin Epidemiol*. 2002;55:809–817.
11. Martin H, Slyk MP, Deymann S, et al. Safety profile assessment of risperidone and olanzapine in long-term care patients with dementia. *J Am Med Dir Assoc*. 2003;4:183–188.
12. Joo JH, Lenze EJ, Mulsant BH, et al. Risk factors for falls during treatment of late-life depression. *J Clin Psychiatry*. 2002;63:936–941.
13. Nyberg L, Gustafson Y, Janson A, et al. Incidence of falls in three different types of geriatric care. *Scand Soc Med*. 1997;25:8–13.
14. Koski K, Luukinen H, Laippala P, et al. Physiological factors and medications as predictors of injurious falls by elderly people: a prospective population-based study. *Age Ageing*. 1996;25:29–38.
15. Souverein PC, Van Staa TP, Egberts ACG, et al. Use of alpha-blockers and the risk of hip/femur fractures. *J Intern Med*. 2003;254:548–554.
16. Schoofs M, van der Klift M, Hofman A, et al. Thiazide diuretics and risk for hip fracture. *Ann Intern Med*. 2003;139:476–482.
17. Ivers RQ, Cumming RG, Mitchell P, et al. Visual impairment and falls in older adults: the Blue Mountains Eye Study. *J Am Geriatr Soc*. 1998;46:58–64.
18. Mendelson WB. The use of sedative/hypnotic medication and its correlation with falling down in the hospital. *Sleep*. 1996;19:698–701.
19. Salgado RI, Lord SR, Ehrlich F, et al. Predictors of falling in elderly hospital patients. *Arch Gerontol Geriatr*. 2004;38:213–219.
20. Bergland A, Jarmlö GB, Laake K. Predictors of falls in the elderly by location. *Aging Clin Exp Res*. 2003;15:43–50.
21. Richardson DR, Hicks MJ, Walker RB. Falls in rural elders: an empirical study of risk factors. *J Am Board Fam Pract*. 2002;15:178–182.
22. Bueno-Cavanillas A, Padilla-Ruiz F, Jimenez-Moleon JJ, et al. Risk factors in falls among the elderly according to extrinsic and intrinsic precipitating causes. *Eur J Epidemiol*. 2000;16:849–859.
23. Ensrud EK, Blackwell T, Mangione CM, et al. Central nervous system active medications and risk for fractures in older women. *Arch Intern Med*. 2003;163:949–957.
24. Bae JM, Koo HW, Jung KO. A cohort study on the association between psychotropics and hip fracture in Korean elderly women. *J Korean Med Sci*. 2002;17:65–70.
25. Stenbacka M, Jansson B, Leifman A, et al. Association between use of sedatives or hypnotics, alcohol consumption, or other risk factors and a single injurious fall or multiple injurious falls: a longitudinal general population study. *Alcohol*. 2002;28:9–16.
26. Schwartz A, Villa ML, Prill M, et al. Falls in older Mexican-American women. *J Am Geriatr Soc*. 1999;47:1371–1378.
27. Guo Z, Willis P, Viitanen M, et al. Cognitive impairment, drug use, and the risk of hip fracture in persons over 75 years old: a community-based prospective study. *Am J Epidemiol*. 1998;148:887–892.
28. Dargent-Molina P, Favier F, Grandjean H, et al. Fall-related factors and risk of hip fracture: the EPIDOS prospective study. *Lancet*. 1996;348:145–149.
29. Weiner DK, Hanlon JT, Studenski SA. Effects of central nervous system polypharmacy on falls liability in community-dwelling elderly. *Gerontology*. 1998;44:217–221.
30. Bergland A, Wyller TB. Risk factors for serious fall related injury in elderly women living in home. *Inj Prev*. 2004;10:308–313.
31. Katz IR, Rupnow M, Kozma C, et al. Risperidone and falls in ambulatory nursing home residents with dementia and psychosis or agitation: secondary analysis of a double-blind placebo-controlled trial. *Am J Geriatr Psychiatry*. 2004;12:499–508.
32. Kallin K, Gustafsson Y, Sandman PO, et al. Drugs and falls in older people in geriatric care settings. *Aging Clin Exp Res*. 2004;16:270–276.
33. Lawlor DA, Patel R, Ebrahim S. Association between falls in elderly women and chronic diseases and drug use: cross sectional study. *BMJ*. 2003;327:712–717.
34. Kelly KD, Pickett W, Yiannakoulis N, et al. Medication use and falls in community-dwelling older persons. *Age Ageing*. 2003;32:503–509.
35. Ensrud EK, Blackwell T, Mangione CM, et al. Central nervous system-active medications and risk for falls in older women. *J Am Geriatr Soc*. 2002;50:1629–1637.
36. Rozenfeld S, Camacho LA, Veras P. Medications as a risk factor for falls in older women in Brazil. *Rev Panam Salud Publica*. 2003;13:369–375.
37. Hubbard R, Farrington P, Smith C, et al. Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture. *Am J Epidemiol*. 2003;158:77–84.
38. Heitterachi E, Lord SR, Meyerkort P, et al. Blood pressure changes on upright tilting predict falls in older people. *Age Ageing*. 2002;31:181–186.
39. Neutel CI, Perry S, Maxwell C. Medication use and risk of falls. *Pharmacoepidemiol Drug Saf*. 2002;11:97–104.
40. Kallin K, Lundin-Olsson L, Jensen J, et al. Predisposing and precipitating factors for falls among older people in residential care. *Public Health*. 2002;116:263–271.
41. Wang PS, Bohn RL, Glynn RJ, et al. Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. *Am J Psychiatry*. 2001;158:892–898.
42. Wang PS, Bohn RL, Glynn RJ, et al. Zolpidem use and hip fractures in older people. *J Am Geriatr Soc*. 2001;49:1685–1690.
43. Pierfitte C, Macouillard G, Thicoipe M, et al. Benzodiazepines and hip fractures in elderly people: case-control study. *BMJ*. 2001;322:704–708.
44. Tromp AM, Pluijm SMF, Smit JH, et al. Fall-risk screening test: a prospective study on predictors for falls in community-dwelling elderly. *J Clin Epidemiol*. 2001;54:837–844.
45. Arfken CL, Wilson JG, Aronson SM. Retrospective review of selective serotonin reuptake inhibitors and falling in older nursing home residents. *Int Psychogeriatr*. 2001;13:85–91.
46. Ray WA, Thapa PB, Gideon P. Benzodiazepines and risk of falls in nursing home residents. *J Am Geriatr Soc*. 2000;48:682–685.
47. Sgadari A, Lapane KL, Landi F, et al. Oxidative and nonoxidative benzodiazepines and the risk of femur fracture. The Systematic Assessment of Geriatric Drug Use via Epidemiology Study Group. *J Clin Psychopharmacol*. 2000;20:234–239.
48. Schwab M, Röder F, Aleker T, et al. Psychotropic drug use, falls and hip fractures in the elderly. *Aging Clin Exp Res*. 2000;12:234–239.
49. Thapa PB, Gideon P, Cost TW, et al. Antidepressants and the risk of falls among nursing home residents. *N Engl J Med*. 1998;339:875–882.
50. Chaimowicz F, Ferreira T de J, Miguel DF. Use of psychoactive drugs and related falls among older people living in a community in Brazil. *Rev Saude Publica*. 2000;34:631–635.
51. Liu B, Anderson G, Mittmann N, et al. Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people. *Lancet*. 1998;351:1303–1307.
52. Kiely DK, Kiel DP, Burrows AB, et al. Identifying nursing home residents at risk for falling. *J Am Geriatr Soc*. 1998;46:551–555.
53. Nygaard HA. Falls and psychotropic drug consumption in long-term care residents: is there an obvious association? *Gerontology*. 1998;44:46–50.
54. Mustard CA, Mayer T. Case-control study of exposure to medication and risk of injurious falls requiring hospitalization among nursing home residents. *Am J Epidemiol*. 1997;145:738–745.
55. Ebly E, Hogan DB, Fung TS. Potential adverse outcomes of psychotropic and narcotic drug use in Canadian seniors. *J Clin Epidemiol*. 1997;50:857–863.
56. Graafmans WC, Ooms ME, Hofstee HM, et al. Falls in the elderly: a prospective study of risk factors and risk profiles. *Am J Epidemiol*. 1996;143:1129–1136.
57. Neutel CI, Hirdes JP, Maxwell CJ, et al. New evidence on benzodiazepine use and falls: the time factor. *Age Ageing*. 1996;25:273–278.
58. Thapa PB, Brockman KG, Gideon P, et al. Injurious falls in non-ambulatory nursing home residents: a comparative study of circumstances, incidence, and risk factors. *J Am Geriatr Soc*. 1996;44:273–278.
59. World Health Organization (WHO) Guidelines for ATC classification and DDD assignment. WHO collaborating Centre for Drug Statistics Methodology. Oslo, 2003.
60. Glass J, Lancôt KL, Herrmann N, et al. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ*. 2005;331:1169–1176.
61. Cummings RG, Le Couteur DG. Benzodiazepines and a risk of hip fractures in older people. A review of evidence. *CNS Drugs*. 2003;17:825–837.
62. Albercht S, Ihmsen H, Hering W, et al. The effect of age on the pharmacokinetics and pharmacodynamics of midazolam. *Clin Pharmacol Ther*. 1999;65:630–639.

63. Kanto J, Kangas L, Aaltonen L, et al. Effect of age on the pharmacokinetics and sedative effects of flunitrazepam. *Int J Clin Pharmacol Ther Toxicol*. 1981;19:400–404.
64. Stenbach H. The serotonin syndrome. *Am J Psychiatry*. 1991;148:705–713.
65. Liu BA, Mittmann N, Knowles SR, et al. Hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone associated with the use of selective serotonin reuptake inhibitors: a review of spontaneous reports. *Can Med Assoc J*. 1996;155:519–527.
66. Pacher P, Ungvari Z. Selective serotonin-reuptake inhibitor antidepressants increase the risk of falls and hip fractures in elderly people by inhibiting cardiovascular ion channels. *Med Hypotheses*. 2001;57:469–471.
67. Maixner SM, Mellow AM, Tandon R. The efficacy, safety, and tolerability of antipsychotics in the elderly. *J Clin Psychiatry*. 1999;60:29–41.
68. Verhaeverbeke I, Mets T. Drug-induced orthostatic hypotension in the elderly: avoiding its onset. *Drug Saf*. 1997;17:105–118.
69. Ziere G, Dieleman JP, Hofman A, Pols HA, van de Cammen TJ, Stricker BH. Polypharmacy and falls in the middle-aged and elderly population. *Br J Clin Pharmacol*. 2005;61:218–223.
70. Jyrkkä J, Vartiainen L, Hartikainen S, et al. Increasing use of medicines in elderly persons: a five-year follow-up of the Kuopio 75+ Study. *Eur J Clin Pharmacol*. 2006;62:151–158.
71. Nieminen T, Ylitalo R, Kööbi T, et al. The vasodilator effects of alfuzosin and tamsulosin in passive orthostasis: a randomized, double-blind, placebo-controlled study. *Eur Urol*. 2005;47:340–345.
72. Chirschilles E, Rubinstein L, Chao J, et al. Initiation of nonselective α_1 -antagonists therapy and occurrence of hypotension-related adverse effects among men with benign prostatic hyperplasia: a retrospective cohort study. *Clin Ther*. 2001;23:727–743.
73. Hauer K, Lamb SE, Jorstad EC, et al. Systematic review of definitions and methods of measuring falls in randomized controlled fall prevention trials. *Age Ageing*. 2006;35:5–10.
74. Moore N, Pierfitte C, Pehourcq F, et al. Comparison of patient questionnaire, medical records, and plasma assays in assessing exposure to benzodiazepines in elderly subjects. *Clin Pharmacol Ther*. 2001;69:445–450.

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