Medication as a Risk Factor for Falls: Critical Systematic Review

Sirpa Hartikainen,1,2 Eija Lönnroos,1,3 and Kirsti Louhivuori4

1School of Public Health and Clinical Nutrition, Department of Geriatrics, University of Kuopio, Finland.  
2Social and Health Centre of Kuopio, Finland.  
3Central Finland Hospital, Jyväskylä, Finland.  
4School of Public Health and Clinical Nutrition, Department of Public Health, University of Kuopio, Finland.

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.
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 (33,36,45,46,49,50,55,59), 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 (30,33,35,36,38,40,44,50,55,56), 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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting/Study Population</th>
<th>Number and Age of Participants</th>
<th>Target Medication</th>
<th>Outcome Measure Association Between Medication Use and Falls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergland and Wyller, 2004 (30)</td>
<td>P</td>
<td>(N = 307) women (\text{Age} \geq 75)</td>
<td>All</td>
<td>Injurious falls: (\uparrow) antihypertensives (\downarrow) no association: other medication groups</td>
</tr>
<tr>
<td>Katz et al., 2004 (31)</td>
<td>RCT</td>
<td>(N = 537) persons (\text{Mean age} = 83)</td>
<td>Risperidone</td>
<td>Falls among residents with dementia: (\downarrow) risperidone 1 mg/d (\downarrow) risperidone 2 mg/d</td>
</tr>
<tr>
<td>Kallin et al., 2004 (32)</td>
<td>P, CS, RC, RH, Re, H</td>
<td>(N = 3669) persons (\text{Age} \geq 65)</td>
<td>All</td>
<td>(\uparrow) antidepressants, antipsychotics</td>
</tr>
<tr>
<td>Lawlor et al., 2003 (33)</td>
<td>P, R, CS, PB</td>
<td>(N = 4050) women (\text{Age} \geq 60)</td>
<td>All</td>
<td>Any falls: (\uparrow) hypnics/antihypnotics, antidepressants (\downarrow) no association: analgesics, cardiovascular/endocrine/respiratory system drugs</td>
</tr>
<tr>
<td>Kelly et al., 2003 (34)</td>
<td>CC, CD</td>
<td>(N = 11,390) persons (\text{Age} \geq 66)</td>
<td>All</td>
<td>Injurious falls: (\uparrow) opioids, anticonvulsants, antidepressants (\downarrow) no association: other medication groups</td>
</tr>
<tr>
<td>Ensrud et al., 2002 (35)</td>
<td>P, CD</td>
<td>(N = 8127) women (\text{Age} \geq 65)</td>
<td>CNS drugs</td>
<td>Falls/recurrent falls: (\uparrow) BZDs, antidepressants, anticonvulsants (\downarrow) no association: opioids</td>
</tr>
<tr>
<td>Rozenfeld et al., 2003 (36)</td>
<td>R, CS, CD</td>
<td>(N = 634) women (\text{Age} \geq 60)</td>
<td>All</td>
<td>Falls/recurrent falls: (\uparrow) diuretics, beta-blockers, antihypertensives/β-blockers, antidepressants, anxiolytics/sedatives</td>
</tr>
<tr>
<td>Hubbard et al., 2003 (37)</td>
<td>CC, R, PB</td>
<td>(N = 46,230) persons (\text{Mean age} = 79)</td>
<td>SSRIs TCAs</td>
<td>Hip fracture: (\uparrow) TCAs, SSRIs</td>
</tr>
<tr>
<td>Heitlerachi et al., 2002 (38)</td>
<td>P, CD</td>
<td>(N = 70) persons (\text{Age} \geq 62)</td>
<td>All</td>
<td>Falls: (\uparrow) no association: antihypertensives, antidepressants</td>
</tr>
<tr>
<td>Neutel et al., 2002 (39)</td>
<td>P, NH</td>
<td>(N = 227) persons (\text{Age} \geq 65)</td>
<td>All</td>
<td>Falls: (\uparrow) five or more medicines (\downarrow) a new prescription of BZDs or antipsychotics (\downarrow) no association: other medication groups</td>
</tr>
<tr>
<td>Kallin et al., 2002 (40)</td>
<td>P, R, RC</td>
<td>(N = 83) persons (\text{Mean age} = 80)</td>
<td>All</td>
<td>Falls: (\uparrow) antidepressants (SSRIs) (\downarrow) no association: other medication groups</td>
</tr>
<tr>
<td>Wang et al., 2001 (41)</td>
<td>CC, R, PB</td>
<td>(N = 6110) persons (\text{Age} \geq 65)</td>
<td>BZDs</td>
<td>Hip fracture: (\uparrow) BZD (\leq 3) mg/d in diazepam equivalents (\downarrow) BZD (\geq 3) mg/d in long-term use</td>
</tr>
<tr>
<td>Wang et al., 2001 (42)</td>
<td>CC, R, PB</td>
<td>(N = 6110) persons (\text{Age} \geq 65)</td>
<td>Psychotropics</td>
<td>Hip fracture: (\uparrow) zolpidem, BZDs, antipsychotics, antidepressants (\downarrow) no association: exposure to BZD</td>
</tr>
<tr>
<td>Pierfitte et al., 2001 (43)</td>
<td>CC, PB</td>
<td>(N = 1062) persons (\text{Age} \geq 65)</td>
<td>BZDs</td>
<td>Hip fracture: (\downarrow) lorazepam in plasma, reported use of (\geq 2) BZDs</td>
</tr>
<tr>
<td>Tromp et al., 2001 (44)</td>
<td>P, CD</td>
<td>(N = 1285) persons (\text{Mean age} = 75)</td>
<td>All</td>
<td>Falls: (\uparrow) use of (\geq 4) drugs, BZDs, antiepileptics</td>
</tr>
<tr>
<td>Arfken et al., 2001 (45)</td>
<td>R, NH</td>
<td>(N = 368) persons (\text{Age} \geq 60)</td>
<td>Antidepressants</td>
<td>Falls: (\uparrow) SSRIs</td>
</tr>
<tr>
<td>Ray et al., 2000 (46)</td>
<td>R, NH</td>
<td>(N = 2510) persons (\text{Age} \geq 65)</td>
<td>BZDs</td>
<td>Falls: (\uparrow) BZDs (\leq 2) mg/d in diazepam equivalents (\downarrow) BZDs (&gt; 8) mg/d in diazepam equivalents (\uparrow) BZD, BZD started within 1 wk, BZD use (\geq 30) d (\uparrow) no association: elimination half-life (\leq 12) h (\downarrow) nightly falls when half-life (&gt; 12) h (\downarrow) elimination half-life (\geq 12) h</td>
</tr>
<tr>
<td>Sgadari et al., 2000 (47)</td>
<td>CC, NH</td>
<td>(N = 46,803) persons (\text{Age} \geq 65)</td>
<td>BZDs</td>
<td>Hip fracture: (\uparrow) nonoxidative BZDs</td>
</tr>
<tr>
<td>Schwab et al., 2000 (48)</td>
<td>CC, CD</td>
<td>(N = 187) persons (\text{Mean age} = 80.0)</td>
<td>TCA Barbiturates</td>
<td>BZD</td>
</tr>
<tr>
<td>Thapa et al., 1998 (49)</td>
<td>R, NH</td>
<td>(N = 2428) persons (\text{Age} \geq 65)</td>
<td>Antidepressants</td>
<td>(\uparrow) TCAs, SSRIs, trazodone</td>
</tr>
<tr>
<td>Chaimowicz et al., 2000 (50)</td>
<td>R, CD</td>
<td>(N = 161) persons (\text{Age} \geq 65)</td>
<td>Psychoactive drugs</td>
<td>Falls: (\uparrow) BZDs, BZDs, and/or antidepressants</td>
</tr>
<tr>
<td>Liu et al., 1998 (51)</td>
<td>CC, R, PB</td>
<td>(N = 49,648) persons (\text{Age} \geq 66)</td>
<td>Antidepressants</td>
<td>Hip fracture: (\uparrow) SSRIs, TCAs</td>
</tr>
</tbody>
</table>
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 (34,37,39,40–43,46,47,49,53,54,56,58).

**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 two 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 vasodilator (OR 3.8; 95% CI, 1.4–10.2) (56) and use of diuretics (OR 2.3; 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
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 (EC50) 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

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**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.
serotonergic drugs. Both TCAs and SSRIs can promote inappropriate antidiuretic hormone secretion (SIADH) and hyponatremia (64,65) and can cause cardiovascular depressive 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
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
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 atypical antipsychotics. Moreover, other medicines commonly used by elderly persons need to be studied as risk factors for falls, including serum lipid-modifying agents, diypiridamole, 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.

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

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

Sirpa Hartikainen, MD, PhD, School of Public Health and Clinical Nutrition, Department of Geriatrics, University of Kuopio, P.O. Box 1627, FI-70211 Kuopio, Finland. E-mail: sirpa.hartikainen@uku.fi
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