Original Study
Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: II. Psychotropics

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Abstract
Background and objective: Falls are a major public health problem in older adults. Earlier studies showed that psychotropic medication use increases the risk of falls. The aim of this study is to update the current knowledge by providing a comprehensive systematic review and meta-analysis on psychotropic medication use and falls in older adults.

Methods and design: This study is a systematic review and meta-analysis. A search was conducted in Medline, PsychINFO, and Embase. Key search concepts were "falls," "aged," "medication," and "causality." Studies were included that investigated psychotropics (antipsychotics, antidepressants, anxiolytics, sedatives, and hypnotics) as risk factors for falls in participants ≥60 years of age or participants with a mean age of ≥70 years. Meta-analyses were performed using generic inverse variance method pooling unadjusted and adjusted odds ratio (OR) estimates separately.

Results: In total, 248 studies met the inclusion criteria for qualitative synthesis. Meta-analyses using adjusted data showed the following pooled ORs: antipsychotics 1.54 [95% confidence interval (CI) 1.28–1.85], antidepressants 1.57 (95% CI 1.43–1.74), tricyclic antidepressants 1.41 (95% CI 1.07–1.86), selective serotonin reuptake inhibitors 2.02 (95% CI 1.85–2.20), benzodiazepines 1.42 (95%, CI 1.22–1.65), long-acting benzodiazepines 1.81 (95%, CI 1.05–3.16), and short-acting benzodiazepines 1.27 (95%, CI 1.04–1.56). Most of the meta-analyses resulted in substantial heterogeneity that did not disappear after stratification for population and healthcare setting.

Conclusions: Antipsychotics, antidepressants, and benzodiazepines are consistently associated with a higher risk of falls. It is unclear whether specific subgroups such as short-acting benzodiazepines and selective serotonin reuptake inhibitors are safer in terms of fall risk. Prescription bias could not be accounted for. Future studies need to address pharmacologic subgroups as fall risk may differ depending on specific medication properties. Precise and uniform classification of target medication (Anatomical Therapeutic Chemical Classification) is essential for valid comparisons between studies.

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public health concern, now even more in light of the world’s aging population.

Psychotropic medication has consistently been reported to increase the risk of falls. However, earlier meta-analyses have predominantly used unadjusted data, thus, being susceptible to major bias. Only Leipzig et al and Woolcott et al performed a meta-analysis of limited medication groups using adjusted data. Furthermore, despite the well-established association between psychotropics and fall risk, knowledge on potential risk differences between specific pharmacologic subgroups is scarce.

The objective of this systematic review and meta-analysis is to appraise the associations between falls (any falls, recurrent falls, injurious falls) and specific psychotropic medication groups, thus, providing a comprehensive update of current knowledge on this topic.

**Methods**

**Identification of Studies**

A search was performed in Medline, PsycINFO, and Embase from onset until September 28, 2016. A customized search strategy was conducted for each database with the help of a clinical librarian (J.D.). The search contained the following key search concepts: “fall,” “aged,” “causality,” and “medication.” The key search term medication contained all known fall-risk-increasing drugs (FRIDs). Medication was used to identify other possible medication classes to be added to the “medication” concept of the search. The full search is available as a supplement (Appendix 1).

**Selection of Studies**

All the titles and abstracts were screened by one author (L.S.). A 40% random subselection of articles was screened by a second reviewer (M.V. or A.W.). After selection of potential articles, the latter were assessed by 2 reviewers (L.S. and M.V. or A.W.). In case of disagreement concerning the final selection of articles, a third author (N.V.) was consulted. Furthermore, reference checking was performed to search for potentially eligible studies from original and review articles.

Randomized controlled trials (RCTs), cohort studies, case-control studies, cross-sectional studies, and case-crossover studies that investigated the association between psychotropic medications and any fall, recurrent falls (2 or more), or injurious falls were included. Psychotropics were defined as medications that are classified under N05 “psycholeptics” (antipsychotics, anxiolytics, hypnotics, and sedatives) or N06A “psychoanalpeptics” (antidepressants) according to the Anatomical Therapeutic Chemical (ATC) classification system, and the general term psychotropics was also included. Only studies with participants aged ≥60 years, participants with a mean age of 70 years or over, and studies that reported results of suitable age subgroups were included. We included studies from all settings (population-based, community-dwellers, hospital wards, long-term care institutions, and outpatient clinics). Articles were excluded if they were not written in English or if they were case reports, reviews, conference abstracts, letters, or articles concerning the withdrawal of medications. If an article used the same population and exposure for the second time, only 1 article was included giving priority to the one with adjusted analysis and a bigger sample size when both provided an adjusted analysis. Articles that used unclear medication definitions were excluded.

**Data Extraction**

A standardized form was designed to extract information systematically. Data were extracted by 2 reviewers (L.S. and M.V. or A.W. or K.P.) independently. In case of disagreement concerning the data extraction, a third author (N.V.) was consulted. The following information was collected: study design; number and mean age of participants; setting; definition of falls; medication classification; type and method of medication and fall ascertainment; the effect of medication use duration and/or medication dose on fall risk; the outcome (odds ratios (ORs), relative risk, incidence rate ratio, hazard ratios, 95% confidence interval, P values) and possible confounders. Definitions of a fall by Prevention of Falls Network Europe, Tinetti and Kellog group were used to compare with the definition in the articles.

**Quality Assessment**

The quality of the included studies was assessed by same reviewers (L.S. and M.V., or A.W., or K.P.). In case of disagreement concerning the quality assessment, a third author (N.V.) was consulted. The Newcastle Ottawa Scale for observational studies and the Cochrane tool for randomized controlled trials were used for quality assessment. The Newcastle Ottawa Scale was slightly adjusted to fit the review topic and optimize quality assessment of falls (Appendix 2). A score of 7 or higher was considered high quality, a score of 4–6 intermediate quality and a score of 0–3 low quality in case of observational studies.

**Data Synthesis and Analysis**

The included studies were categorized per medication class using the ATC classification system. Study characteristics and outcomes of all included studies can be found in tables (Appendix 3, Supplementary Tables S1–S6) and a descriptive approach was used to report the study results. In case of anxiolytics, sedatives, and hypnotics, the descriptive approach was used only for the studies using ATC classification.

Meta-analyses were performed when there were 3 or more high or intermediate quality studies that provided OR. Adjusted and unadjusted estimates were pooled separately. The random-effects generic inverse variance method was used. Assessing heterogeneity between studies was done by using I² statistics and by judging the overlap of confidence intervals of the studies. In accordance with the Cochrane handbook, an I² value of 30%–60% represented moderate heterogeneity, 50%–90% substantial heterogeneity, and 75%–100% considerable heterogeneity. In case of substantial heterogeneity (>50%), the potential sources of heterogeneity (setting, fall type) were explored through subgroup analyses. The software Review Manager was used for all statistical tests (Review Manager, RevMan v 5, The Cochrane Collaboration, 2014; The Nordic Cochrane Center, Copenhagen, Denmark).

Short-acting and long-acting benzodiazepines were subjected to meta-analyses. We used the definitions used in included studies. The definition of short-acting benzodiazepines in the studies was half-life shorter than 24 or 20 hours, or the exposure term included only benzodiazepines with a half-life shorter than 24 hours. The definition of long-acting benzodiazepines in the studies was half-life longer than 20 or 24 hours, or the exposure term included only benzodiazepines with a half-life longer than 24 hours. In addition, we performed meta-analyses adding the studies without the definition of short- or long-acting benzodiazepines.

**Results**

The initial search provided 8927 articles after the removal of duplicates. Of these articles, 1156 full texts were assessed, and 248 articles were included in the qualitative synthesis (Figure 1). Supplementary Tables S1–S6 show the characteristics of included studies. One hundred thirty-eight studies were cohort studies, 57 were cross-sectional, 43 were case-control, 7 were randomized controlled trials, and 3 were case-crossover studies. Of the included studies, 101
were set in the community, 69 in long-term care institutions and 32 in hospital. The remaining 46 studies were conducted in other settings or included patients from various settings. Medication ascertainment at the time of fall for example by using pharmacy dispensing data was done in 14% of studies. Fifteen percent of observational studies used the ATC classification system for classifying medication, and 73 percent of observational studies did not mention how classification was done. In the 7 RCTs, falls were collected as adverse events. However, 3 RCTs did not give a definition for falls, and 5 studies were unclear about the method of fall ascertainment. A summary table of the quality assessment of included RCTs can be found in Appendix 3.

Antipsychotics

Seventy-five studies investigated the use of antipsychotics as a group (Supplementary Table S1) as a risk factor for falls. Fifty-two studies were scored as high or intermediate quality (52 of 75). Twenty-four studies showed an association with increased risk of falls (24 of 75). Three studies showed a protective association (3 of 75).

Sixteen studies were included in the meta-analysis using unadjusted data, which resulted in a pooled OR of 1.48 (1.23–1.79) with substantial to considerable heterogeneity, I² = 82%.

Five studies investigated atypical antipsychotics as a risk factor for falls. Four studies were scored high or intermediate quality (4 of 5). Five studies found a positive association (5 of 5). Also, 5 studies investigated the use of typical antipsychotics as an exposure. All studies were intermediate to low quality. Two studies found a significant positive association (2 of 5).

Eight studies investigated risperidone as an exposure. One intermediate quality study found a positive multivariably adjusted association (1 of 8). Results of the other individual antipsychotics are provided in Appendix 3.

Antidepressants

A total amount of 107 studies investigated antidepressant use (Supplementary Table S2) as an exposure for falls. Sixty-seven of those studies were scored as high or intermediate quality (67 of 107). Forty-eight studies showed an association with increased risk of falls (48 of 107). Twenty-two studies were included in the meta-analysis of antidepressants using adjusted data, which resulted in a pooled OR of 1.57 (1.43–1.74) with substantial to considerable heterogeneity I² = 76%. Table 1 shows the results of
subgroup analysis. Forty-eight studies were included in the meta-analysis using unadjusted data, which resulted in a pooled OR of 1.69 (1.52–1.88) with substantial to considerable heterogeneity, $I^2 = 76\%$.

Twenty-three studies investigated selective serotonin reuptake inhibitors (SSRI) as an exposure. Fifteen studies found a positive association (15 of 23). Four studies were included in the meta-analysis of SSRI using adjusted data, which resulted in a pooled OR of 1.98 (1.87–2.10) with low heterogeneity, $I^2 = 0\%$.

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Results of the other antidepressant are provided in Appendix 3. In addition, results of the effect of the duration of the antidepressant therapy and dosage are provided in Appendix 3.

### Benzodiazepines

Sixty-seven studies investigated the use of benzodiazepines (Appendix, Supplementary Table S3) as a group as an exposure. Forty-four studies were scored high or intermediate quality (44 of 67). Twenty-five studies showed an association with increased risk of falls (25 of 67).

Fourteen studies were included in the meta-analysis of benzodiazepines using adjusted data, which resulted in a pooled OR of 1.42 (1.22–1.65) with substantial heterogeneity, $I^2 = 67\%$. Table 1 shows the results of subgroup analysis. Twenty-six studies were included in a meta-analysis using unadjusted data, which resulted in a pooled OR of 1.73 (1.49–2.01) with substantial heterogeneity, $I^2 = 64\%$.

Seventeen studies assessed long-acting benzodiazepines as an exposure. Eight studies showed an association with increased risk of falls (8 of 17). Four studies were included in the meta-analysis of long-acting benzodiazepines using adjusted data, which resulted in a pooled OR of 1.81 (1.05–3.16) with substantial heterogeneity $I^2 = 56\%$. When 2 studies without a definition of long-acting benzodiazepines were added in a meta-analysis a pooled OR 1.63 (1.20–2.23), $I^2 = 32\%$ was found. Four studies were included in the meta-analysis of long-acting benzodiazepines using unadjusted data, which resulted in a pooled OR of 1.54 (1.28–1.85) with low heterogeneity, $I^2 = 0\%$.

Thirteen studies investigated short-acting benzodiazepines as an exposure. Three studies showed an association with increased risk of falls (3 of 13). Four studies were included in the meta-analysis of short-acting benzodiazepines using adjusted data, which resulted in a pooled OR of 1.27 (1.04–1.56) with low heterogeneity $I^2 = 0\%$. When two studies without a definition of short-acting benzodiazepines were added in a meta-analysis a pooled OR of 1.27 (1.09–1.48), $I^2 = 0\%$ was found. Four studies were included in the meta-analysis of short-acting benzodiazepines using unadjusted data, which resulted in a pooled OR of 1.42 (1.22–1.65) with low heterogeneity, $I^2 = 0\%$.

For individual benzodiazepines diazepam was most often investigated. Six studies assessed it as an exposure. Three studies showed a positive association (3 of 6). Results of the other individual benzodiazepines are provided in Appendix 3.

Results of the effect of the duration of the benzodiazepine therapy and dosage are provided in Appendix 3.

### Benzodiazepine-Related Drugs

Six studies assessed benzodiazepine-related drugs as a group as an exposure. One study reported an association (1 of 6).

### Anxiolytics, Hypnotics, and Sedatives and Psychotropic Medication

Results of both pharmacologic groups of anxiolytics, and hypnotics and sedatives and psychotropic medication are described in Appendix 3.

### Discussion

This systematic review comprehensively included 248 articles in a qualitative synthesis that evaluated the association between psychotropic medication use and the risk of falling in older adults. Seven medication classes (antipsychotics, antidepressants, TCAs, SSRIs, benzodiazepines, short-acting benzodiazepines, long-acting benzodiazepines) were associated with increased risk of falls in meta-analyses of adjusted data. In the qualitative synthesis, we observed inconsistent associations for antipsychotics (24 of 75), antidepressants (48 of 107), SSRIs (15 of 23), TCAs (9 of 24), benzodiazepines (25 of 67), long-acting benzodiazepines (8 of 17), short-acting benzodiazepines (3 of 13), hypnotics/sedatives (2 of 6), and anxiolytics (2 of 6). Initiation of antidepressants and benzodiazepines appear to increase fall-risk. Higher dosages of psychotropics also appear to result in a higher fall-risk.

We found a significantly increased fall risk in meta-analyses among antidepressant users as well as both subgroups of TCA and SSRI users. Our findings on antidepressants are supported by the results of earlier meta-analyses. When first launched it was generally assumed that SSRIs would be safer to use in older adults than TCAs. However, our systematic review and meta-analysis, together
with earlier systematic reviews,\(^8,9\) suggest that the use of SSRIs results in a comparable fall risk. Nevertheless, it has been shown that factors contributing to falls (eg, orthostatic hypotension) are less common among SSRI users than among TCA users.\(^6\) Possibly our outcomes are the result of preferential prescribing: prescribing SSRIs instead of TCAs to frail older adults with a higher fall risk. There are very few data on the use of SNRI and other antidepressants and fall risk. Thus, whether specific groups of antidepressants are safer in terms of fall risk needs to be assessed in prospective trials.

Also, benzodiazepine use was associated with an increased risk of falls. This finding is in line with the meta-analysis of adjusted data by Woolcott et al.\(^7\) Both our qualitative synthesis and meta-analysis suggest that long-acting benzodiazepines might be more fall-risk-increasing than short-acting benzodiazepines, which is in contrast with the results of Leipzig et al,\(^4\) who found no difference between the benzodiazepines. Somewhat different studies were included in the meta-analyses due to different availability of the data and different quality criteria. We were able to conduct meta-analyses using adjusted data in contrast to Leipzig et al.\(^4\) Studies on benzodiazepine related drugs are limited and therefore further research is warranted.

Antipsychotic use was associated with increased risk of falls in our meta-analysis. Our findings are in line with the meta-analysis by Woolcott et al.\(^7\) There were too few studies to perform a separate meta-analysis of typical or atypical antipsychotics. Our findings in the qualitative synthesis do not point toward a difference in fall risk between atypical and typical antipsychotics. However, more research is needed to evaluate whether typical and atypical antipsychotics differ concerning fall-risk-increasing properties.

**Strengths and Limitations**

Our systematic review provides an extensive overview of the literature available on different pharmacologic groups, subgroups, and chemical substances belonging to psychotropics and fall risk. Moreover, we were able to perform several meta-analyses using adjusted data. To our knowledge, TCAs, SSRIs, and long- and short-acting benzodiazepines were subjected to meta-analysis using adjusted data for the first time.

Several databases were used to perform a broad search. We might have missed some relevant articles by including only English language articles. Also, the results of cohorts of participants from age 50 years and over was beyond the scope of this review as well as evaluating the relationship between medications and syncope, though there is a considerable overlap between syncope and falls.\(^117\)

By reporting pooled ORs of adjusted and unadjusted data, we present all available evidence on this topic. Adjusted ORs account for potential confounding and reporting unadjusted data as well prevents overestimation of the association. Substantial heterogeneity was apparent in most of the meta-analyses and did not mostly disappear after stratification for setting and population.

The literature has significant limitations. The majority of observational studies collected data on medication only at baseline, which makes it likely that medication use by participants changed during follow-up.\(^118\) Furthermore, the validity of fall ascertainment is another major limitation of the literature. In addition, polypharmacy among older people is high. However, even if the studies included other FRIDs in their multivariate adjusted analysis, possible drug-drug interactions were not studied. Moreover, these observational studies are prone to confounding by indication. However, many of the studies are adjusted for medical disorders related to psychotropic medication use.

**Future Implications and Clinical Perspectives**

Psychotropics are established risk factors in fall-prevention guidelines, and this systematic review and meta-analysis supports their status as FRIDs. In addition, psychotropic medication withdrawal has been shown to be effective in lowering the fall risk.\(^119\) However, deprescribing is challenging with a high risk of noncompliance because of beneficial effects of medications and beliefs of patients and prescribers.

In the future, falls as adverse events should be collected in clinical trials of new medications. To contribute better to current understanding, observational studies should use a precise definition and classification of their target medication. Medication classification systems, preferably ATC, are essential to enable valid comparisons between studies. Furthermore, pharmacologic subgroups and individual medications need more investigation (eg, benzodiazepine related drugs and antidepressants beyond TCAs and SSRIs). To accomplish safer prescribing, more studies should investigate the effect of dosage and duration of medication use in relation to fall-risk.

**Conclusions**

This systematic review and meta-analysis indicates consistent associations between use of antipsychotics, antidepressants, and benzodiazepines and an increased risk of falls in older adults. Because of limited data, evaluation of pharmacologic subgroups and chemical substances was limited to qualitative analysis. To contribute better to current findings henceforward, observational studies should use a clear definition of their target medication and use ATC classification. In addition, studies should investigate the effect of dosage and duration of medication use in relation to fall-risk, as well as pharmacologic subgroups. To raise the level of evidence, falls as adverse events should be included in clinical trials of new medication.

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**Supplementary Data**

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jamda.2017.12.098.

**References**


