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## Original Study

## Fall-Risk-Increasing Drugs: A Systematic Review and Meta-analysis: III. Others



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## A B S T R A C T

**Keywords:**  
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**Background and objective:** The use of psychotropic medication and cardiovascular medication has been associated with an increased risk of falling. However, other frequently prescribed medication classes are still under debate as potential risk factors for falls in the older population. The aim of this systematic review and meta-analysis is to evaluate the associations between fall risk and nonpsychotropic and noncardiovascular medications.

**Methods and design:** A systematic review and meta-analysis. A search was conducted in Medline, PsycINFO, and Embase. Key search concepts were “falls,” “aged,” “medication,” and “causality.” Studies were included that investigated nonpsychotropic and noncardiovascular medications as risk factors for falls in participants  $\geq 60$  years or participants with a mean age  $\geq 70$  years. A meta-analysis was performed using the generic inverse variance method, pooling unadjusted and adjusted odds ratio (OR) estimates separately.

**Results:** In a qualitative synthesis, 281 studies were included. The results of meta-analysis using adjusted data were as follows (a pooled OR [95% confidence interval]): analgesics, 1.42 (0.91–2.23); nonsteroidal anti-inflammatory drugs (NSAIDs), 1.09 (0.96–1.23); opioids, 1.60 (1.35–1.91); anti-Parkinson drugs, 1.54 (0.99–2.39); antiepileptics, 1.55 (1.25–1.92); and polypharmacy, 1.75 (1.27–2.41). Most of the meta-analyses resulted in substantial heterogeneity that did not disappear after stratification for population and setting in most cases. In a descriptive synthesis, consistent associations with falls were observed for long-term proton pump inhibitor use and opioid initiation. Laxatives showed inconsistent associations with falls (7/20 studies showing a positive association).

**Conclusion:** Opioid and antiepileptic use and polypharmacy were significantly associated with increased risk of falling in the meta-analyses. Long-term use of proton pump inhibitors and opioid initiation might increase the fall risk. Future research is necessary because the causal role of some medication classes as fall-risk-increasing drugs remains unclear, and the existing literature contains significant limitations.

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Falls are a major and further growing public health challenge. Approximately one-third of people older than 65 experience at least 1 fall each year.<sup>1</sup> This high prevalence is accompanied by 20% risk of injuries.<sup>1</sup> There are almost 40,000 fatal falls each year across the European Union among older people.<sup>2</sup> In 2015, direct fall-related costs were estimated to be more than \$31 billion in the United States.<sup>3</sup> A rising and worrisome trend in fall-related injuries has been observed in Western countries.<sup>4–6</sup>

Use of certain medication has been shown to be a major fall-risk factor.<sup>7–10</sup> Until now, systemic reviews and meta-analyses have been predominantly focusing on cardiovascular and psychotropic medication use.<sup>7,8,11–14</sup> Nevertheless, several other frequently prescribed medication classes are under debate as potential fall-risk-increasing drugs (FRIDs). A recent meta-analysis of Bloch et al. showed significant odds ratios (ORs) for the use of any medication, polypharmacy, laxatives, antiepileptics, anti-Parkinson drugs, nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics, and metabolic and endocrine medication.<sup>14</sup> However, all these estimates were pooled from unadjusted results and thus vulnerable to major bias.

As medication withdrawal has been shown to be effective in lowering fall risk, it is vital to recognize FRID in the older population.<sup>15</sup> As mentioned above, a systematic evaluation of the associations for nonpsychotropic and noncardiovascular medications and fall risk is still lacking. Thus, the aim of this systematic review and meta-analysis was to evaluate the associations between falls (any fall, recurrent falls, injurious falls) and a comprehensive list of medications (except cardiovascular and psychotropic medication), polypharmacy, and inappropriate medication use, thereby providing a broad overview and a needed update of the available literature.

## Methods

### Identification of Studies

Medline, Embase, and PsycINFO were systematically searched on September 28, 2016, for literature published from onset until September 28, 2016. A customized search strategy was conducted for each database with the help of a clinical librarian (J.D.). Key search concepts were “falls,” “aged,” “medication,” and “causality.” The search terms for “medication” included all known FRIDs.<sup>7–9,11,16,17</sup> VOSviewer was used to identify other possible drug classes to be added to the “drugs” concept of the search.<sup>18</sup> The full search strategy is provided as supplementary data ([Appendix 1](#)).

### Selection of Studies

All the titles and abstracts were screened by one author (L.S.). A subselection of 40% of the articles was screened by another reviewer as well (M.V.). After this selection of potential articles, the full texts were assessed by 2 reviewers (L.S. and M.V./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.

Eligible studies had to examine the association between medication and falling, recurrent falling, or injurious falling. Medications of interest for this study were all medications except cardiovascular medication and psychotropics (antipsychotics, anxiolytics, hypnotics, sedatives, and antidepressants). Also, polypharmacy, the number of medications and medications labeled as “inappropriate” (eg, according to Beer’s criteria) were the medications of interest in this review. Randomized controlled trials (RCT), cohorts (retrospective and prospective), case-control, case-crossover, and cross-sectional studies were included. Participants needed to be at least 60 years old, or the mean age of the participants had to be 70 years or more, or the results of the older age group needed to be reported separately. 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 and if they were case reports, reviews, conference abstracts, letters, or articles concerning the withdrawal of medications. In case of different studies using the same population twice, the priority was given to the study

with adjusted analysis or the biggest sample size. Articles were also excluded if they used nonspecific medication terms.

### Data Extraction

A standardized data extraction form was designed to extract information systematically. Data were extracted by 2 reviewers (L.S. and M.V./A.W./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, the outcome (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 (PROFANE), Tinetti et al., and the Kellogg Group were compared with definitions in articles.<sup>19–21</sup>

Medications were classified according to the Anatomical Therapeutic Chemical (ATC) system, except for all of the analgesics (opioids, nonopioids, NSAIDs), which were categorized under “analgesics.”<sup>22</sup> The medication exposure term *analgesics* was combined with the terms *pain relief medication*, *analgesics and antipyretics*, *analgesics and anti-inflammatories*, and prescription pain killers for the analyses.

### Quality Assessment

The quality of the included studies was estimated by the same reviewers (L.S. and M.V./A.W./K.P.). The Newcastle-Ottawa Scale was used to assess the risk of bias in the observational studies.<sup>23</sup> In case of disagreement concerning the quality assessment, a third author (N.V.) was consulted. The Newcastle-Ottawa Scale was slightly adjusted to fit the review topic and optimize quality assessment of fall. A score of 0–3 was considered low quality, 4–6 intermediate, and 7 or more high quality. A detailed description of the adjusted Newcastle-Ottawa Scale can be found in the appendix ([Appendix 2](#)). The Cochrane Collaboration’s tool was used for assessing the risk of bias in randomized trials.<sup>24</sup>

### Data Synthesis and Analysis

Study characteristics and outcomes of the included studies were summarized in an evidence table, categorized per drug class ([Appendix 3](#)), and the results are additionally summarized with a descriptive approach. The results are included in the Results section if there were 5 or more studies per specific medication class and fall risk. In other cases, the results are provided in the supplementary material ([Appendix 3](#)). A meta-analysis was conducted if there were 3 or more high- or intermediate-quality studies providing OR for a particular medication class and fall risk or if the OR could be calculated. The random effects method of generic inverse variance was used to pool unadjusted and adjusted estimates separately. The results of the meta-analyses for the medication classes that could be pooled using only unadjusted data are provided as supplementary data ([Appendix 4](#)).

Heterogeneity between studies was investigated using the  $I^2$  statistics. In accordance with the Cochrane handbook,  $I^2$  values between 30% and 60% represented a moderate heterogeneity,  $I^2$  values between 50% and 90% a substantial heterogeneity, and  $I^2$  values between 75% and 100% considerable heterogeneity between studies.<sup>25</sup> In case of  $I^2$  value >50%, the potential sources of heterogeneity (setting, fall type) were explored through subgroup analyses. All statistical tests were carried out with the Review Manager (RevMan) software suite (version 5.3, The Cochrane Collaboration, Copenhagen). Statistical significance was defined as a *P* value <.05.

## Results

The initial search provided 8927 articles after the removal of duplicates. Of these articles, 1156 full texts were assessed, and 281 articles were included in the qualitative synthesis (Figure 1). Among included studies, 138 were cohorts, 39 were case-control studies, 84 were cross-sectional, 17 were RCTs, and 3 were case-crossover studies. Participants were community-dwelling older persons in 137 studies, 33 studies were conducted in hospital wards, and 39 studies included only long-term care patients. The remaining 72 studies were conducted in other settings or included patients from various settings.

A medication classification system was used only in 64 of the 265 observational studies. ATC classification was used in 34 studies. In 13% of the observational studies, the medication ascertainment was performed at the time of the fall. Falls were studied as adverse events in 16 RCTs and as a primary outcome in 1 RCT. In 12 RCTs, no definition for falls was provided, and 7 RCTs did not report how the data on falls as adverse events were collected.

### Anti-Parkinson Drugs

Twenty-two studies assessed *anti-Parkinson drugs* as an exposure. In 4 studies,<sup>26–29</sup> a positive association was found (4/22). Two studies<sup>30,31</sup> showed a protective effect (2/22). Three studies were

included in the meta-analysis of adjusted data, which resulted in pooled OR of 1.54 (0.99–2.39), with low heterogeneity,  $I^2 = 0\%$ . Thirteen studies were included in the meta-analysis of unadjusted data, which resulted in a pooled OR of 1.52 (0.95–2.43), with substantial to considerable heterogeneity,  $I^2 = 77\%$ . Table 1 shows the results of meta-analyses and subgroup analyses.

### Antiepileptics

Thirty studies investigated *antiepileptics* as an exposure. Nine studies<sup>27,28,32–38</sup> found a positive association (9/30). Seven studies were included in the meta-analysis of adjusted data, which resulted in pooled OR of 1.55 (1.25–1.92), with low heterogeneity,  $I^2 = 20\%$ . Sixteen studies were included in the meta-analysis of unadjusted data, which resulted in pooled OR of 1.95 (1.65–2.31), with low heterogeneity,  $I^2 = 27\%$ . Table 1 shows the results of the meta-analysis and subgroup analysis.

### Analgesics

Thirty studies investigated *analgesics* as an exposure. Six studies<sup>39–44</sup> found a positive association (6/30). One study<sup>45</sup> showed a protective effect (1/30). Five studies were included in the meta-analysis of adjusted data, which resulted in a pooled OR of 1.42 (0.91–2.23), with substantial heterogeneity,  $I^2 = 74\%$ . Thirteen

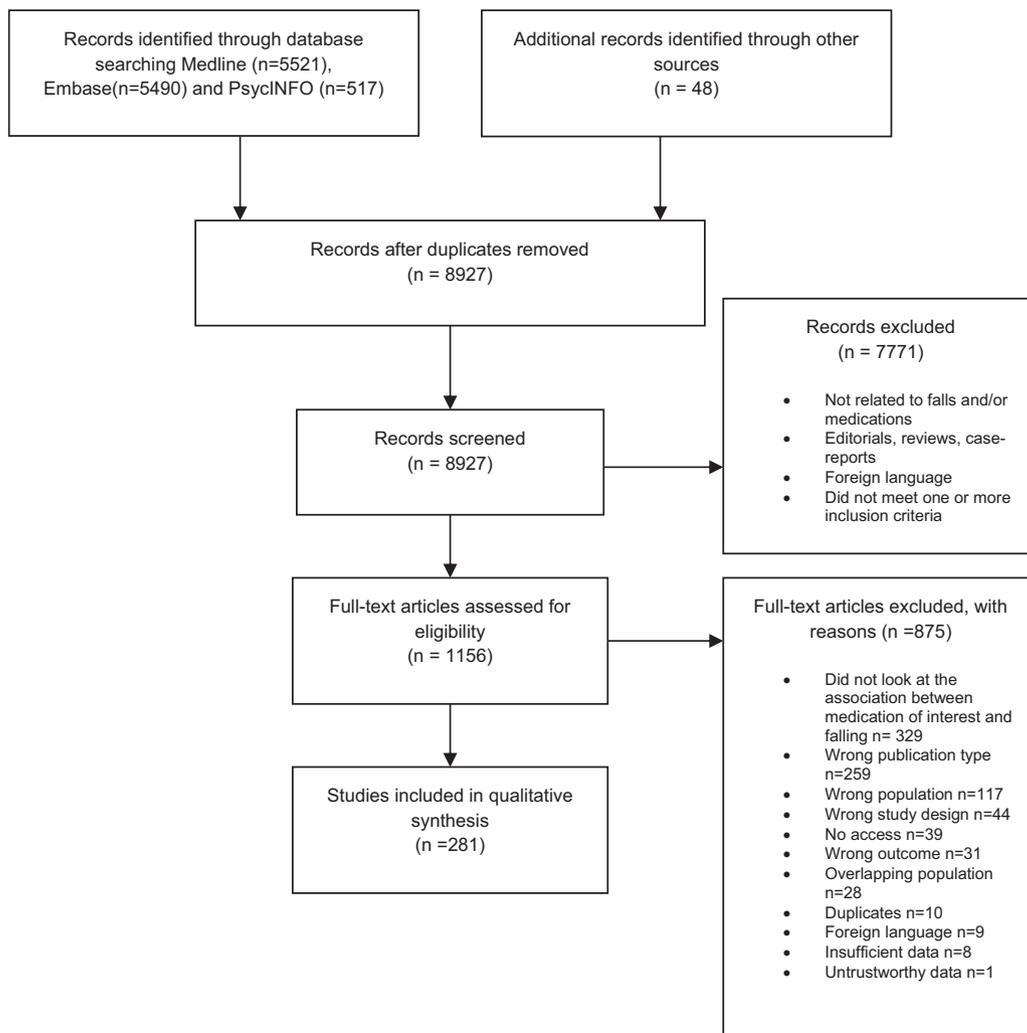


Fig. 1. Flow chart of study screening and inclusion.

**Table 1**  
Pooled Odds Ratios and Subgroup Sensitivity Analysis

|                    | Anti-Parkinson |                             | Antiepileptics |                             | Analgesics |                             | Opioids |                             | NSAIDs |                             |
|--------------------|----------------|-----------------------------|----------------|-----------------------------|------------|-----------------------------|---------|-----------------------------|--------|-----------------------------|
|                    | n              | OR (95% CI), I <sup>2</sup> | n              | OR (95% CI), I <sup>2</sup> | n          | OR (95% CI), I <sup>2</sup> | n       | OR (95% CI), I <sup>2</sup> | n      | OR (95% CI), I <sup>2</sup> |
| Unadjusted studies | 13             | 1.52 (0.95-2.43), 77%       | 16             | 1.95 (1.65-2.31), 27%       | 13*        | 1.16 (0.85-1.60), 70%       | 14*     | 1.51 (1.15-1.91), 97%       | 17*    | 1.31 (1.11-1.55), 85%       |
| Population         |                |                             |                |                             |            |                             |         |                             |        |                             |
| Community-dwelling | 2              | 4.45 (1.51-13.06), 36%      | 4              | 2.55 (1.84-3.52), 4%        | 3          | 1.15 (0.41-3.23), 80%       | 2       | 1.15 (0.66-2.00), 71%       | 2      | 2.02 (0.78-5.24), 67%       |
| Long-term care     | 2              | 1.21 (0.32-4.59), 78%       | 0              |                             | 7          | 1.09 (0.72-1.64), 72%       | 3       | 1.19 (0.77-1.84), 46%       | 6      | 1.39 (0.83-2.34), 55%       |
| In-hospital        | 6              | 0.81 (0.33-1.98), 71%       | 7              | 1.53 (1.14-2.04), 0%        | 1          | 2.17 (0.93-5.07), N/A       | 6       | 1.30 (0.96-1.75), 49%       | 5      | 1.17 (0.68-1.99), 73%       |
| Other              | 3              | 2.83 (2.47-3.23), 0%        | 4              | 2.00 (1.48-2.71), 57%       | 2          | 1.12 (0.71-1.78), 0%        | 3*      | 2.25 (1.37-3.70), 99%       | 5*     | 1.27 (1.00-1.61), 94%       |
| Outcome            |                |                             |                |                             |            |                             |         |                             |        |                             |
| Any fall           | 10             | 1.06 (0.58-1.95), 65%       | 12             | 1.81 (1.46-2.24), 0%        | 12*        | 1.17 (0.80-1.50), 68%       | 10      | 1.22 (0.98-1.52), 48%       | 9      | 1.30 (0.91-1.84), 61%       |
| Injurious fall     | 2              | 2.83 (2.47-3.23), 0%        | 2              | 2.07 (1.49-2.88), 82%       | 0          | N/A                         | 4*      | 2.03 (1.31-3.14), 99%       | 5*     | 1.28 (1.03-1.61), 37%       |
| Recurrent fall     | 2              | 2.38 (0.19-30.47), 84%      | 4              | 3.18 (2.07-4.88), 0%        | 1          | 2.57 (1.14-5.81), N/A       | 1       | 1.69 (1.29-2.21), N/A       | 3      | 1.70 (1.00-2.87), 94%       |
| Adjusted studies   | 3              | 1.54 (0.99-2.39), 0%        | 7*             | 1.55 (1.25-1.92), 20%       | 5          | 1.42 (0.91-2.23), 74%       | 8*      | 1.60 (1.35-1.91), 88%       | 6*     | 1.09 (0.96-1.23), 59%       |
| Population         |                |                             |                |                             |            |                             |         |                             |        |                             |
| Community-dwelling |                |                             | 2              | 2.42 (0.98-6.03), 56%       | 2          | 1.70 (1.19-2.44), 0%        | 2       | 1.32 (0.61-2.88), 55%       | 1      | 1.02 (0.78-1.33), N/A       |
| Long-term care     |                |                             | 1              | 0.69 (0.23-2.08), N/A       | 3          | 1.34 (0.70-2.56), 73%       | 2       | 1.17 (0.96-1.42), 0%        | 2      | 1.12 (0.93-1.35), 0%        |
| In hospital        |                |                             | 2              | 1.82 (0.95-3.48), 48%       | 0          |                             | 1       | 0.33 (0.11-0.99), N/A       | 1      | 10.02 (2.60-38.62), N/A     |
| Other              |                |                             | 2*             | 1.43 (1.10-1.86), 0%        | 0          |                             | 3*      | 1.99 (1.81-2.19), 65%       | 2*     | 1.06 (0.96-1.17), 41%       |
| Outcome            |                |                             |                |                             |            |                             |         |                             |        |                             |
| Any fall           |                |                             | 4              | 1.58 (1.14-2.18), 30%       | 4          | 1.48 (0.86-2.55), 80%       | 4       | 0.98 (0.60-1.62), 53%       | 3      | 2.25 (0.64-7.97), 82%       |
| Injurious fall     |                |                             | 2*             | 1.43 (1.10-1.86), 0%        | 0          |                             | 5*      | 1.78 (1.54-2.06), 85%       | 4*     | 1.08 (1.00-1.16), 14%       |
| Recurrent fall     |                |                             | 2              | 2.83 (1.73-4.64), 0%        | 1          | 1.27 (0.62-2.60), N/A       | 1       | 0.99 (0.68-1.44), N/A       | 1      | 1.10 (0.79-1.53), N/A       |

CI, confidence interval.

\*Study calculated only once in number of studies if results of men and women were reported separately. Both results were pooled.

studies were included in the meta-analysis of unadjusted data, which resulted in pooled OR of 1.16 (0.85-1.60), with substantial heterogeneity,  $I^2 = 70%$ . Table 1 shows the results of the meta-analysis and subgroup analysis.

Thirty studies investigated *opioids* as an exposure. Seven studies<sup>27,33,36,46-49</sup> found a positive association (7/30). One study<sup>50</sup> showed a protective association (1/30). Eight studies were included in the meta-analysis of adjusted data, which resulted in pooled OR of 1.60 (1.35-1.91), with considerable heterogeneity,  $I^2 = 88%$ . Fourteen studies were included in the meta-analysis of unadjusted data, which resulted in pooled OR of 1.51 (1.15-1.99), with considerable heterogeneity,  $I^2 = 97%$ . Table 1 shows the results of the meta-analysis and subgroup analysis.

Twenty-six studies assessed *NSAIDs* as an exposure. Six studies<sup>42,48,50-53</sup> showed an association (6/26). Six studies were included in the meta-analysis of adjusted data, which resulted in pooled OR of 1.09 (0.96-1.23), with substantial heterogeneity,  $I^2 = 59%$ . Seventeen studies were included in the meta-analysis of unadjusted data, which resulted in pooled OR of 1.31 (1.11-1.55), with substantial to considerable heterogeneity,  $I^2 = 85%$ . Table 1 shows the results of the meta-analysis and subgroup analysis.

### Polypharmacy

The studies used a broad range of definitions for *polypharmacy*. The most commonly used definition was *4 or more medications*. Thirty studies assessed it as an exposure. Nineteen of the studies<sup>35,40,51,54-69</sup> showed an association (19/30). Five studies were included in the meta-analysis of adjusted data, which resulted in pooled OR of 1.75 (1.27-2.41), with substantial heterogeneity,  $I^2 = 59%$ . Nine studies were included in the meta-analysis of unadjusted data, which resulted in pooled OR of 1.62 (1.34-1.96) with moderate heterogeneity,  $I^2 = 46%$ . The results of the other definitions of polypharmacy are described in Appendix 3.

One hundred one studies investigated the *number of medication* as an exposure and 45 studies<sup>31,47,52,70-111</sup> showed an association (45/101).

### Other Medication Classes

Six studies assessed *antibiotics* as an exposure. Two studies<sup>42,97</sup> showed an unadjusted association (2/6).

Five studies investigated *antiplatelets* as an exposure. Two studies<sup>112,113</sup> found an association (2/5). Six studies assessed *anticoagulants* as an exposure. The studies found no associations (0/6).

Twenty studies investigated *diabetes medication* as an exposure. In 3 studies,<sup>114-116</sup> a positive association was found (3/20). The fourth study<sup>117</sup> found an association between recurrent falling and diabetes medication but not between any falling and diabetes medication. One study<sup>118</sup> showed a protective effect (1/20). Nine studies investigated *insulin* as an exposure. Two studies<sup>119,120</sup> showed an association (2/9). Ten studies assessed *oral glucose-lowering drugs* as an exposure. An unadjusted association was found in 1 study (1/10).<sup>89</sup>

Twenty studies<sup>28,37,42,43,52,114,121</sup> assessed *laxatives* as an exposure. Seven studies<sup>28,37,42,43,52,114,121</sup> showed a positive association (7/20). One of the studies<sup>45</sup> showed a protective association (1/20). Fifteen studies assessed *antihistamines* as an exposure. Two studies<sup>46,122</sup> found an association (2/15). However, one of the studies<sup>122</sup> showed the association only in the younger age group. Six studies investigated *corticosteroids* as an exposure. Two studies<sup>112,123</sup> found an unadjusted positive association (2/6).

Five studies assessed *antidementia drugs* as an exposure. In 1 study,<sup>124</sup> an association was shown (1/5). Five studies investigated *anticholinesterases* as an exposure, and 2 studies<sup>27,125</sup> found an association (2/5). Five studies assessed *donepezil* as an exposure. Three RCTs<sup>126-128</sup> showed no differences between the users and nonusers (0/3). In 2 of the remaining observational studies,<sup>50,129</sup> no associations were found (0/2). *Memantine* was studied as an exposure in 7 studies. Five of them were RCTs,<sup>130-134</sup> and no differences between the groups were observed in falling (0/5). In one of the remaining observational studies,<sup>125</sup> an association was found (1/2).

Seven studies assessed the use of *anticholinergic drugs*. Two of those studies,<sup>135,136</sup> with the best quality, showed a multivariably adjusted association between anticholinergic use and falls (2/7). Eleven studies investigated *any medication* as an exposure. Seven studies<sup>51,80,137-141</sup> showed an association (7/11). Six studies investigated medications that were labeled as *potentially inappropriate*. Four studies<sup>124,142-144</sup> showed an association (4/6). Additionally, one study<sup>145</sup> found an association between inappropriate medication use and falls but not injurious falls. The results of the medication groups and medications that were investigated in fewer than 5 studies are described in Appendix 3.

## Discussion

This comprehensive systematic review included 281 articles in a qualitative synthesis providing information about associations between falls and several medication classes. Additionally, 5 medication classes and polypharmacy were subjected to meta-analysis using adjusted data. A positive association between antiepileptics, opioids, polypharmacy and increased fall risk was found in the meta-analyses. In the qualitative synthesis, associations were consistent with exposure to long-term use of proton pump inhibitor (PPI) (2/2) and opioid initiation (2/2). Inconsistent associations were observed for laxatives (7/20), antiplatelets (2/5), analgesics (6/30), opioids (7/30), NSAIDs (6/26), antiepileptics (9/30), polypharmacy (4 or more medications) (19/31), and anticholinergics (anticholinergic medication use 2/7; risk scales 3/4). Most of the medication groups included in this systematic review did not show associations with fall risk. However, many medication classes were investigated in only a few or single studies, and the quality of some of these studies was low. Therefore, it is likely that there are additional FRIDs than those currently identified.

Opioids use was associated with increased risk of falls with a pooled OR of 1.60 (1.35–1.91) using adjusted data. However, considerable heterogeneity was observed that remained after stratification. Our results are in line with a recent meta-analysis by Bloch et al., who found a pooled OR of 1.43. Previous meta-analyses by Woolcott and Leipzig et al. have not found a fall-risk-increasing association. The included studies that were published in recent years showed a strong association between opioid use and fall risk and can explain the different findings. Opioids can cause sedation, dizziness and cognitive impairment, all of which are risk factors for falls. It is possible that the greatest risk related to opioid treatment is after the initiation as reported in 2 of the studies included in the review.

Also, antiepileptics use increased fall risk with a pooled OR of 1.55 (1.25–1.92) using adjusted data. The finding of increased fall risk related to antiepileptic use is in line with a previous study by Bloch et al.<sup>14</sup> Dizziness, unsteadiness and blurred vision, possible side effects of antiepileptics, may lead to falls in older adults. However, the definition of a fall can potentially influence the associations observed between antiepileptics and fall incidents. None of the studies included in the meta-analysis using adjusted data used a clear definition by which the falls caused by a seizure were excluded. Users of this medication class are undoubtedly more prone to the outcome when seizure-related falls are not excluded.

Polypharmacy was associated with increased risk of falling with a pooled OR of 1.75 (1.27–2.41) using adjusted data. This finding has also been reported previously.<sup>14</sup> However, the majority of the available studies did not perform a multivariate analysis and did not properly take the role of FRIDs into account. Use of multiple medications could be associated with falls due to comorbidity associated with polypharmacy or due to increased likelihood to use FRID, or increased probability of drug-drug interactions. Ziere et al. showed that polypharmacy was associated with falls in people over 55 years only when at least 1 of the medications was a FRID.<sup>146</sup> In contrast with those findings, the number of medication has been associated with injurious falls after adjusting for FRID in 2 studies.<sup>85,147</sup>

We found a pooled OR of 1.31 using unadjusted data for NSAID users, in line with earlier reported pooled ORs 1.16–1.25.<sup>8,9,14</sup> However, the association did not remain significant when using adjusted data. The association between NSAID use and fall risk might be mediated through the confounders. We found no significant association between the anti-Parkinson drug and analgesics use and fall risk in contrast to Bloch et al. They found associations for both groups.<sup>14</sup> Although the pooled ORs are in line with the ORs reported by Bloch, our confidence intervals were broader.<sup>14</sup>

Interesting results were also observed between gastrointestinal medications and falls. PPI use was associated with falls only in 1 of 4

studies, whereas long-term use was associated with falls in 2 of 2 studies in older women. PPI therapy has also been associated with functional decline and with fracture risk. Laxatives were associated with falls inconsistently (7/20). The association between falls and laxatives may not be a causal one, though laxatives can result in electrolyte or nutritional deficiencies. Furthermore, they could lead to falls in patients with poor motoric function due to rushing to the toilet caused by the increased speed of digestive transit. Supposedly, laxatives are a proxy of, for example, parkinsonism, opioid use, or being bedridden.<sup>148,149</sup>

Studies investigating anticholinergic medication as a binomial variable showed inconsistent associations with falls, whereas when anticholinergic risk scales were investigated the association was consistent. Thus, it appears that the cumulative burden of multiple medications with anticholinergic properties is associated with falls. Anticholinergic medications are associated with impaired physical activity and cognitive impairment, known risk factors for falls.<sup>150</sup>

## Clinical Implications and Future Perspectives

The findings of our systematic review and meta-analysis are in line with the fall-prevention guidelines that recommend reviewing all medications with potential fall risk properties. Evidence of possible fall-risk-increasing properties of several medication classes was updated, giving new insights in fall-prevention, as the knowledge of the actual contribution of each risk factor is essential. From a clinical perspective, there are still obvious lacunae in knowledge concerning the differences in fall-risk related to individual medications.

In the development and evaluation of new medicines, it is crucial to consider that falls are a possible adverse medication reaction that has to be taken into account in older adults. Thus, subjects aged 70 years and older should be strongly represented in RCTs as they eventually will be a major group of users in clinical practice. To further increase the quality of reporting, the definition and method of collecting adverse events should be precisely defined, both in RCTs and in observational studies. Furthermore, the quality issues of observational studies should be resolved in the future. The use of continuous prescription data, use of classification system for medication, describing the studied medication per exposure group explicitly and investigating chemical substances instead of broad pharmacologic groups are methods to improve the medication ascertainment. Increased knowledge about the effect of medication duration and dosage to fall-risk is compulsory to understand the precise medication-related fall-risk.

## Strengths and Limitations

This systematic review successfully updated knowledge about fall-risk-increasing drugs in an extensive descriptive synthesis including several medication classes that earlier have not been evaluated systematically. Another major strength of the present study was that the meta-analyses were performed using adjusted outcomes. That has never been carried out for the medication classes studied in this review.

Aiming to find all the relevant studies, multiple databases were used for the search. However, including only English-language studies could have led to missing relevant papers. Also, the results of cohorts of participants aged 50 years and older are beyond the scope of this review. Furthermore, evaluating the relations between medications and syncope was not feasible in this review, though there is a considerable overlap between syncope and falls.<sup>151</sup>

Unfortunately, the literature has serious shortcomings. A vast majority of the cohort studies do not have the availability of continuous medication data. Because of lack of these data, misclassification might have occurred. The lack of use of a medication classification system and unclear description of target

medication have made it difficult to compare the results from different studies. Additionally, the fall ascertainment was often based on a long-term recall that can lead to underreported fall incidents. These primary origins of bias are covered in our evidence tables. Furthermore, even though the other medications would be considered in the multivariate analysis, the possible drug-drug interactions are disregarded.

Meta-analyses using adjusted outcomes attempt to control for confounding. However, using adjusted outcomes may have led to an overestimation of the association. In addition to meta-analysis using adjusted data, a meta-analysis using unadjusted data was performed, and the increased fall risk associated with antiepileptics, polypharmacy, and opioid use was observed in both analyses.

Most of the meta-analyses resulted in substantial heterogeneity that remained after stratification. Even though the meta-analysis was stratified for setting, the community-dwelling older adults can comprise cohorts including healthier or frailer older adults. Also, analyzing broad pharmacologic groups can lead to increase in heterogeneity between the studies because the studies might differ in prevalence of different pharmacologic subgroups. In addition, the dosage of the medication between studies may vary. Also, the studies varied in the confounders added to the multivariate analysis.

## Conclusion

Opioid and antiepileptic use and polypharmacy were significantly associated with a higher fall risk in meta-analyses. Many medication groups, for example, laxatives, antiplatelets, analgesics, PPI use, NSAID, and anticholinergics showed inconsistent associations in a qualitative synthesis. Serious quality issues were observed in studies including the lack of medication classification system use and medication and fall ascertainment. These quality issues in observational studies should be resolved in the future. In addition, falls should be consistently collected as adverse events in RCTs when developing new medications.

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## Supplementary Data

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