Meta-analysis of the Impact of 9 Medication Classes on Falls in Elderly Persons

John C. Woolcott, MA; Kathryn J. Richardson, MSc; Matthew O. Wiens, BSc, Pharm, PharmD; Bhavini Patel, MPharm; Judith Marin, BPharm, PharmD; Karim M. Khan, MD, PhD; Carlo A. Marra, BSc, Pharm, PharmD, PhD

Background: There is increasing recognition that the use of certain medications contributes to falls in seniors. Our objective was to update a previously completed meta-analysis looking at the association of medication use and falling to include relevant drug classes and new studies that have been completed since a previous meta-analysis.

Methods: Studies were identified through a systematic search of English-language articles published from 1996 to 2007. We identified studies that were completed on patients older than 60 years, looking at the association between medication use and falling. Bayesian methods allowed us to combine the results of a previous meta-analysis with new information to estimate updated Bayesian odds ratios (ORs) and 95% credible intervals (95% CrIs).

Results: Of 11,118 identified articles, 22 met our inclusion criteria. Meta-analyses were completed on 9 unique drug classes, including 79,081 participants, with the following Bayesian unadjusted OR estimates: antihypertensive agents, OR, 1.24 (95% CrI, 1.01-1.50); diuretics, OR, 1.07 (95% CrI, 1.01-1.14); β-blockers, OR, 1.01 (95% CrI, 0.86-1.17); sedatives and hypnotics, OR, 1.47 (95% CrI, 1.35-1.62); neuroleptics and antipsychotics, OR, 1.59 (95% CrI, 1.37-1.83); antidepressants, OR, 1.68 (95% CrI, 1.47-1.91); benzodiazepines, OR, 1.57 (95% CrI, 1.43-1.72); narcotics, OR, 0.96 (95% CrI, 0.78-1.18); and nonsteroidal anti-inflammatory drugs, OR, 1.21 (95% CrI, 1.01-1.44). The updated Bayesian adjusted OR estimates for diuretics, neuroleptics and antipsychotics, antidepressants, and benzodiazepines were 0.99 (95% CrI, 0.78-1.25), 1.39 (95% CrI, 0.94-2.00), 1.36 (95% CrI, 1.13-1.76), and 1.41 (95% CrI, 1.20-1.71), respectively. Stratification of studies had little effect on Bayesian OR estimates, with only small differences in the stratified ORs observed across population (for β-blockers and neuroleptics and antipsychotics) and study type (for sedatives and hypnotics, benzodiazepines, and narcotics). An increased likelihood of falling was estimated for the use of sedatives and hypnotics, neuroleptics and antipsychotics, antidepressants, benzodiazepines, and nonsteroidal anti-inflammatory drugs in studies considered to have “good” medication and falls ascertainment.

Conclusion: The use of sedatives and hypnotics, antidepressants, and benzodiazepines demonstrated a significant association with falls in elderly individuals.


Author Affiliations: Faculty of Pharmaceutical Sciences (Mr Woolcott and Drs Wiens and Marra) and Department of Family Practice (Dr Khan), University of British Columbia, Collaboration for Outcomes Research and Evaluation (Mr Woolcott, Ms Richardson, and Dr Marra), Centre for Health Evaluation and Outcome Sciences (Mr Woolcott and Dr Marra), and Centre for Hip Health and Mobility, Vancouver Coastal Research Institute (Mr Woolcott and Drs Khan and Marra), Vancouver, Canada; School of Pharmacy, University of London, London, England (Ms Patel); and Fraser Health Authority Renal Program, Surrey, British Columbia, Canada (Dr Marin).

FALLING IN ELDERLY PERSONS IS a major, yet underrecognized public health concern. Falls and fall-related complications are the fifth leading cause of death in the developed world, and more than 30% percent of persons older than 65 years will fall at least once annually.1,2 Furthermore, falls are the primary reason for 85% of all injury-related admissions to hospital3 and for more than 40% of nursing home admissions.4 The annual costs associated with falls and fall-related complications have been estimated to be in the billions of dollars worldwide.5-10 As a result, research examining the contributions of different risk factors on falls and fall risks is urgently needed.

Fall risk is multifactorial, with many intrinsic and extrinsic risk factors.11 Prescribed medications are an important contributor to falls and the risk of falling in seniors. Several commonly used medications have been implicated in the probability of both falling and sustaining fractures after a fall.12-13 However, determining which medications contribute to falls and which do not remains a clinical challenge. Although a number of studies have assessed the association between specific medications and medication classes on the probability of experiencing 1 or more falls during the time frame being studied, differences in methods of study, setting, power, and fall definitions have made it difficult to conclusively state the impact of the use of various medications on fall-
ing. Also, although there is evidence that certain medications are associated with falls, the prevalence of prescribing of medications to seniors has increased substantially over the past decade. Using articles published between 1966 and 1996, Leipzig et al\textsuperscript{15,16} published 2 meta-analyses that assessed the association between falling and the use of various medications in seniors. Subsequent to Leipzig and colleagues’ meta-analyses, Hartikainen et al\textsuperscript{17} completed a systematic review describing studies published after 1996 that examined the impact of medication use on falls but conducted no formal statistical techniques to pool these data. Our study provides a quantitative update to the previous meta-analyses of Leipzig and colleagues. We completed a Bayesian meta-analysis incorporating the results of Leipzig and colleagues’ work with new study data for medications that were previously assessed. Furthermore, we sought to complete meta-analyses on additional drug classes that were not originally assessed by Leipzig and colleagues.

METHODS

DATA SOURCES AND SEARCHES

We conducted a computerized EBM, CINAHL, EMBASE, and MEDLINE search of literature published between April 1996 and August 2007 to identify all potentially eligible studies. The MeSH term therapeutic uses, which encompasses all indexed classes of drugs and individual agents, was combined with the MeSH terms accidental fall or home accident. All MeSH terms were expanded to include all subheadings. Furthermore, the MeSH terms epidemiology or pharmacoepidemiology were combined with accidental fall or home accident to capture studies in which exposure to drugs was not the primary objective but may have been a secondary objective. A similar algorithm was applied in EMBASE. The MeSH terms analgesic, anti-inflammatory, antirheumatic, and antigout agents; central nervous system agents; agents interacting with transmitter, hormone, or drug receptors; or cardiovascular agents were combined with the MeSH terms accident, falling, or home accident. All terms were expanded to capture all relevant articles. All potentially eligible studies were considered regardless of publication type. All references of retrieved articles were searched for potentially eligible studies. Furthermore, leading investigators in the area of falls in elderly people were contacted to obtain studies that may have not been captured with our search strategy.

STUDY SELECTION

Studies were considered eligible for inclusion if they presented original data of randomized, controlled trial, case-control, cohort, or cross-sectional designs assessing the association between medication use and falls in persons aged 60 years or older.

DATA EXTRACTION AND QUALITY ASSESSMENT

Studies were assessed independently by at least 2 authors (J.C.W. and/or M.W., B.P., and J.M.) for methodological quality using a published checklist by Downs and Black,\textsuperscript{18} and disagreements were resolved by a third author (C.A.M.). In addition to the quality assessment checklist,\textsuperscript{18} we also looked at the methods of fall and medication ascertainment. Using the criteria of Leipzig et al,\textsuperscript{15} a study that ascertained medications at the time of the fall and documented fall occurrence prospectively or from fall reports was identified as having “good” medication and falls ascertainment, and a study using any other method was identified as having “poor” medication and falls ascertainment.

Many studies have evaluated outcomes of several classes of drugs; therefore, 1 study could provide the risks for several exposure types. All exposures were required to be presented as the odds ratios (ORs) associated with exposure or nonexposure or as 2×2 tables of reporting falls by given exposure relative to nonexposure along with 95% confidence intervals (CIs). When these values were not published, the authors were contacted to provide the necessary data to calculate them. If the risks could not be calculated, the exposure was excluded from final analysis. Additional information collected from the included studies consisted of study type, study setting (hospital or long-term care facility vs community), mean age of the participants, time of medication ascertainment, and method of fall ascertainment. If provided, adjusted ORs and 95% CIs and the covariates that were adjusted for were also extracted.

We compared the study-specific fall definition with the Prevention of Falls Network Europe (ProFaNE) fall definition. The ProFaNE fall definition of “an unexpected event in which participants come to rest on the ground, floor, or lower level”\textsuperscript{19} is the current criterion standard for fall definition and is recommended for use in fall injury prevention trials. We also mirrored the methodology of the meta-analysis by Leipzig et al\textsuperscript{15} by comparing each study’s fall definition with the Kellogg Working Group’s fall definition. The Kellogg fall definition is different from the ProFaNE fall definition because it excludes those falls that are “a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in a stroke, or an epileptic seizure.”\textsuperscript{20}

DATA SYNTHESIS AND ANALYSIS

Our primary method for the assessment of medication risk was through pooled OR estimates updated using Bayesian meta-analysis methodology. Using Bayesian random-effects models allowed the integration of prior information with newly available information to provide a posterior OR estimate with a 95% credible interval (CrI) (the Bayesian equivalent to the frequentist CI). These methods have been identified as having a number of advantages over the frequentist methods of meta-analysis, such as the ability to adjust for greater uncertainty and complexity of issues, while incorporating pertinent or prior known information regarding the association to be assessed.\textsuperscript{21} The Bayesian results also allow us to make probabilistic statements about the effect size; ie, we are able to answer the following question: “Given the observed data, what is the probability that medication use increases the chances of falling?”

Using the fixed-effects pooled results from the previous meta-analyses completed by Leipzig et al\textsuperscript{15,16} as prior unadjusted ORs, we calculated updated Bayesian pooled estimates of the ORs for the impact of medication use on the likelihood of falling during the study period. The reported ORs for each study were assumed to follow a log-normal distribution, and the between-study precision was modeled using a vague prior with a \(\gamma\) distribution. The prior is suitably vague as it has a large variance to represent a lack of information about the possible heterogeneity between studies and is a commonly chosen prior for the between-study precision.\textsuperscript{22} For medication classes not assessed by Leipzig and colleagues, we used a noninformative prior with a log-normal distribution centered at 0, with a wide variance (10,000) to reflect the lack of previous evidence.
Although Leipzig et al.\textsuperscript{13,14} reported the results of fixed-effects meta-analyses, they found evidence of heterogeneity in the medication classes of sedatives and hypnotics and neuroleptics and antipsychotics. Ideally, a random-effects meta-analysis would have been performed for these classes to make allowance for the between- and within-study variability and would have had the effect of reducing the relative weight that is given to the more precise studies. Therefore, as we were skeptical about the fixed-effects pooled estimates for sedatives and hypnotics and neuroleptics and antipsychotics, we also performed a sensitivity analysis in which we inflated the variance of the fixed-effects estimate to 5 times its original variance as a prior estimate, thus giving it less weight in the Bayesian analysis. To provide a contrast to the Bayesian results and a comparison to Leipzig and coauthors' previous findings, we also estimated pooled frequentist ORs and 95% CIs for the newly identified studies using random-effects models by weighting each study by the inverse of its variance.

Meta-analyses were performed on those medication classes with 4 or more published studies that were completed in the period 1996 to 2007. Also, pooled results were estimated by subgroups of studies defined by residential type (long-term care, community, or other), falling frequency (>35% or <35%), age of participants (mean age >75 years or <75 years), ascertainment of medications and falls (good or poor), and study design (cohort, case-control, or cross-sectional). When there were only 1 or 2 new studies, and study instability in the Bayesian models, frequentist random-effects inverse-variance models were used to provide a pooled OR only. Bayesian posterior-adjusted ORs were also estimated for those medication classes with 4 or more studies providing adjusted ORs and 95% CIs. WinBUGS version 1.4 (Medical Research Council Biostatistics Unit, Cambridge, England) was used to perform the Bayesian analyses with 2 separate chains with 10,000 Markov chain Monte Carlo iterations completed for each medication class.

As shown in Figure 1, our search strategy identified 11,118 articles, 22 of which were used in our meta-analyses. Of the 22 studies that met our inclusion criteria, none were randomized, controlled trials. Table 1 presents a summary of the medications that were assessed in each included study.\textsuperscript{23-44} While Table 2 displays the specific settings, size, and characteristics of populations, as well as the temporal relationships between medication ascertainment, falls ascertainment, and index fall.\textsuperscript{23-44} Of the observational studies assessed, 10 were cohort studies,\textsuperscript{23-32} 5 were case-control studies,\textsuperscript{33-37} and 7 were cross-sectional studies.\textsuperscript{38-44} Of the cohort studies, 8 were prospective cohort studies,\textsuperscript{23-32} with follow-up ranging from 6 months\textsuperscript{12} to 37.8 months,\textsuperscript{20} with all other prospective cohort studies using a 1-year follow-up interval. The definition of a fall used in 3 of the analyses\textsuperscript{25,33,44} was that of the Kellogg working group,\textsuperscript{20} while 9 of the analyses\textsuperscript{20,30,34,36,30,41,47} used a fall definition similar to that of the ProFaNE group.\textsuperscript{19} Six studies were considered to have good medication or falls ascertainment.\textsuperscript{28,34-37,40}

The meta-analyses, which included 79,081 participants, were completed on 9 unique drug classes. For each drug class assessed, Figure 2 shows the ORs and 95% CIs for each independent study alongside the associated frequentist random-effects pooled ORs with 95% CIs and the Bayesian pooled ORs, with 95% CrIs updated from the prior information.\textsuperscript{22-30,31,44} The use of antidepressants had the strongest association with a fall experience, with an updated Bayesian OR of 1.68 (95% CrI, 1.47-1.91). The lowest OR point estimate was for the narcotics class, with a pooled OR of 0.96 (95% CrI, 0.78-1.18).

In many cases, our updated Bayesian estimates were similar to the prior OR estimates by Leipzig et al.\textsuperscript{15,16} However, one notable exception was the β-blocker drug class, with a previous OR estimate of 0.93 (95% CI, 0.77-1.11), a new frequentist OR estimate of 1.14 (95% CI, 0.97-1.33), and an updated Bayesian OR of 1.01 (95% CrI, 0.86-1.17). The difference between the prior OR and the new frequentist OR was close to statistical significance ($P = .05$). In many cases, the prior OR differed from the new frequentist OR estimates, although the differences were not statistically significant ($P > .05$). Antihypertensives were not included in the previous meta-analysis by Leipzig et al.,\textsuperscript{15,16} and the use of a “noninformative” prior in the Bayesian update resulted in a positive association with falling (OR, 1.24; 95% CrI, 1.01-1.50), similar to the frequentist random-effects result (OR, 1.26; 95% CI, 1.08-1.46).

The use of sedatives and hypnotics and neuroleptics and antipsychotics was associated with falling (OR, 1.47; 95% CrI, 1.35-1.62; and OR, 1.59; 95% CrI, 1.37-1.83, respectively) when the fixed-effects estimate from Leipzig and colleagues was used as a prior. The conclusions did not differ when the skeptical priors (variance inflated by a factor of 5) of 1.54 (95% CI, 1.24-1.91) and 1.50 (95% CI, 1.00-2.24) were used instead, as they resulted in Bayesian pooled estimates of 1.38 (95% CrI, 1.22-1.60) and 1.68 (95% CrI, 1.36-2.07), respectively. The between-study variance estimated by the Bayesian models for...
the new studies was 0.29 for narcotics, 0.03 for antidepressants, and 0.01 for nonsteroidal anti-inflammatory drugs, and it was less than 0.006 for the remaining 6 drug classes. The evidence of considerable heterogeneity between the new narcotic studies was mainly attributable to the study by Walker et al,27 who reported a protective association with falling.

Stratification of the studies by participants residing in a long-term care facility or community or other type of residence, the percentage of fallers greater than 35%, mean age of participants older than 75 years, ascertainment of medications and falls (retrospective or prospective), or study design had little effect on the Bayesian OR estimates (Table 3). A few differences in the stratified ORs were observed, particularly across populations (in β-blockers and neuroleptics and antipsychotics) and study types (in sedatives and hypnotics, benzodiazepines, and narcotics). An increased likelihood of falling (ie, the entire 95% CI >1) was estimated for the medication classes of sedatives and hypnotics, neuroleptics and antipsychotics, antidepressants, benzodiazepines, and nonsteroidal anti-inflammatory drugs for those studies considered to have good medication and falls ascertainment.

A subset of studies provided adjusted ORs for the drug classes included in this meta-analysis (Table 1). Most of these studies adjusted for age, sex, and comorbidities, while disability, cognition, previous falls, and other medications were also commonly adjusted for (Table 2). The updated Bayesian posterior ORs for diuretics, neuroleptics and antipsychotics, antidepressants, and benzodiazepines using a prior estimate of 1.85 (95% CI, 1.20-2.85) for antidepressants from the meta-analyses by Leipzig et al15,16 and a noninformative prior for the rest were 0.99 (95% CI, 0.78-1.25), 1.39 (95% CI, 0.94-2.00), 1.36 (95% CI, 1.13-1.76), and 1.41 (95% CI, 1.20-1.71), respectively.26,30-32,34,36-38,40-43

Using Bayesian methodology, we completed one of the first meta-analyses to use informed priors in our OR calculations. By incorporating the results of previous meta-analyses by Leipzig et al15,16 our OR estimates provided a needed update of the association between falls and 9 different medication classes. We also estimated frequentist pooled ORs to measure the association between falls and medication classes using research completed since 1996 for comparison to the Bayesian estimates. Our results extend the current knowledge on specific medication classes’ impact on the risk of falls, while complementing previous meta-analyses and systematic reviews that incorporated research completed before 1996 and 2004, respectively.13-17

The use of diuretics was associated with increased fall risk in the unadjusted meta-analysis but not when it was adjusted for covariates. For the other cardiac drug classes, antihypertensives were associated with falling, and although the OR point estimate for β-blocker was greater than 1, the posterior probability that their use increased the risk of falling was 55%. Also of note was the difference between the prior and the new information regarding the β-blocker class, which led to a combined updated Bayesian estimate of no association with falling. We also noticed that the post-1996 studies had a higher prevalence of β-blocker use than that reported by Leipzig et al.16

This meta-analysis also showed that psychotropic drugs were associated with increased falls. The overall pooled Bayesian OR estimate and the sensitivity analyses undertaken on the sedatives and hypnotics, antidepressants, and benzodiazepine classes revealed that their use substantially increased the likelihood of
### Table 2. Study Characteristics

<table>
<thead>
<tr>
<th>Source</th>
<th>Setting</th>
<th>Years and Duration of Data Collection</th>
<th>No. of Participants</th>
<th>Mean Age, y</th>
<th>Drugs</th>
<th>Time of Medication Ascertainment</th>
<th>Method and Recall Time of Fall Ascertainment</th>
<th>Study Design</th>
<th>Confounders Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arfan et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Long-term care facility</td>
<td>1995 (mean of 3 mo)</td>
<td>368</td>
<td>81</td>
<td>Ad</td>
<td>Baseline</td>
<td>Incident report</td>
<td>Cohort</td>
<td>NA</td>
</tr>
<tr>
<td>Chu et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Community</td>
<td>1998-1999 (12 mo)</td>
<td>1516</td>
<td>73</td>
<td>Hy, Se</td>
<td>Baseline</td>
<td>Interview</td>
<td>Recall (2 mo)</td>
<td>Cohort</td>
</tr>
<tr>
<td>Ebly et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Community</td>
<td>1991-1992 (not stated)</td>
<td>2035</td>
<td>80</td>
<td>Ad, B, N, Na</td>
<td>Interview</td>
<td>Recall (not stated)</td>
<td>Cross-sectional</td>
<td>NA</td>
</tr>
<tr>
<td>Ensrud et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Community</td>
<td>1992-1994 (12 mo)</td>
<td>8127</td>
<td>77</td>
<td>Ad, B, Na</td>
<td>Interview</td>
<td>Recall (4 mo)</td>
<td>Cohort</td>
<td>A, G, Sr, Mc, Fp, Di, F, De, Wc, C, De&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fisher et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Long-term care facility</td>
<td>Not stated (12 mo)</td>
<td>119</td>
<td>87</td>
<td>Be, D, Hy</td>
<td>Baseline</td>
<td>Incident report</td>
<td>Case-control</td>
<td>NA</td>
</tr>
<tr>
<td>Frels et al&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Hospital, acute medical</td>
<td>Not stated (4 mo)</td>
<td>362</td>
<td>73</td>
<td>B, D, Hy</td>
<td>At fall</td>
<td>Incident report</td>
<td>Case-control</td>
<td>A, G, S, Hc, F, Dis, Ma</td>
</tr>
<tr>
<td>Gerdhem et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Community</td>
<td>1995-1999 (12 mo)</td>
<td>978</td>
<td>75</td>
<td>D, Hy</td>
<td>Baseline</td>
<td>Recall (12 mo)</td>
<td>Cohort</td>
<td>Case-control</td>
</tr>
<tr>
<td>Glueck et al&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Hospital, acute medical</td>
<td>Not stated</td>
<td>100</td>
<td>84</td>
<td>Ad, D, NSAID, Se</td>
<td>At fall</td>
<td>Incident report</td>
<td>Case-control</td>
<td>Matched on A and G</td>
</tr>
<tr>
<td>Hanlon et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Community</td>
<td>1989-1990 (12 mo)</td>
<td>2996</td>
<td>72</td>
<td>B, D</td>
<td>Interview</td>
<td>Recall (12 mo)</td>
<td>Cohort</td>
<td>A, G, R, E, In, U, O, Aic, Sm, De, Nag, Art, Di, Fr, St, Ul, Sr, Red, Opzy, Other</td>
</tr>
<tr>
<td>Kallin et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Long-term care facility</td>
<td>2000 (1 wk)</td>
<td>3604</td>
<td>83</td>
<td>Ad, B, Be, D, N, Na, NSAID</td>
<td>At fall</td>
<td>Incident report</td>
<td>Cross-sectional</td>
<td>A, G, F, C, W, P, Cp</td>
</tr>
<tr>
<td>Landi et al&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Community</td>
<td>2000-2002 (90 d)</td>
<td>2654</td>
<td>77</td>
<td>Ad, B, N, Ne</td>
<td>Interview</td>
<td>Recall (90 d)</td>
<td>Cross-sectional</td>
<td>A, G, Mc, De, Adl, Cp, Fp, Wa, G, Fof</td>
</tr>
<tr>
<td>Lawlor et al&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Community</td>
<td>Not stated (12 mo)</td>
<td>4050</td>
<td>69</td>
<td>Ad, Se</td>
<td>Interview</td>
<td>Recall (12 mo)</td>
<td>Cross-sectional</td>
<td>A, G, BMI, Hg, Cd, Di, Td, As, De, V, Art, Aic, Soc</td>
</tr>
<tr>
<td>Lee et al&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Community</td>
<td>2001-2003 (12 mo)</td>
<td>4000</td>
<td>72</td>
<td>Be, D, NSAID</td>
<td>Interview</td>
<td>Recall (12 mo)</td>
<td>Cross-sectional</td>
<td>A, G, V, He, Lmp, Di, S, Sr, Sm, M</td>
</tr>
<tr>
<td>Neutel et al&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Long-term care facility</td>
<td>1995-1996 (12 mo)</td>
<td>227</td>
<td>80-90</td>
<td>Ad, B, D</td>
<td>At fall</td>
<td>Incident report</td>
<td>Case-control</td>
<td>A, G, LOS, Fr, Cp, M</td>
</tr>
<tr>
<td>Passaro et al&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Hospital, acute medical</td>
<td>1991-1993 (8 mo)</td>
<td>7908</td>
<td>65-80</td>
<td>B</td>
<td>At fall</td>
<td>Incident report</td>
<td>Cohort</td>
<td>NA</td>
</tr>
<tr>
<td>Rozenfeld et al&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Community</td>
<td>1996 (12 mo)</td>
<td>631</td>
<td>69</td>
<td>Be, D, Hy, Se</td>
<td>Interview</td>
<td>Recall (12 mo)</td>
<td>Cross-sectional</td>
<td>NA</td>
</tr>
<tr>
<td>Tromp et al 1998&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Community</td>
<td>1992-1995 (38 mo)</td>
<td>1370</td>
<td>73</td>
<td>Hy, Se</td>
<td>Baseline</td>
<td>Recall (12 mo)</td>
<td>Cohort</td>
<td>NA</td>
</tr>
<tr>
<td>Tromp et al 2001&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Community</td>
<td>1995-1996 (12 mo)</td>
<td>1285</td>
<td>75</td>
<td>B</td>
<td>Baseline</td>
<td>Recall (daily)&lt;sup&gt;1b&lt;/sup&gt;</td>
<td>Cohort</td>
<td>U, F</td>
</tr>
<tr>
<td>Walker et al&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Hospital, acute medical</td>
<td>2002 (12 mo)</td>
<td>124</td>
<td>74</td>
<td>Ad, B, D, N, Na, NSAID</td>
<td>At fall</td>
<td>Incident report</td>
<td>Case-control</td>
<td>A, G, Ac, Art, Chf, Cp, Fp, Hip, F, V, G, Pef, P, Sur, U</td>
</tr>
<tr>
<td>Weiner et al&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Community</td>
<td>Not stated (6 mo)</td>
<td>305</td>
<td>74.4</td>
<td>B, N, Na</td>
<td>Baseline</td>
<td>Recall (daily)&lt;sup&gt;1c&lt;/sup&gt;</td>
<td>Cohort</td>
<td>A, Cp, De, Mo</td>
</tr>
</tbody>
</table>

**Drug Abbreviations:** Ad, antidepressants; B, benzodiazepines; Be, β-blockers; D, diuretics; Hy, antihypertensives; N, neuroleptics; Na, narcotic analgesics; NSAID, nonsteroidal anti-inflammatory drugs; Se, sedative hypnotics.

**Confounder Abbreviations:** A, age; AcI, acute illness or infection; Adl, activities of daily living level of impairment; Alc, heavy alcohol consumption; Altc, admission to LTC; Art, arthritis; As, asthma or bronchitis; B, balance test score; BMI, body mass index; Boi, burden of illness; C, difficulty/ability to rise from chair; Cd, circulatory disease; Chf, congestive heart failure; Cp, cognitive performance or impairment; De, depression; Di, diabetes; Dis, disoriented; E, education; Ed, emergency department visit; F, previous falls; Fof, reported fear of falling; Fp, foot problems; Fr, broken bones; G, gender; Ga, gait speed or problems; Hc, additional health conditions; Hf, heart failure; Hg, hemoglobin concentration; Hip, hip fracture; Hs, health status; In, income; Lm, leg muscle strength; Lmp, lower muscular pain; LOS, length of stay; M, number of medications/presence of polypharmacy; Ma, requires maximum assistance while in hospital; Mc, medical conditions; Mo, mobility issues; NA, not applicable; Nag, Nagi disability; O, overweight; Oe, oral estrogen use; Opzy, other psychotropic drug use; P, reports pain; Peri, peripheral neuropathy; Pr, programs/intensity of care provided to individual; R, race; Red, reduced activities; Rug, resource use group; S, previous stroke; Sl, sleeping problems; Sln, stride length; Sm, smoking status; Soc, adult social class; Sr, self-rated health; SS, study site; Sur, surgery or anesthesia; Td, thyroid disease; U, underweight; Ul, urinary continence issues; V, vision problems; W, walks with helper; Wa, wandering; Wc, weight change; Wt, 6-m walk time.

<sup>a</sup> Ensrud et al<sup>26</sup> used Oe only for the adjusted odds ratio for Ad.

<sup>b</sup> Tromp et al<sup>41</sup> used daily completed falls calendars collected every 3 months for ascertainment of falls.

<sup>c</sup> Weiner et al<sup>44</sup> used daily completed falls calendars collected every 30 days for ascertainment of falls.
falls. Although neuroleptics and antipsychotics were associated with falling in the main unadjusted results of the meta-analysis, after adjustment for other confounders they were not statistically associated with falling. In contrast to the results of Leipzig et al., who suggested that hospitalized patients who used neuroleptics or antipsychotics would have fewer falls, we observed no such association between the use of neuroleptics and antipsychotics and falls in that setting.

An important consideration when estimating the level of association between specific medication use and falling is the impact of and adjustment for confounding, specifically confounding by indication. In a study of association between medi-

---

**Figure 2. Medications and falls: meta-analysis results**

<table>
<thead>
<tr>
<th>Medications</th>
<th>Odds Ratio (Log Scale)</th>
<th>Odds Ratio (Log Scale)</th>
<th>Odds Ratio (Log Scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensives</td>
<td>Decreased</td>
<td>Increased</td>
<td>Source</td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroleptics/antipsychotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narcotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

©2009 American Medical Association. All rights reserved.
Table 3. Pooled Bayesian Odds Ratios and Subgroup Sensitivity Analysis

<table>
<thead>
<tr>
<th>Study Characteristic</th>
<th>Antihypertensives</th>
<th>Diuretics</th>
<th>β-Blockers</th>
<th>Sedatives/Hypnotics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (^a) OR (95% CI)</td>
<td>No. (^a) OR (95% CI)</td>
<td>No. (^a) OR (95% CI)</td>
<td>No. (^a) OR (95% CI)</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>4976</td>
<td>10,145</td>
<td>8354</td>
<td>44,684</td>
</tr>
<tr>
<td>No. taking drug</td>
<td>1482</td>
<td>2374</td>
<td>1432</td>
<td>1737</td>
</tr>
<tr>
<td>Population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td>4</td>
<td>1.29 (1.00-1.65)</td>
<td>3</td>
<td>1.08 (1.01-1.16)</td>
</tr>
<tr>
<td>&lt;35% Fallers</td>
<td>3</td>
<td>1.34 (0.93-1.91)</td>
<td>2</td>
<td>1.09 (1.00-1.17)</td>
</tr>
<tr>
<td>≥35% Fallers</td>
<td>1</td>
<td>1.11 (0.78-1.58)</td>
<td>1</td>
<td>1.04 (0.87-1.24)</td>
</tr>
<tr>
<td>Long-term care</td>
<td>1</td>
<td>0.80 (0.40-1.60)</td>
<td>3</td>
<td>1.02 (0.84-1.25)</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1.19 (0.77-1.83)</td>
<td>3</td>
<td>1.06 (0.82-1.38)</td>
</tr>
<tr>
<td>Mean age of study subjects, y</td>
<td>4</td>
<td>1.33 (1.03-1.68)</td>
<td>4</td>
<td>1.11 (1.03-1.20)</td>
</tr>
<tr>
<td></td>
<td>&gt;75</td>
<td>2</td>
<td>1.04 (0.79-1.38)</td>
<td>5</td>
</tr>
<tr>
<td>Medication/falls ascertainment</td>
<td>1</td>
<td>1.19 (0.77-1.83)</td>
<td>5</td>
<td>1.04 (0.89-1.23)</td>
</tr>
<tr>
<td>Good</td>
<td>5</td>
<td>1.24 (0.97-1.54)</td>
<td>4</td>
<td>1.09 (1.02-1.16)</td>
</tr>
<tr>
<td>Poor</td>
<td>2</td>
<td>1.09 (0.80-1.50)</td>
<td>5</td>
<td>1.11 (0.94-1.32)</td>
</tr>
<tr>
<td>Study type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case-control</td>
<td>2</td>
<td>1.34 (0.93-1.91)</td>
<td>1</td>
<td>1.05 (0.97-1.15)</td>
</tr>
<tr>
<td>Cohort</td>
<td>3</td>
<td>1.11 (0.79-1.58)</td>
<td>3</td>
<td>1.11 (1.00-1.24)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.
\(^a\)Refers to new studies only.
\(^b\)Greater than 95% posterior probability that the difference between ORs is greater than 0.
\(^c\)Attained by random-effects inverse-variance model (frequentist) owing to unstable Bayesian model.
ability that the ORs are greater than 1 in cases in which the associated 95% CrI includes 1. Although using a frequentist random-effects model to pool all of the new studies and either the old studies or the Leipzig and colleagues’ pooled estimate would give similar estimates to the Bayesian methodology, the Bayesian methodology permits the between-study variance to differ from Leipzig and colleagues’ studies and the new studies, taking into account the fact that different types of evidence are being synthesized.21 The Bayesian methodology also allows greater uncertainty than the frequentist approach, as both the overall population effect and the within-study precision in the random-effects meta-analyses are estimated by the data.36

A limitation of our meta-analysis is that relatively few studies met our inclusion criteria of using falls as an outcome. Although the number of new studies included was small for every drug class assessed besides diuretics, the total number of additional participants included in the meta-analysis was greater than that in the previous meta-analyses by Leipzig et al.15,16 A second limitation is the method of falls and medication ascertainment in many of the studies. Using the previously mentioned methodology of Leipzig et al.,15,16 16 of the studies were noted to be of poor quality when the timing and the reporting method of the falls and the medications used by study participants at the time of the fall were considered.

Medications are identified as a preventable risk factor for falling, yet only 1 randomized controlled trial has looked at the impact of withdrawing medications from a population of users and the impact on falls.57 Although that study showed that the removal of psychotropics can reduce the probability that an individual would fall,57 to our knowledge no other randomized controlled trials have assessed the impact of introduction or withdrawal of specific medication classes on falls in elderly persons. Given the divergent results shown by some observational assessments within specific medication classes,13,16 the results of our meta-analysis reiterate the need for caution when prescribing these medications to seniors. It is hoped that future research in this area can be completed with larger sample sizes in both community and long-term care facility settings and thus improve the quality of information about fall risks that is available to physicians and pharmacists when they are deciding which types of pharmacotherapy to provide.

Accepted for Publication: August 12, 2009.

Correspondence: Carlo A. Marra, BSc, Pharm, PharmD, Centre for Health Evaluation and Outcome Sciences, 620-1081 Burrard St, Vancouver, BC V6Z 1Y6, Canada (carlo.marra@ubc.ca).

Author Contributions: Study concept and design: Woolcott, Richardson, Patel, Marin, Khan, and Marra. Acquisition of data: Woolcott, Richardson, Wiens, Patel, and Marin. Analysis and interpretation of data: Woolcott, Richardson, Khan, and Marra. Drafting of the manuscript: Woolcott, Richardson, Patel, and Khan. Critical revision of the manuscript for important intellectual content: Woolcott, Richardson, Wiens, Marin, Khan, and Marra. Statistical analysis: Woolcott and Richardson. Obtained funding: Marra. Administrative, technical, and material support: Richardson, Wiens, Patel, Marin, and Marra. Study supervision: Richardson, Marin, Khan, and Marra.

Financial Disclosure: None reported.

Funding/Support: This research was supported in part by the Canadian Institutes of Health Research (J.C.W. and K.M.K.), the Michael Smith Foundation for Health Services Research (J.C.W., K.M.K., and C.A.M.), and the Government of Canada Research Chair in Pharmaceutical Outcomes (C.A.M.).

Previous Presentations: This study was presented as an oral presentation at the Third Australian and New Zealand Falls Prevention Conference; October 13, 2008; Melbourne, Australia; and at the BC Injury Prevention Conference; November 19, 2008; Vancouver.

REFERENCES

32. Weiner DK, Hanlon JT, Studenski SA. Effects of
ability in community dwelling elderly. Gerontology.
33. Fisher AA, McLean AK, Davis MW, Le Couteur DG.
A multicenter, case-control study of the effects of
anthipyretic therapy on orthostatic hypoten-
sion, postprandial hypotension, and falls in octo-
and nonagenarians in residential care facilities. 
34. Freis C, Williams P, Narayanan S, Gariballa SE.
Iatrogenic causes of falls in hospitalized elderly
patients: a case control study. Postgrad Med J.
35. Gluck T, Wintjens HJ, Rai GS. An evaluation of risk
factors for in-patient falls in acute and rehabilita-
tion elderly care wards. Gerontology. 1996;42
36. Neutel CI, Perry S, Maxwell C. Medication use and
risk of falls. Pharmacoepidemiol Drug Saf. 2002;
11(2):97-104.
37. Walker PC, Airawi A, Mitchell JF, Regal RE, Khanderia
U. Medication use as a risk factor for falls among
hospitalized elderly patients. Am J Health
38. de Rekeneire N, Visscher M, Pella R, et al. Is a fall
just a fall: correlates of falling in healthy older
persons: the Health, Aging and Body Composition
39. Ebly EM, Hogan DB, Fung TS. Potential adverse
outcomes of psychotropic and narcotic drug use
50(7):857-863.
40. Kallin K, Gustafson Y, Sandman PO, Karlsson S.
Drugs and falls in older people in geriatric care
41. Landi F, Onder G, Cesari M, Barillaro C, Russo A,
Bertabe R; Silver Network Home Care Study
Group. Psychotropic medications and risk for falls
among community-dwelling frail older people: an
42. Lawlor DA, Patel R, Ebrahim S. Association be-
tween falls in elderly women and chronic disease
and drug use: cross sectional study. BMJ. 2003;
327(7417):712-717.
43. Lee JSW, Kivok T, Leung PC, Woo J. Medical ill-
nesses are more important than medications as
risk factors of falls in older community dwellers:
a cross sectional study. Age Ageing. 2006;35
(3):246-251.
44. Rozenfeld S, Camacho LA, Veras RP. Medication
as a risk factor for falls in older women in Brazil.
45. Psaty BM, Koepsell TD, Lin D, et al. Assessment
and control for confounding by indication in ob-
46. Stürmer T, Glynn RJ, Rothman KJ, Avorn J, Schnee-
weiss S. Adjustments for unmeasured confound-
ors in pharmacoepidemiologic database studies
using external information. Med Care. 2007;
47. Stürmer T, Joshi M, Glynn RJ, Avorn J, Roth-
man KJ, Schneweiss S. A review of the applica-
tion of propensity score methods yielded increas-
ing use, advantages in specific settings, but not
substantially different estimates when compared
with conventional multivariable methods. J Clin
48. Hien TT, Cumming RG, Cameron ID, et al. Atypi-
cal antipsychotic medications and risk of falls in
residents of aged care facilities. J Am Geriatr
49. Flicker L, Mead K, Macnris RJ, et al. Serum vi-
mamin D and falls in older women in residential care
1533-1538.
50. Hiettarechi E, Lord SR, Meyerkort P, McCloskey
I, Fitzpatrick R. Blood pressure changes on up-
right tilting predict falls in older people. Age
risk factors for falls in nursing home and inter-
mediate-care residents who can and cannot stand
unaided. J Am Geriatr Soc. 2003;51(11):1645-
1650.
52. Maurer MS, Burcham J, Cheng H. Diabetes mellitus
is associated with an increased risk of falls in elderly residents of a long-term care
60(9):1157-1162.
54. Ray WA, Thapa PB, Gideon P. Benzodiazepines
and risk of falls in nursing home residents. J
55. Vellas BJ, Wayne SJ, Garry PJ, Baumgartner RN.
A two-year longitudinal study of falls in 482 com-
unity-dwelling elderly adults. J Gerontol A Biol
Wailoo A. Comprehensive decision analytical mod-
ing in economic evaluation: a Bayesian approach.
57. Campbell AJ, Robertson MC, Gardner MM, Nor-
ton RM, Buchner DM. Psychotropic medication
withdrawal and a home-based exercise program
to prevent falls: a randomized controlled trial.