

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

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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.

Arch Intern Med. 2009;169(21):1952-1960

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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.¹⁻⁵ Furthermore, falls are the primary reason for 85% of all injury-related admissions to hospital⁶ and for more than 40% of

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nursing home admissions.⁷ The annual costs associated with falls and fall-related complications have been estimated to be in the billions of dollars worldwide.⁸⁻¹⁰ 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.¹⁴

Using articles published between 1966 and 1996, Leipzig et al^{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 al¹⁷ 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 coauthors. 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 ar-

ticles. 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,¹⁸ and disagreements were resolved by a third author (C.A.M.). In addition to the quality assessment checklist,¹⁸ we also looked at the methods of fall and medication ascertainment. Using the criteria of Leipzig et al,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 defini-

tion. The ProFaNE fall definition of "an unexpected event in which participants come to rest on the ground, floor, or lower level"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 al¹⁵ 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."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.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^{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 γ 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.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 (1000) to reflect the lack of previous evidence.

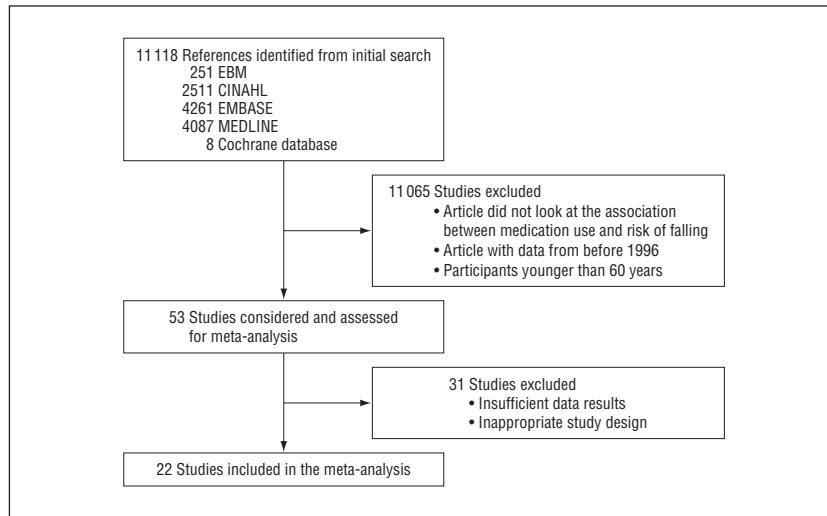


Figure 1. Flow diagram of study selection process.

Although Leipzig et al^{15,16} 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 weighting 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, owing to 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.

RESULTS

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,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.²³⁻⁴⁴ Of the observational studies assessed, 10 were cohort studies,²³⁻³² 5 were case-control studies,³³⁻³⁷ and 7 were cross-sectional studies.³⁸⁻⁴⁴ Of the cohort studies, 8 were prospective cohort studies²⁵⁻³² with follow-up ranging from 6 months³² to 37.8 months,²⁹ with all other prospective cohort studies using a 1-year follow-up interval. The definition of a fall used in 3 of the analyses^{25,33,44} was that of the Kellogg working group,²⁰ while 9 of the analyses^{28-30,34,36,39-41,43} used a fall definition similar to that of the ProFaNE group.¹⁹ Six studies were considered to have good medication or falls ascertainment.^{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.^{22-30,33-44} 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.^{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.^{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

Table 1. Drugs and Studies Included in the Meta-analysis

Source	Antihypertensives	Diuretics	β-Blockers	Sedatives/ Hypnotics	Neuroleptics/ Antipsychotics	Antidepressants	Benzodiazepines	Narcotic Analgesics	NSAIDs
Arfken et al, ²³ 2001						X			
Avidan et al, ²⁴ 2005				X, A					
Chu et al, ²⁵ 2005	X			X					
de Rekeneire et al, ³⁸ 2003							X, A		
Ebly et al, ³⁹ 1997					X	X	X	X	
Ensrud et al, ²⁶ 2002						X, A	X, A	X, A	
Fisher et al, ³³ 2003	X	X	X						
Frels et al, ³⁴ 2002	X	X, A					X, A		
Gerdhem et al, ²⁷ 2005	X	X							
Gluck et al, ³⁵ 1996		X		X		X			X
Hanlon et al, ³¹ 2002		A					A		A
Kallin et al, ⁴⁰ 2004		X	X		X, A	X, A	X	X	X
Landi et al, ⁴¹ 2005				X, A	X, A	X, A	X, A		
Lawlor et al, ⁴² 2003				X, A		X, A			
Lee et al, ⁴³ 2006		X, A	X, A						X, A
Neutel et al, ³⁶ 2002		X, A				X, A	X, A		
Passaro et al, ²⁸ 2000							X		
Rozenfeld et al, ⁴⁴ 2003	X	X	X	X					
Tromp et al, ²⁹ 1998	X			X					
Tromp et al, ³⁰ 2001							X, A		
Walker et al, ³⁷ 2005		X, A			X, A	X, A	X, A	X, A	X, A
Weiner et al, ³² 1998					A		A	A	

Abbreviations: A, adjusted odds ratio (OR) provided (see Table 2 for list of confounders adjusted for); NSAIDs, nonsteroidal anti-inflammatory drugs; X, crude OR or data to calculate crude OR provided.

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,³⁷ 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% CrI > 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 ad-

justed 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 al^{15,16} and a noninformative prior for the rest 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.^{26,30-32,34,36-38,40-43}

COMMENT

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 al,^{15,16} 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 es-

timates. 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.¹⁵⁻¹⁷

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-blockers 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

Source	Setting	Years and Duration of Data Collection	No. of Participants	Mean Age, y	Drugs	Time of Medication Ascertainment	Method and Recall Time of Fall Ascertainment	Study Design	Confounders Adjusted
Arfkan et al ²³	Long-term care facility	1995 (mean of 3 mo)	368	81	Ad	Baseline	Incident report	Cohort	NA
Avidan et al ²⁴	Long-term care facility	2001 (150-210 d)	34 163	84	Se	Baseline	Recall (180 d)	Cohort	A, G, Adl, Cp, Rug, Boi, V, B, M, Ed, Altc
Chu et al ²⁵	Community	1998-1999 (12 mo)	1516	73	Hy, Se	Baseline	Recall (2 mo)	Cohort	NA
de Rekeneire et al ²⁸	Community	1997-1998 (12 mo)	3050	70-79	B	Interview	Recall (12 mo)	Cross-sectional	A, R, Ss, BMI, Ui, Wt, B, C, Lm
Ebly et al ²⁹	Community	1991-1992 (not stated)	2035	80	Ad, B, N, Na	Interview	Recall (not stated)	Cross-sectional	NA
Ensrud et al ²⁶	Community	1992-1994 (12 mo)	8127	77	Ad, B, Na	Interview	Recall (4 mo)	Cohort	A, G, Sr, Mc, Fp, Di, F, De, Wc, C, Oe ^a
Fisher et al ³³	Long-term care facility	Not stated (12 mo)	119	87	Be, D, Hy	Baseline	Incident report	Case-control	NA
Frels et al ³⁴	Hospital, acute medical	Not stated (4 mo)	362	73	B, D, Hy	At fall	Incident report	Case-control	A, G, S, Hc, F, Dis, Ma
Gerdhem et al ²⁷	Community	1995-1999 (12 mo)	978	75	D, Hy	Baseline	Recall (12 mo)	Cohort	NA
Gluck et al ³⁵	Hospital, acute medical	Not stated	100	84	Ad, D, NSAID, Se	At fall	Incident report	Case-control	Matched on A and G
Hanlon et al ³¹	Community	1989-1990 (12 mo)	2996	72	B, D	Interview	Recall (12 mo)	Cohort	A, G, R, E, In, U, O, Alc, Sm, De, Nag, Art, Di, Fr, Sl, Ui, Sr, Red, Opsy
Kallin et al ⁴⁰	Long-term care facility	2000 (1 wk)	3604	83	Ad, B, Be, D, N, Na, NSAID	At fall	Incident report	Cross-sectional	A, G, F, C, W, P, Cp
Landi et al ⁴¹	Community	2000-2002 (90 d)	2854	77	Ad, B, N, Se	Interview	Recall (90 d)	Cross-sectional	A, G, Mc, De, Adl, Cp, Fp, Wa, G, Fof
Lawlor et al ⁴²	Community	Not stated (12 mo)	4050	69	Ad, Se	Interview	Recall (12 mo)	Cross-sectional	A, BMI, Hg, Cd, Di, Td, As, De, V, Art, Alc, Soc
Lee et al ⁴³	Community	2001-2003 (12 mo)	4000	72	Be, D, NSAID	Interview	Recall (12 mo)	Cross-sectional	A, G, V, He, Lmp, Di, S, Sr, Sln, M
Neutel et al ³⁶	Long-term care facility	1995-1996 (12 mo)	227	80-90	Ad, B, D	At fall	Incident report	Case-control	A, G, LOS, Pr, Cp, M
Passaro et al ²⁸	Hospital, acute medical	1991-1993 (8 mo)	7908	65-80	B	At fall	Incident report	Cohort	NA
Rozenfeld et al ⁴⁴	Community	1996 (12 mo)	631	69	Be, D, Hy, Se	Interview	Recall (12 mo)	Cross-sectional	NA
Tromp et al 1998 ²⁹	Community	1992-1995 (38 mo)	1370	73	Hy, Se	Baseline	Recall (12 mo)	Cohort	NA
Tromp et al 2001 ³⁰	Community	1995-1996 (12 mo)	1285	75	B	Baseline	Recall (daily) ^b	Cohort	U, F, V
Walker et al ³⁷	Hospital, acute medical	2002 (12 mo)	124	74	Ad, B, D, N, Na, NSAID	At fall	Incident report	Case-control	A, G, Aci, Art, Chf, Cp, Fp, Hip, F, V, Ga, Peri, S, Sur, U
Weiner et al ³²	Community	Not stated (6 mo)	305	74.4	B, N, Na	Baseline	Recall (daily) ^c	Cohort	A, Cp, De, Mo

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; He, heart disease; 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; Opsy, 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; Ui, urinary continence issues; V, vision problems; W, walks with helper; Wa, wandering; Wc, weight change; Wt, 6-m walk time.

^aEnsrud et al²⁶ used Oe only for the adjusted odds ratio for Ad.

^bTromp et al³⁰ used daily completed falls calendars collected every 3 months for ascertainment of falls.

^cWeiner et al³² used daily completed falls calendars collected every 30 days for ascertainment of falls

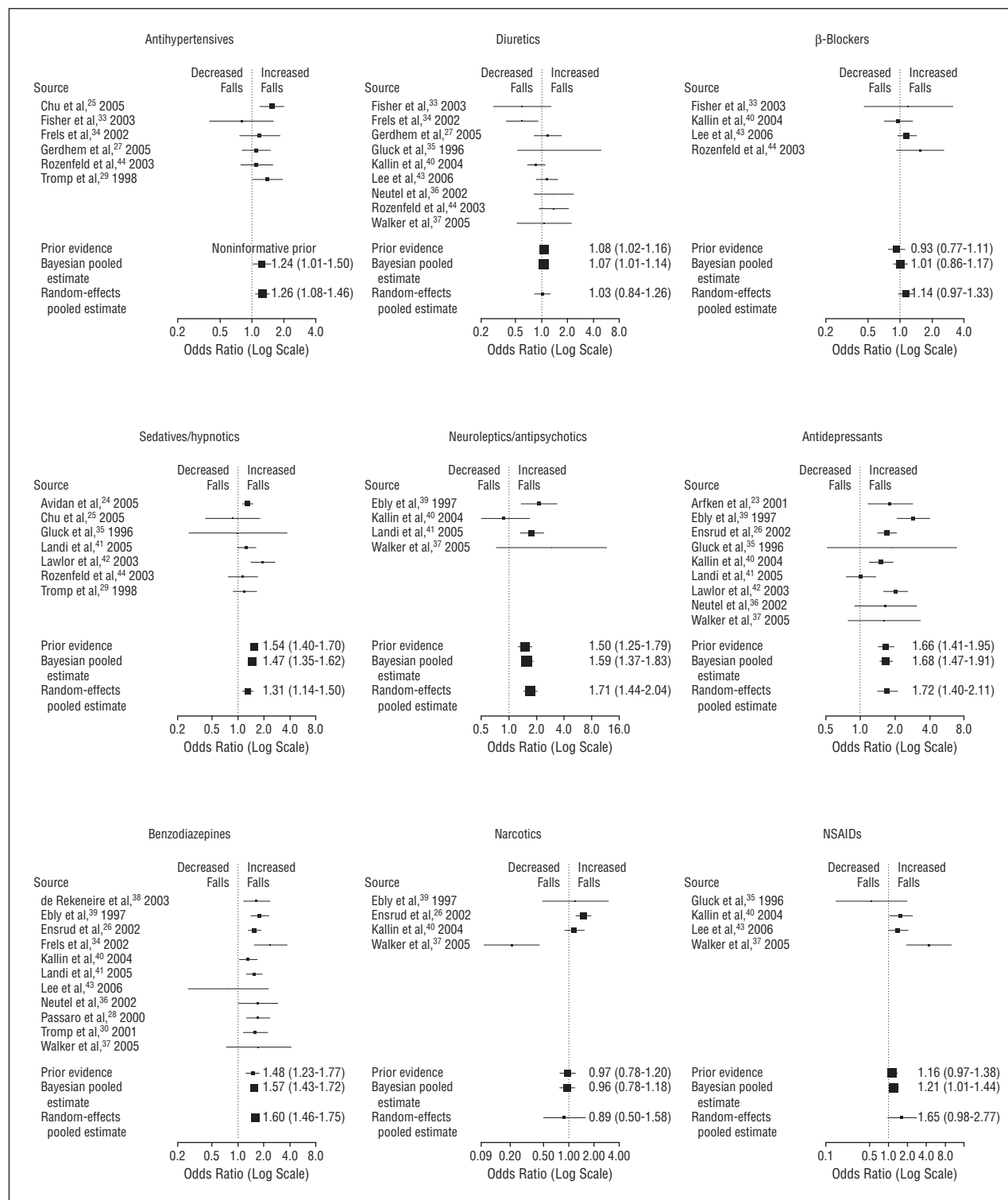


Figure 2. Medications and falls: meta-analysis results.²³⁻⁴⁴ Odds ratios and 95% credible intervals or 95% confidence intervals on a logarithmic scale for individual or pooled study data for each class of medication. Outcome is occurrence of at least 1 fall. NSAIDs indicates nonsteroidal anti-inflammatory drugs.

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 re-

sults of Leipzig et al,^{15,16} 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-

Table 3. Pooled Bayesian Odds Ratios and Subgroup Sensitivity Analysis

Study Characteristic	Antihypertensives		Diuretics		β-Blockers		Sedatives/Hypnotics	
	No. ^a	OR (95% CI)	No. ^a	OR (95% CI)	No. ^a	OR (95% CI)	No. ^a	OR (95% CI)
No. of subjects	4976		10 145		8354		44 684	
No. taking drug	1482		2374		1432		1737	
All studies	6	1.24 (1.01-1.50)	9	1.07 (1.01-1.14)	4	1.01 (0.86-1.17)	7	1.47 (1.35-1.62)
Population								
Community	4	1.29 (1.00-1.65)	3	1.08 (1.01-1.16)	2	0.98 (0.79-1.18) ^b	5	1.50 (1.36-1.67)
<35% Fallers	3	1.34 (0.93-1.91)	2	1.09 (1.00-1.17)	1	0.94 (0.75-1.16)	3	1.62 (1.44-1.84) ^b
≥35% Fallers	1	1.11 (0.78-1.58) ^c	1	1.04 (0.87-1.24)	1	1.13 (0.72-1.70)	2	1.22 (1.00-1.48) ^b
Long-term care	1	0.80 (0.40-1.60) ^c	3	1.02 (0.84-1.25)	2	1.18 (0.83-1.88) ^b	1	1.38 (1.14-1.74)
Other	1	1.19 (0.77-1.83) ^c	3	1.06 (0.82-1.38)	0	0.43 (0.19-0.97) ^b	1	1.56 (1.19-2.05)
Mean age of study subjects, y								
≤75	4	1.33 (1.03-1.68)	4	1.11 (1.03-1.20) ^b	2	0.93 (0.71-1.18)	4	1.54 (1.39-1.72)
>75	2	1.04 (0.79-1.38) ^c	5	0.96 (0.84-1.08) ^b	2	1.02 (0.81-1.28)	3	1.37 (1.19-1.60)
Medication/falls ascertainment								
Good	1	1.19 (0.77-1.83) ^c	5	1.04 (0.89-1.23)	1	0.87 (0.69-1.07)	1	1.66 (1.25-2.22)
Poor	5	1.24 (0.97-1.54)	4	1.09 (1.02-1.16)	3	1.02 (0.84-1.21)	6	1.43 (1.30-1.58)
Study type								
Case-control	2	1.09 (0.80-1.50) ^c	5	1.11 (0.94-1.32)	1	0.87 (0.55-1.37)	1	1.62 (1.31-2.00) ^b
Cohort	3	1.34 (0.93-1.91)	1	1.05 (0.97-1.15)	0	1.00 (0.78-1.30)	3	1.24 (1.05-1.45) ^b
Cross-sectional	1	1.11 (0.78-1.58) ^c	3	1.11 (1.00-1.24)	3	1.02 (0.79-1.24)	3	1.56 (1.39-1.76) ^b

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.

cation use and falling, confounding by indication can occur when the medication class assessed is a marker for a clinical diagnosis that in itself changes the risk of experiencing a fall and also requires treatment with the medication being assessed.⁴⁵ Adjustment for confounding by indication is usually completed by the use of propensity score methods. Propensity scores can estimate the probability of exposure and permit the matching of individuals across groups with similar propensity scores or probabilities of exposure and are thought to be most appropriate when the treatment is frequent, with rare outcomes.^{46,47} Multivariable modeling incorporates potential confounders into regression analysis to estimate adjusted measures of association. However, the results are dependent on the potential confounders that are included in the regression models.⁴⁶ None of the studies included in the meta-analysis used propensity score matching to control for confounding by indication, yet many included multivariable modeling and reported adjusted ORs. However, recent evidence suggests that similar results are often achieved using conventional multivariable models as compared with propensity score

methods.⁴⁷ Reassuringly, we found that the pooled adjusted ORs were similar to the unadjusted ORs, leading us to conclude that the role of confounding was quite small in this regard.

During our search for relevant articles, we identified 6 studies that reported an unadjusted hazard ratio (HR) or relative risk (RR)⁴⁸⁻⁵³ and 4 studies that reported an adjusted HR or RR^{48,49,54,55} for a specific medication class included in this meta-analysis and its association with falling. The high incidence of falling in elderly persons did not allow us to compare the reported RRs and HRs with the OR estimates of the other identified studies and could not be included in the main meta-analysis. Furthermore, there were too few of these studies reporting on the same medication class to pool their results. However, the individual studies' adjusted and unadjusted HR estimates and our OR estimates resulted in similar conclusions.

Also, it should be noted that the number of participants included in the studies completed after 1996 was generally greater than that included in Leipzig and colleagues'¹⁵ initial meta-analysis of psychotropics. This increase in study sample sizes could be partly attributed either to a larger

population available for assessment owing to increased prevalence of diseases requiring psychotropic treatment or to increased prescription of these types of drugs or to a combination of both. We observed a slight increase in the percentage of participants who were taking each psychotropic in the studies completed after 1996 when compared with the studies completed before 1996 and included in the meta-analysis by Leipzig et al.¹⁵ The single exception to this trend of increased proportion of psychotropic use in studies completed after 1996 was in the sedatives and hypnotics drug class. However, if the larger sample sizes are a result of increased prevalence of conditions for which psychotropics are indicated, it is possible that the results are confounded by indication, as many of these conditions themselves are associated with an increased likelihood of falling.

A primary strength of our study is the use of Bayesian meta-analyses, which allowed us to incorporate information from the previous meta-analysis with the more recently completed studies to evaluate the level of association between drug classes and experiencing a fall. Bayesian methodology also allows us to make statements about the prob-

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 methods, 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 between-study precision in the random-effects meta-analyses are estimated by the data.⁵⁶

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.^{5,57} 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,^{15,16} 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.

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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

1. Campbell AJ, Borrie MJ, Spears GF. Risk Factors for falls in a community-based prospective study

- of people 70 years of age and older. *J Gerontol.* 1989;44(4):M112-M117.
2. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med.* 1988;319(26):1701-1707.
3. O'Loughlin JL, Robitaille Y, Boivin JF, Suissa S. Incidence of risk factors for falls and injurious falls among the community dwelling elderly. *Am J Epidemiol.* 1993;137(3):342-354.
4. Lord SR, Ward JA, Williams P, Anstey KJ. Physiological factors associated with falls in older community-dwelling women. *J Am Geriatr Soc.* 1994; 42(10):1110-1117.
5. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. Guideline for the prevention of falls in older persons. *J Am Geriatr Soc.* 2001;49(5):664-672.
6. Weir E, Culmer L. Fall prevention in the elderly population. *CMAJ.* 2004;171(7):724.
7. Donaldson MG, Khan KM, Davis JC, et al. Emergency department fall-related presentations do not trigger fall risk assessment: a gap in care of high-risk outpatient fallers. *Arch Gerontol Geriatr.* 2005; 41(3):311-317.
8. Scuffham P, Chaplin S, Legood R. Incidence and costs of unintentional falls in older people in the United Kingdom. *J Epidemiol Community Health.* 2003;57(9):740-744.
9. Lewin Group. Estimated savings from falls prevented by targeted home modifications. Washington, DC: AARP Public Policy Institute; October 2000.
10. The economic burden of unintentional injury in Canada. Smartrisk Foundation Web site. http://www.smartrisk.ca/researchers/economic_burden_studies/canada.html. Accessed March 19, 2009.
11. Graafmans WC, Ooms ME, Hofstee HM, Bezemer PD, Bouter LM, Lips P. Falls in the elderly: a prospective study of risk factors and risk profiles. *Am J Epidemiol.* 1996;143(11):1129-1136.
12. Yip YB, Cumming RG. The association between medications and falls in Australian nursing home residents. *Med J Aust.* 1994;160(1):14-18.
13. Lord SR, Menz HB, Tiedemann A. A physiological profile approach to falls risk assessment and prevention. *Phys Ther.* 2003;83(3):237-252.
14. Morgan S, Raymond CB, Mooney D, Martin D. *The Canadian Rx Atlas.* 2nd ed. Vancouver, BC, Canada: UBC Centre for Health Services and Policy Research; 2008.
15. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis, I: psychotropic drugs. *J Am Geriatr Soc.* 1999;47(1):30-39.
16. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis, II: cardiac and analgesic drugs. *J Am Geriatr Soc.* 1999;47(1):40-50.
17. Hartikainen S, Lönnroos E, Louhivuori K. Medication as a risk factor for falls: critical systematic review. *J Gerontol A Biol Sci Med Sci.* 2007; 62(10):1172-1181.
18. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality of both the randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6): 377-384.
19. Lamb SE, Jørstand-Stein EC, Hauer K, Becker C; Prevention of Falls Network Europe and Outcomes Consensus Group. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe

- consensus *J Am Geriatr Soc.* 2005;53(9):1618-1622.
20. Kellogg International Work Group on the Prevention of Falls by the Elderly. The prevention of falls in later life: a report of the Kellogg International Work Group on the Prevention of Falls by the Elderly. *Dan Med Bull.* 1987;34(suppl 4):1-24.
 21. Sutton AJ, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. *Stat Methods Med Res.* 2001;10(4):277-303.
 22. Spiegelhalter DJ, Thomas A, Best NG, Gilks WR. *BUGS: Bayesian Inference Using Gibbs Sampling Version 0.50.* Cambridge, England: MRC Biostatistics Unit; 1995.
 23. Arfken CL, Wilson JG, Aronson SM. Retrospective review of selective serotonin reuptake inhibitors and falling in older nursing home residents. *Int Psychogeriatr.* 2001;13(1):85-91.
 24. Avidan AY, Fries BE, James ML, Szafara KL, Wright GT, Chervin RD. Insomnia and hypnotic use, recorded in the minimum data set, as predictors of falls and hip fractures in Michigan nursing homes. *J Am Geriatr Soc.* 2005;53(6):955-962.
 25. Chu LW, Chi I, Chiu AY. Incidence and predictors of falls in the Chinese elderly. *Ann Acad Med Singapore.* 2005;34(1):60-72.
 26. Ensrud KE, Blackwell TL, Mangione CM, et al; Study of Osteoporotic Fractures Research Group. Central nervous system-active medications and risk for falls in older women. *J Am Geriatr Soc.* 2002;50(10):1629-1637.
 27. Gerdhem P, Ringsberg KA, Akesson K, Obrant KJ. Clinical history and biologic age predicted falls better than objective functional tests. *J Clin Epidemiol.* 2005;58(3):226-232.
 28. Passaro A, Volpato S, Romagnoni F, Manzoli N, Zuliani G, Fellin R. Benzodiazepines with different half-life and falling in a hospitalized population: the GIFA study. *J Clin Epidemiol.* 2000;53(12):1222-1229.
 29. Tromp AM, Smit JH, Deeg DJ, Bouter LM, Lips P. Predictors for falls and fractures in the Longitudinal Aging Study Amsterdam. *J Bone Miner Res.* 1998;13(12):1932-1939.
 30. Tromp AM, Pluijm SM, Smit JH, Deeg DJ, Bouter LM, Lips P. Fall-risk screening test: a prospective study on predictors for falls in community-dwelling elderly. *J Clin Epidemiol.* 2001;54(8):837-844.
 31. Hanlon JT, Landerman LR, Fillenbaum GG, Studenski S. Falls in African American and white community-dwelling elderly residents. *J Gerontol A Biol Sci Med Sci.* 2002;57(7):M473-M478.
 32. Weiner DK, Hanlon JT, Studenski SA. Effects of central nervous system polypharmacy of falls liability in community dwelling elderly. *Gerontology.* 1998;44(4):217-221.
 33. Fisher AA, McLean AK, Davis MW, Le Couteur DG. A multicenter, case-control study of the effects of antihypertensive therapy on orthostatic hypotension, postprandial hypotension, and falls in octo- and nonagenarians in residential care facilities. *Curr Ther Res.* 2003;64(3):206-214.
 34. Frels C, Williams P, Narayanan S, Gariballa SE. Iatrogenic causes of falls in hospitalized elderly patients: a case control study. *Postgrad Med J.* 2002;78(922):487-489.
 35. Gluck T, Wientjes HJ, Rai GS. An evaluation of risk factors for in-patient falls in acute and rehabilitation elderly care wards. *Gerontology.* 1996;42(2):104-107.
 36. Neutel CI, Perry S, Maxwell C. Medication use and risk of falls. *Pharmacoepidemiol Drug Saf.* 2002;11(2):97-104.
 37. Walker PC, Alrawi A, Mitchell JF, Regal RE, Khan-deria U. Medication use as a risk factor for falls among hospitalized elderly patients. *Am J Health Syst Pharm.* 2005;62(23):2495-2499.
 38. de Rekeneire N, Visser M, Peila R, et al. Is a fall just a fall: correlates of falling in healthy older persons: the Health, Aging and Body Composition Study. *J Am Geriatr Soc.* 2003;51(6):841-846.
 39. Eby EM, Hogan DB, Fung TS. Potential adverse outcomes of psychotropic and narcotic drug use in Canadian seniors. *J Clin Epidemiol.* 1997;50(7):857-863.
 40. Kallin K, Gustafson Y, Sandman PO, Karlsson S. Drugs and falls in older people in geriatric care settings. *Aging Clin Exp Res.* 2004;16(4):270-276.
 41. Landi F, Onder G, Cesari M, Barillaro C, Russo A, Bernabei R; Silver Network Home Care Study Group. Psychotropic medications and risk for falls among community-dwelling frail older people: an observational study. *J Gerontol A Biol Sci Med Sci.* 2005;60(5):622-626.
 42. Lawlor DA, Patel R, Ebrahim S. Association between falls in elderly women and chronic disease and drug use: cross sectional study. *BMJ.* 2003;327(7417):712-717.
 43. Lee JSW, Kwok T, Leung PC, Woo J. Medical illnesses 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. *Rev Panam Salud Publica.* 2003;13(6):369-375.
 45. Psaty BM, Koepsell TD, Lin D, et al. Assessment and control for confounding by indication in observational studies. *J Am Geriatr Soc.* 1999;47(6):749-754.
 46. Stürmer T, Glynn RJ, Rothman KJ, Avorn J, Schneeweiss S. Adjustments for unmeasured confounders in pharmacoepidemiologic database studies using external information. *Med Care.* 2007;45(10)(suppl 2):S158-S165.
 47. Stürmer T, Joshi M, Glynn RJ, Avorn J, Rothman KJ, Schneeweiss S. A review of the application of propensity score methods yielded increasing use, advantages in specific settings, but not substantially different estimates when compared with conventional multivariable methods. *J Clin Epidemiol.* 2006;59(5):437-447.
 48. Hien TT, Cumming RG, Cameron ID, et al. Atypical antipsychotic medications and risk of falls in residents of aged care facilities. *J Am Geriatr Soc.* 2005;53(8):1290-1295.
 49. Flicker L, Mead K, MacInnis RJ, et al. Serum vitamin D and falls in older women in residential care in Australia. *J Am Geriatr Soc.* 2003;51(11):1533-1538.
 50. Heitterachi E, Lord SR, Meyerkort P, McCloskey I, Fitzpatrick R. Blood pressure changes on upright tilting predict falls in older people. *Age Ageing.* 2002;31(3):181-186.
 51. Lord SR, March LM, Cameron ID, et al. Differing risk factors for falls in nursing home and intermediate-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 facility. *J Gerontol A Biol Sci Med Sci.* 2005;60(9):1157-1162.
 53. Schwartz AV, Villa ML, Prill M, et al. Falls in older Mexican-American women. *J Am Geriatr Soc.* 1999;47(11):1371-1378.
 54. Ray WA, Thapa PB, Gideon P. Benzodiazepines and risk of falls in nursing home residents. *J Am Geriatr Soc.* 2000;48(6):682-685.
 55. Vellas BJ, Wayne SJ, Garry PJ, Baumgartner RN. A two-year longitudinal study of falls in 482 community-dwelling elderly adults. *J Gerontol A Biol Sci Med Sci.* 1999;53(4):M264-M274.
 56. Cooper NJ, Sutton AJ, Abrams KR, Turner D, Wailoo A. Comprehensive decision analytical modelling in economic evaluation: a Bayesian approach. *Health Econ.* 2004;13(3):203-226.
 57. Campbell AJ, Robertson MC, Gardner MM, Norton RM, Buchner DM. Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized controlled trial. *J Am Geriatr Soc.* 1999;47(7):850-853.