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Cause or Effect? Selective Serotonin Reuptake Inhibitors and Falls in Older Adults: A Systematic Review

Marie Anne Gebara, M.D.[1], **Kim L. Lipsey, M.L.S**[2], **Jordan F. Karp, M.D.**[1], **Maureen C. Nash, M.D.**[3], **Andrea Iaboni, M.D., D.Phil**[4], and **Eric J. Lenze, M.D.**[5]

[1]Department of Psychiatry, University of Pittsburgh School of Medicine, University of Pittsburgh, PA

[2]Bernard Becker Medical Library, Washington University, St. Louis, MO

[3]Department of Psychiatry, Oregon Health and Science University School of Medicine, Oregon Health and Science University, OR

[4]Department of Psychiatry, University of Toronto, Toronto, ON and University Health Network, Toronto, ON

[5]Department of Psychiatry, Washington University School of Medicine, Washington University, St. Louis, MO

Abstract

A 2012 update of the Beers criteria categorizes selective serotonin reuptake inhibitors (SSRIs) as potentially inappropriate medications in all older adults based on fall risk. The application of these recommendations, not only to frail nursing home residents, but also to all older adults, may lead to changes in health policy or clinical practice with harmful consequences. A systematic review of studies on the association between SSRIs and falls in older adults was conducted to examine the evidence for causation. Twenty-six studies met the inclusion criteria. The majority of studies were observational and suggest an association between SSRIs and falls. The direction of the relationship – causation or effect- cannot be discerned from this type of study. Standardized techniques for determining likely causation were then used to see if there was support for the hypothesis that SSRI's lead to falls. This analysis did not suggest causation was likely. There is no Level 1 evidence that SSRIs cause falls. Therefore, changes in the current treatment guidelines or policies on the use of SSRIs in older adults based on fall risk may not be justified at this time given the lack of an established evidence base. Given its significance to public health, well-designed experimental studies are required to address this question definitively.

Corresponding author: Marie Anne Gebara, Western Psychiatric Clinic and Institute, 3811 O'Hara Street, E908, Pittsburgh, PA 15213, gebarama@upmc.edu, Phone: 412 246 5951, Fax: 412 586 9300.

Conflicts of Interest

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Keywords

Falls; SSRI; older adults

INTRODUCTION

The Beers criteria aim to promote safe and effective prescribing for all older adults through the identification of inappropriate medications. In 2012, the American Geriatrics Society (AGS) updated Beers criteria(1) categorized, with high quality of evidence and strong recommendations, selective serotonin reuptake inhibitors (SSRIs) as Potentially Inappropriate Medications (PIMs) for older adults with a history of falls or fractures. The Beers criteria were created in 1991 with a focus on potential adverse effects and excessive use of medications in frail residents of long-term care. The list has been updated twice and is now widely applied to older adults in all settings regardless of frailty status.(2) Older versions of this list included amitriptyline(2, 3) and doxepin(3) as antidepressant medications to avoid independent of diagnosis, and only recommended the avoidance of SSRIs in patients with SIADH/hyponatremia.(4) In 2012, the AGS released the latest Beers criteria. This updated list now includes most classes of psychotropic drugs.(1)

This shift in the Beers criteria towards covering entire classes of antidepressant drugs is a major shift with implications for practice, policy, and public health. The Beers Criteria are influential and have an impact on clinical guidelines, healthcare policy and quality monitoring. Moreover, falls and antidepressant use are highly prevalent in older adults. Around thirty percent of community dwelling older adults fall at least once a year(5–8) and the yearly cost of falls is estimated at $30 billion.(9) Several systematic reviews and meta-analyses have concluded that the use of psychotropic medications in general and antidepressants in particular are associated with an increased risk of falls.(10–13) Furthermore, there has been an increased focus on SSRIs and the possible association with falls and fractures.(14–18) At least one in seven community-dwelling older adults(19) and one in two nursing home residents are prescribed antidepressants.(20) Before eliminating or decreasing use of SSRIs it is vital to understand the relationship to falls. It is possible there is a common risk factor leading those at higher risk of falls to be treated with SSRIs.

If the AGS Beers recommendations are to be followed, then SSRIs (and serotonin-norepinephrine reuptake inhibitors (SNRIs)) should be avoided in most older adults because the risks and burden clearly exceed benefits.(21) Such a recommendation may lead to policies to decrease the use of antidepressants, as has been the case for antipsychotics in older adults with dementia.(22) Up to 15% of older adults have clinically significant depressive symptoms resulting in impairments in quality of life, increased morbidity and mortality and increased risk of suicide.(23–28) Therefore, a decrease in SSRI use, in the absence of a safer alternative, will either increase the prevalence of untreated depression in older adults or shift prescribing towards other, potentially more harmful medications. This may create a scenario analogous to that observed in children and adolescents, in which the observation of elevated rates of suicidality with antidepressants led to a decrease in prescribed SSRIs following the issuance of public health warnings and the possible

unintended consequence of increased rates of suicidal behavior (although this point remains controversial).(29) (30)

Multiple expert panels have examined inappropriate medication prescription in older adults, but have not found reason or evidence to include SSRIs. Stefanacci et al. used the same technique as the AGS did to develop the Beers criteria to actually recommend the use of certain preferred medications in older adults and they included two SSRIs in their list, citalopram hydrochloride and escitalopram oxalate.(31) Not all instruments for improving prescribing in older adults use the Beers criteria, i.e. the Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) criteria.(32) A systematic review identified several prescribing criteria in older adults(33) which included French,(34) Canadian,(35) Norwegian(36) and Italian(37) expert consensus panels that have not identified SSRIs as medications to avoid in older adults, and in fact, recommend SSRIs over tricyclic antidepressants (TCAs).

Given the significant clinical, public health and policy concerns related to SSRIs and falls, we conducted a systematic review to examine the current literature on this topic. While a lack of evidence supporting causation does not indicate that SSRIs do not cause falls, a threshold of evidence is in fact needed to demonstrate causation. Thus, we applied the Bradford-Hill criteria(38) for the critical examination of the results. In doing so, we examine not only whether studies are "positive" or "negative," but other elements of the association- such as strength and specificity of the association, experimental design, and alternative explanations- elements that are key in establishing causality.

METHODS

Search strategy

We followed the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.(39) A research librarian conducted a detailed systematic biomedical literature search in PubMed/MEDLINE, EMBASE, the Cochrane Library, PsycInfo and ClinicalTrials.gov from the inception of the database to February 2014. We also checked reference lists to identify relevant publications and used the authors' knowledge of the literature to obtain additional references. The search was performed using standardized subject terms for *Accidental Falls, Serotonin Uptake Inhibitors, Psychotropic Drugs, Antidepressive Agents, Second-Generation, Central Nervous System Agents* and plain language for the terms according to the databases including synonyms. Finally, limits included human studies, English for language, and age limits were set from middle aged adults to 80 plus years.

Selection criteria

Exclusion criteria included mean age of the study sample below 60 years. Studies that examined antidepressant use in general but did not specify SSRI use were excluded. Although fracture was not the primary outcome, studies that examined injurious falls and/or fractures were included. Studies that examined particular disease populations where falls are

more likely to occur (e.g. Parkinson's disease or Alzheimer's dementia) were excluded to reduce confounding.(40–44)

Data collection and extraction

Two reviewers (MG and EL) conducted independent title, abstract, and full text reviews to determine eligibility. Disagreements between reviewers were resolved by discussion. MG and EL extracted data from eligible studies. Data extracted from the tables and text included: First author and publication year, study design, study setting, sample size, method of falls assessment, association and odds ratio (OR) (when applicable) between SSRI use and falls. A flow chart summarizing the article selection process is shown in Figure 1.

RESULTS

The search strategy identified 3,085 articles, of which 2,880 were excluded after an initial title and abstract review. An additional 180 were excluded after full text review and one article was added based on the authors' knowledge of the literature. A total of 26 articles were included, two of which were from the same study.(45, 46) The results are summarized in Table 1.

Positive studies

Seventeen studies found an increased association of falls or injurious falls with SSRI users.(14–17, 45, 47–58) Several of these studies showed that SSRI users had other risk factors that may be associated with frailty such as multiple comorbidities, higher number of medications(15, 16), baseline higher rate of falls(48), or higher age (i.e. the oldest old).(49, 54–57) This raises concerns about biased risk estimates of falls due to confounds, as described in the discussion.

Negative studies

Nine studies did not find a significant association between SSRI use and falls or injurious falls.(46, 59–65) Only one study was a randomized controlled trial which assessed the treatment of psychotic depression.(61) Although there was no statistically significant increase in the rate of falls with sertraline (compared to placebo), the wide confidence interval of the odds ratio suggest that the study was underpowered, as the authors themselves reported; OR= 1.56 (95% CI: 0.63–3.83). A study with weekly follow up did not find SSRIs to increase the risk of falls. (65) One study found that SSRIs only increases the risk of outdoor falls and not indoor falls.(66)

Study design

All the studies were observational except for one randomized controlled trial (RCT).(61) Nine studies were retrospective and used healthcare databases (16, 48, 49, 52, 53, 56, 60, 62, 63) while ten were prospective(14, 17, 45–47, 51, 57, 64–66) and one was a case-crossover design.(59) There were five case-control studies,(15, 50, 54, 55, 58) with one(58) that also included a self-controlled case series.

Study setting

Seventeen of the studies were conducted among community dwelling older adults,(14, 15, 17, 45–48, 50, 55, 58, 61–66) two study populations were selected from inpatients, admitted either to a psychiatric unit(60) or to a medical/surgical unit,(54) and one(57) used both nursing home and community dwelling subjects.(57) Six studies were conducted in nursing homes or residential care.(16, 49, 51, 52, 56, 59) In comparison to community dwelling older adults, nursing home residents have a higher rate of falling(51, 67) and mood disorders.(68, 69)

Fall assessment

Fall assessment in nursing homes and residential care generally relied on nursing incident reports or fall logs.(16, 49, 51, 52, 56, 59) Fall assessment was more varied for community dwelling subjects. This includes quarterly postcards on which patients documented number of falls,(45, 46) self-report or clinician-determined, which ranged from past week,(52) month,(17) to past year,(53) and was obtained directly from the patient, from medical records(48, 50, 61–63), or fall calendars.(57, 65, 66) One study also used reporting based on Adverse Drug Reactions (ADR)(55) which could lead to underreporting since it relies on spontaneous reporting by clinicians.

History of falls

Multiple studies reported and factored in a history of falls, often considered as a risk factor for future falls(14, 17, 45, 49, 51, 52, 54, 56–59, 62, 64, 65) but only one study specifically compared the rates of falls before and after SSRI use. Hubbard et al conducted a case-series analysis on the incidence ratio of falls before and after antidepressant exposure.(58) This study included both SSRIs and TCAs and showed an increased rate after TCA (OR= 2.30 [95% CI 1.82–2.90]) and SSRI (OR= 1.96 [95% CI 1.35–2.83]) exposure.

Injurious falls

Eight studies specifically looked at injurious falls and fractures. Hip fractures can be considered a proxy for falls since around 95% of fractures result from falls. Of those, six(14, 15, 17, 47, 54, 58) showed a positive association between SSRI use and fractures or injurious falls requiring medical care. Two studies(14, 15) specifically excluded cases of fractures that were pathological or those that were not likely secondary to falls. One study(14) had a low number of SSRI users (N=18). A third study(47) found that only 5% of hip fractures were attributable to antidepressant exposure. In a fourth study(17) examining the association of falls and fragility fractures, despite adjustment for falls and bone mineral density, the rate of fractures remained elevated suggesting other potential mechanisms (e.g. reduced bone strength) that may play a role in fractures. Furthermore, SSRI users constituted 2.7% of the total participants and were also more likely to have depressive symptoms and have a history of falls. A retrospective case-control study(54) showed that SSRIs did have an increased OR for falls or fractures, (1.99 [95% CI 1.29–3.08]) but it was less than that of non-SSRIs, such as TCA antidepressants (4.39 [95% CI 2.21–8.71]). One case control study(58) also conducted a case-series analysis and found smaller effects in their analysis. Of the two that did not show significant results, one has been mentioned above(46) and the

other(64) found that combinations of risk factors such as TCA use or previous falls to have an increased risk but did not find a significant association with SSRI use with fractures.

Assessing evidence for causation: The Bradford-Hill criteria (Table 2)

The Bradford-Hill criteria(38) call for examination of different aspects of an association to establish causation. A quick review of the results of our search shows that at least one of the criteria, *consistency*, is met, with the majority of studies showing an association between SSRI and falls. Also, some studies(17, 48, 56) have shown *biological gradient* or dose-dependent response with higher doses of SSRIs resulting in more falls. However, there are several other criteria to consider before making the conclusion of causation. For example, there is no *strength* of the association with odds ratios or hazard ratios rarely exceeding 2.0. These small effect sizes may reflect a low likelihood of true results.(70) Despite using large samples, the numbers for fallers who used SSRIs were usually small(14, 45, 46, 49, 52, 53, 57, 64, 66) which increase potential for underpowered results. The third criteria, *specificity* is difficult to prove in terms of the association between SSRI use and falls as there is confounding by indication (discussed below). Also, some studies(47, 51) attributed falls to factors such as infections or medical illness despite SSRI use. Bakken et al.(47) calculated the risk of hip fracture attributed to antidepressant use and found the highest (3.6%) risk with SSRI exposure as compared to other antidepressants classes. Next, the criteria of *temporality* cannot be clearly established. There are no clear answers to the question of what came first, falls or SSRI prescription. Older adults with unsteadiness, falls, or a decline in physical function may be more likely to develop depression(71) and to receive medical attention resulting in increased frequency of SSRI therapy. This is best exemplified in the study by Echt et al.(72) which found the highest fall risk 4 days before a new psychotropic drug prescription or dose change. As for *plausibility*, several potential pathways have been suggested in the association between SSRIs and falls, but no clear mechanism has yet been elucidated. It has been suggested that SSRIs may increase the risk of falls because of cardiovascular effects.(73) Other possible mechanisms by which SSRIs may lead to falls are reviewed elsewhere(74) and include but are not limited to arrhythmias, insomnia, and sedation. Other potential implicated pathways have involved postural control as a risk factor for falls, but the results have not been consistent: while some studies did not find any change in postural sway with use of paroxetine in older depressed adults,(75, 76) others have found that sertraline and paroxetine cause an increase in postural sway.(77, 78) Depression itself is associated with impaired gait(79) with improvement in gait after successful treatment of depression with SSRI.(80) There have been inconsistent results regarding the effects of paroxetine on obstructed gait.(78, 81) A recent cross-sectional study found that antidepressants were an independent risk factor for impaired gait that potentially increases fall risk, although SSRIs only constituted around half of all antidepressants used.(82) While other medications have been associated with increased risk of falls in older adults, *coherence and analogy* are not very clear in this case. And lastly, the evidence from *experimental* studies is scarce as we identified only one experimental study that examined the association between SSRI use and falls which was underpowered without finding a statistically increased risk of falls.

Study Quality Assessment (Table 3)

The Bradford-Hill criteria were applied for every study to identify the criteria that were met. Furthermore, the Newcastle-Ottawa scale, which utilizes a star scale system to measure the quality of observational studies was used.(83) For the randomized control trial, the CONSORT assessment scale was used. (84)

DISCUSSION

The results of our systematic review indicate that there are many observational studies pointing to an association between SSRI use and falls, but no experimental studies, such as RCTs, that support this finding. Up to 15% of older adults have clinically significant depressive symptoms, and roughly 10% have an anxiety disorder.(23, 25, 85) (86). Hence, there needs to be a robust evidence base upon which to make recommendations and subsequent policy decisions about the use of SSRIs in older adults. In particular, consideration should be given to the limited ability to determine causality when evaluating observational studies. The Bradford-Hill criteria set out the conditions needed to establish a causal relationship with relative certainty. In the sections below, we describe the inherent limitations of observational studies and demonstrate that the Bradford Hill criteria are not sufficiently met at this time.

Limitations of observational studies

Observational studies have numerous inherent limitations. There are several examples showing opposing and discrepant results between observational studies and RCTs;(87) one of the more well-publicized recent examples is hormone therapy in postmenopausal women in which RCTs showed that combined estrogen plus progestin are not to be used for prevention of coronary heart disease(88) contradicting large observational studies.(89, 90) The reasons for these discrepant results have been described previously,(70, 87, 91–94) but here we highlight some that are particularly relevant to the relationship between SSRI use and falls.

First, adjusting for confounders in analysis does not eliminate the bias or *effect of unmeasured confounders*. (91) Several of the studies used a retrospective design for large population – based databases; however diagnoses such as “depression” are poorly captured by administrative data. This is particularly apparent when variables cannot be measured well and conceptual or measurement errors can be made, such as severity of depression or frailty compared to other variables that can be more easily adjusted for such as age or sex.(93) As a prominent example, while observational studies found antioxidant levels to be protective against cardiovascular disease and cancer, these results were not replicated in RCTs because social and behavioral factors such as socioeconomic position (which is associated with antioxidant levels) could not be adjusted for, and residual confounding remained.(92) The study by Hubbard et al.(58) demonstrates another example that supports the effect of unmeasured confounders. The smaller results obtained from the case-series analysis when compared to the case-control analysis indicates residual bias that was not controlled for. In fact, when previously unaccounted for confounders are included in analysis, there is a decrease in the effect size of the risk between SSRIs and fractures.(18)

Second, these observational studies may suffer from *confounding by indication or indication bias*.(91) Large scale observational follow up studies help to identify adverse drug effects, but the caveat to that is for the adverse effects of the drug to be different from the disease itself.(93) A major limitation to the observational studies linking SSRIs to falls is the evidence from a recent systematic review and meta-analysis showing that depression is associated with an increased risk of falls.(95) Many of the strongest risk factors for falls in older adults are also common risk factors for depression.(96, 97) Additionally, antidepressants are often used off-label in older adults for the treatment of behavioral disturbances in dementia,(98) and both dementia and behavioral disturbance are independent risk factors for falls.(6, 99) In other words, observational studies cannot answer the question: *Is the behavioral condition -or the antidepressants used to treat it - causing falls?* Several studies controlled for potential confounders such as age, gender, measures of frailty, memory problems, number of medications and psychotropic medication classes, history of falls (16, 18, 47, 52, 54, 55, 59, 62) and other studies also specifically accounted for depression or depressive symptoms in their analysis. (14, 15, 17, 45, 46, 51, 53, 56, 57, 63–66) Two studies used case-series analysis to control for depression and eliminate confounding by indication, both showing a positive association between SSRI use and increased risk of falls and fractures(50, 58).

The third limitation to observational studies is *allocation bias*. There must be no link between prescription and prognosis for an observational study to satisfy the condition of unbiased allocation that is provided through randomization. This channeling effect or selective prescribing(15) i.e. prescription of SSRIs to avoid exposure to TCA in patients who are already at higher risk for falls is a potential confounder. One of the advantages of randomized controlled trials lies in the fact that randomization strives to decrease the bias of having certain patients receive a particular treatment while others do not.(93) In contrast, data obtained from observational studies are reflective of medical decisions made based on characteristics of patients and their providers that influenced these decisions and outcomes. It is impossible to delineate whether it is these characteristics or the intervention that led to the outcome being studied.(100)

The *validity of falls reporting* represents another significant limitation to observational studies on falls. Several of the studies relied on medical record reviews or on self- report. This poses a problem relating to the accuracy of falls reported as higher reporting rates are obtained when adverse events are solicited as compared to spontaneous reporting.(101) A review on falls reporting showed that data collection on falls should be gathered at frequent intervals i.e. weekly or monthly compared to quarterly or yearly.(102) Furthermore, the number of reported falls increases with direct assessment.(103)

Other observational study biases that may apply in the case of antidepressants and falls also include *bias due to differential recall of treatment exposure*(94) when patients provide reports that may not be reliable, and *publication bias*(104) with trends towards only reporting positive results.

When they are feasible, RCTs provide a much better estimate of causal effect(92) in comparison to results obtained from observational studies that have been described as “low

grade evidence."(105) Some argue that observational studies may increase the cost of health care and even harm patients due to discrepancies between the results of observational studies and RCTs.(91) Depending on the results obtained from observational studies to make sweeping changes to treatment/non-treatment recommendations is not justified by an absence of RCTs. The quality of results obtained from RCTs surpasses those obtained from observational studies when trying to determine causality. And while observational studies are important in detecting rare outcomes that are typically unrelated to the indication for treatment,(94) they cannot replace randomized trials or exclude the need to have them. Some of the main concerns arising from randomized controlled trials include cost and generalizability; however, it has been argued that researchers could design relatively inexpensive trials with generalizable results.(91) Recent calls for large pragmatic trials by various funding agencies, such as the National Institute for Mental Health(106) (NIMH), National Institute on Aging (NIA), and the Patient-Centered Outcome Research Institute (PCORI), reflect a move towards such studies.

CONCLUSION

We conclude from our systematic review that there is insufficient evidence to support clinical guidelines or policy changes recommending the avoidance of SSRI use in older adults based on fall risk. Given the available evidence, we do not think that clinicians should be deterred from using SSRIs in late-life depression.

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Recommendations

1. In cases of mild depression or subclinical depressive symptoms, cognitive-behavioral therapy and problem- solving therapy are some of the evidence-based psychosocial approaches for treatment in older adults that may be considered as first line treatment.(107) However, in cases of at least moderately severe depression, antidepressants have adequate evidence for efficacy.(103) 2. Clinicians and policy makers should be mindful of the hazard of shifting prescribing towards agents with less evidence for efficacy in older adults and less information regarding potential risk as is the case with SNRIs and the conflicting data with respect to falls.(50, 52, 103) 3. The current literature does not address the question of falls and SSRIs given the limitations of observational studies; thus, there is a need for large, long-term and appropriately powered RCTs similar to those seen other fields of medicine; the high public health importance of this question justifies their cost.(108)

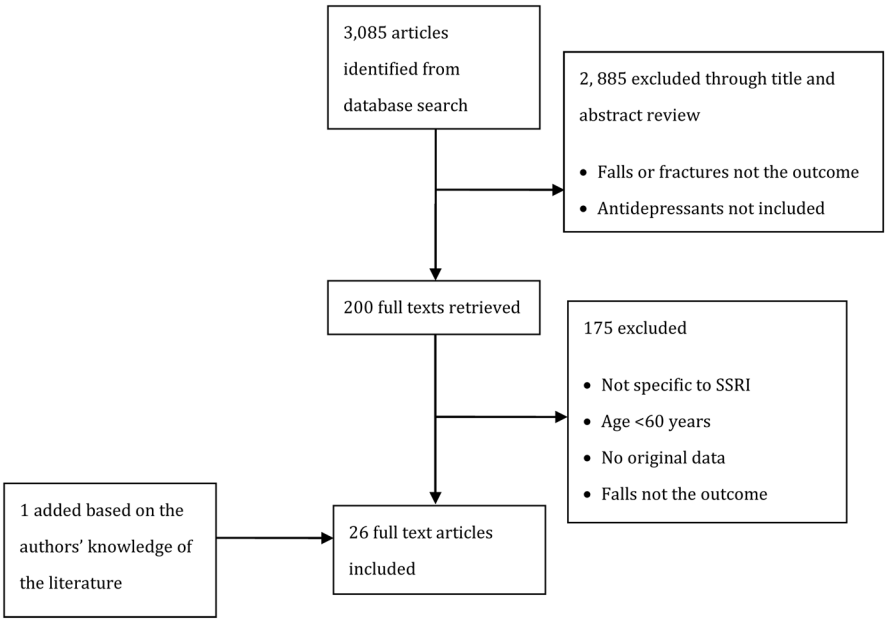

Figure 1.
Flow Chart Describing Review Process for Identification of Eligible Studies

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Table 1

Characteristics of studies assessing Selective Serotonin Reuptake Inhibitors and falls and/or fractures

Authors	Study design	Study setting	Sample size (N)	Fall assessment	SSRI increases risk of fall and/or fracture	Outcome measure	Type of fall
Arafken et al. 2001(16)	Observational/Retrospective	Nursing Home	368	Incident reports and fall logs	Yes	Adjusted OR; at least 1 fall = 2.01 (CI: 1.23–3.28) and injurious fall OR=1.77 (CI: 1.0–3.13)	Falls and injurious falls
Bakken et al. 2013 (47)	Observational/Prospective	Community	906,422	Hip fracture	Yes	SIR= 1.8 (CI: 1.7–1.8)	Injurious falls, fracture
Berry et al. 2011(59)	Case-crossover	Nursing Home	1,181	Nursing incident reports	No	OR= 0.7 (CI: 0.3–1.6)	Falls
Coupland et al. 2011(48)	Retrospective cohort	Community	55,767	ICD 9 code/self report in medical record	Yes	Adjusted HR for falls= 1.66 (CI: 1.58–1.73), adjusted HR for fracture = 1.58 (CI: 1.46–1.68)	Falls and fracture
Ensrud et al. 2002(45)	Observational/Prospective	Community	8,127	Post card for past 4 months	Yes	One fall MOR = 2.61, (CI: 1.51–4.5), frequent falls MOR =3.45 (CI: 1.89–6.30)	Falls
Ensrud et al. 2003(46)	Observational/Prospective	Community	8,127	Fractures	No	Any non-spine fracture HR= 1.44 (CI: 0.93–2.24); hip fracture HR =1.54 (CI: 0.62–3.82)	Injurious, non-spine and hip fracture
De Carle et al. 2001(60)	Observational/Retrospective	Inpatient	1,834	Fall reporting on inpatient	No	Data not available	Falls
Fisher et al. 2005(49)	Observational/Cross-section/Retrospective	Residential care	179	Daily diary nursing records and medical records	Yes	OR =2.3 (CI: 1.00–5.40)	Falls
Flint et al. 2014(61)	Randomized control trial	Community	142	History of fall assessed during study visit	No	OR= 1.56 (underpowered) (CI: 0.63–3.83)	Falls
Formiga et al. 2008(62)	Observational/Cross-section/Retrospective	Community	1,225	Direct history and chart review of recurrent falls prior to index fall	No	Data not available	Injurious falls

Authors	Study design	Study setting	Sample size (N)	Fall assessment	SSRI increases risk of fall and/or fracture	Outcome measure	Type of fall
Gribbin et al. 2011(50)	Case-control/Prospective	Community	61,782	Read Code/Medical record	Yes	Adjusted OR= 1.55 (CI: 1.46–1.65)	Falls
Hubbard et al. 2003(58)	Case control and case series	Community	46,230	Hip fracture	Yes	OR= 1.35 (CI: 1.20–1.51); IR(1st 15 days) =1.96 (CI: 1.35–2.83)	Hip fracture
Kallin et al. 2002(51)	Observational/Prospective	Residential care	83	Nurse reporting	Yes	OR = 4.66 (CI: 1.23 – 17.59)	Falls and injurious falls
Kallin et al. 2004(52)	Observational/Cross-section/Retrospective	Residential care	3,604	Questionnaire for staff	Yes	OR= 1.67 (CI: 1.31–2.13)	Falls
Kerse et al. 2008(53)	Observational/Cross-section/Retrospective	Community	21,900	Mailed questionnaire asking falls over past 12 months	Yes	1 fall OR =1.55 (CI: 1.26–1.90); 2 or more falls OR= 1.66 (CI: 1.36, 2.02), injurious falls OR= 1.52 (CI: 1.25, 1.84)	Falls and injurious falls
Landi et al. 2005(63)	Observational/Cross-section/Retrospective	Community	2,854	Fall history from MDS-HC in past 90 days	No	Adjusted OR= 0.99 (CI: 0.69– 1.41)	Falls
Lewis et al. 2007(64)	Observational/Prospective	Community	5,995	Fractures	No	Adjusted HR= 1.65 (CI: 0.92–2.94)	Injurious falls, fracture
Liu et al. 1998(15)	Case-control	Community (hospital admission for fracture)	49,434	Hip fracture	Yes	Adjusted OR= 2.4 (CI: 2.0–2.7)	Injurious falls, fracture
Mahoney et al. 2000(65)	Observational/Prospective	Community	311	Patient report in calendar and postcards	No	Data not available	Falls
Payne et al. 2013(54)	Case-cohort	Inpatients for fall or fracture	39,813	Hospitalization for fall or fracture	Yes	OR =1.99 (CI: 1.29–3.08)	Injurious falls, fracture
Richards et al. 2007(17)	Observational/Prospective	Community	5,008	Self report for past month	Yes	OR (fall)=2.2 (CI: 1.4–3.5), HR (fragility fracture)= 2.1 (CI: 1.3–3.4)	Falls and fragility fracture
Quach et al. 2013(66)	Observational/Prospective	Community	763	Daily self reporting falls calendar post cards	Yes (outdoor), No (indoor)	SSRI outdoor IRR = 1.53, (CI: 1.05–2.25), AD indoor IRR= 0.94 (CI: 0.64–1.37)	Falls

Authors	Study design	Study setting	Sample size (N)	Fall assessment	SSRI increases risk of fall and/or fracture	Outcome measure	Type of fall
Souchet et al. 2005(55)	Case-control	Community	67,464	ADR reporting system (French)	Yes	Adjusted OR= 2.2 (CI: 1.5–3.1)	Falls
Thapa et al. 1998(56)	Observational/Retrospective	Nursing home	2,428	Nursing home incident reports and medical records	Yes	OR= 1.8 (CI: 1.6 to 2.0)	Falls and injurious falls
von Heideken et al. 2009(57)	Observational/Prospective	Nursing home and community	220	Fall report/daily fall calendar	Yes	HR = 2.103 (CI: 1.242–3.560)	Falls
Ziere et al. 2009(14)	Observational/Prospective	Community	7,983	Non-vertebral fracture	Yes	Adjusted HR= 2.35 (CI: 1.32–4.18)	Injurious falls and fracture

OR= Odds ration, CI = Confidence Interval (95% in all studies), SIR= Standardized Incidence Ration, MOR= Multivariate Odds Ration, IR= Incidence Ratio, HR= Hazard ratio, IRR= Incidence Rate Ration, SSRI= Selective Serotonin Reuptake Inhibitor, AD= Antidepressant

Table 2

Applying the Bradford Hill Criteria(38): (+) Criterion is met; (−) Criterion is not met

Bradford Hill Criterion	Association between SSRI and falls	Supporting evidence
Strength	−	Underpowered results, small effect sizes
Consistency	+	16/25 positive studies
Specificity	−	Confounding by indication
Temporality	−	Unknown fall rates prior to SSRI use
Biological gradient	+	Dose dependent response
Plausibility	−	No clear mechanism of action
Coherence	−	No available evidence
Experiment	−	Only 1 RCT found, underpowered and no statistically significant results
Analogy	−	No available evidence

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Table 3

Study Quality Assessment

Authors	Newcastle-Ottawa Scale	Bradford-Hill Criteria								
		Strength	Consistency	Specificity	Temporality	Biological gradient	Plausibility	Coherence	Experiment	Analogy
Arafken et al. 2001(16)	★★★★★	✗	✓	✗	✗	✗	✗	✗	✗	✗
Bakken et al. 2013 (47)	★★★	✗	✓	✗	✗	✗	✗	✗	✗	✗
Berry et al. 2011(59)	★★★★★★★★	✓	✗	✗	✗	✗	✗	✗	✗	✗
Coupland et al. 2011(48)	★★★★★★	✗	✓	✗	✗	✓	✗	✗	✗	✗
Ensrud et al. 2002(45)	★★★★★★★★	✗	✓	✓	✗	✗	✗	✗	✗	✗
Ensrud et al. 2003(46)	★★★★★★★★	✗	✗	✓	✗	✗	✗	✗	✗	✗
De Carle et al. 2001(60)	★★★★	✗	✗	✗	✗	✗	✗	✗	✗	✗
Fisher et al. 2005(49)	★★★★	✗	✓	✗	✗	✗	✗	✗	✗	✗
Flint et al. 2014(61)	28/37 CONSORT checklist	✗	✗	✗	✗	✗	✗	✗	✓	✗
Formiga et al. 2008(62)	★★★★	✗	✗	✗	✗	✗	✗	✗	✗	✗
Gribbin et al. 2011(50)	★★★★★★	✗	✓	✓	✗	✗	✗	✗	✗	✗
Hubbard et al. 2003(58)	★★★★★★★	✗	✓	✓	✗	✗	✗	✗	✗	✗
Kallin et al. 2002(51)	★★★★★★	✗	✓	✓	✗	✗	✗	✗	✗	✗
Kallin et al. 2004(52)	★★★	✗	✓	✗	✗	✗	✗	✗	✗	✗
Kerse et al. 2008(53)	★★★	✗	✓	✓	✗	✗	✗	✗	✗	✗
Landi et al. 2005(63)	★★★★★★	✓	✗	✓	✗	✗	✗	✗	✗	✗
Lewis et al. 2007(64)	★★★★★	✗	✗	✓	✗	✗	✗	✗	✗	✗
Liu et al. 1998(15)	★★★★★★★	✓	✓	✓	✗	✗	✗	✗	✗	✗
Mahoney et al. 2000(65)	★★★	✗	✗	✓	✗	✗	✗	✗	✗	✗
Payne et al. 2013(54)	★★★★★	✓	✓	✗	✗	✗	✗	✗	✗	✗
Richards et al. 2007(17)	★★★★★★★	✓	✓	✓	✗	✓	✗	✗	✗	✗
Quach et al. 2013(66)	★★★★★	✗	✓ (outdoor) ✗ (indoor)	✓	✗	✗	✗	✗	✗	✗
Souchet et al. 2005(55)	★★★	✓	✓	✗	✗	✗	✗	✗	✗	✗
Thapa et al. 1998(56)	★★★★★★	✗	✓	✓	✗	✓	✗	✗	✗	✗
von Heideken et al. 2009(57)	★★★★	✗	✓	✓	✗	✗	✗	✗	✗	✗

Authors	Newcastle-Ottawa Scale	Bradford-Hill Criteria								
		Strength	Consistency	Specificity	Temporality	Biological gradient	Plausibility	Coherence	Experiment	Analogy
Ziere et al. 2009(14)	★★★★★★★★	✗	✗	✓	✗	✗	✗	✗	✗	✗