The Association Between Overactive Bladder and Falls and Fractures: A Systematic Review

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ABSTRACT

Introduction: Urinary symptoms are associated with an increased risk of falls, but few studies have focused on patients with overactive bladder (OAB). This study aimed to synthesize estimates of the risk of falls and fractures in patients with OAB.

Methods: Medline, EMBASE, the Cumulative Index to Nursing and Allied Health Literature, and Scopus were systematically searched for observational studies that focused on patients with OAB. When available, data from a non-OAB comparison sample were included. Double independent review and data extraction were performed. Falls and fractures data were summarized by unadjusted and adjusted risks, and percent attributable risk (PAR) of falls and fractures associated with OAB.

Results: Fifteen studies were included in the analyses. The proportion of patients with OAB experiencing at least one fall over a year ranged from 18.9% to 50.0%, and the proportion of patients with OAB experiencing recurrent or serious falls ranged from 10.2% to 56.0%. In studies that included a non-OAB comparison sample, a higher risk of falls was observed in patients with OAB compared to those without. A significantly increased (1.3- to 2.3-fold) adjusted OAB-associated risk of falls was reported, while unadjusted PARs for OAB associated falls ranged from 3.7% to 15.5%. Risk was higher among women and those 65 years of age or older. While analysis of fractures showed elevated point estimates, most studies were underpowered to detect a statistically significant difference between groups.

Conclusions: Evidence from the published literature clearly demonstrates the importance of OAB and its symptoms as risk factors for falls and fractures.

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Keywords: Accidental falls; Fractures, bone; Overactive; Review; Urinary bladder; Urology
INTRODUCTION

Falls and fractures are important causes of morbidity and mortality among older adults (65 years of age and older), with one-third experiencing a fall annually, and approximately 10–20% of falls resulting in serious injury or fracture [1]. Unintentional injuries are the fifth leading cause of death among older adults and falls are responsible for two-thirds of deaths resulting from unintentional injuries [2]. Furthermore, fatal and non-fatal falls represent a substantial burden on healthcare resources; in 2015, the total medical costs to treat falls in adults at least 65 years of age in the USA was estimated to exceed $50 billion [3]. As such, considerable effort has gone into identifying risk factors for falls, injurious falls, and fractures, and numerous modifiable and non-modifiable risk factors have been identified [4].

Overactive bladder (OAB) is a clinically defined symptom complex consisting of urinary urgency, with or without urgency incontinence, usually with frequency and nocturia, in the absence of significant urological pathology [5]. Some of these symptoms (urgency, urgency incontinence, and nocturia) are established risk factors for falls and fractures [1, 6, 7]; however, few studies examining the risk of falls and fractures have looked specifically at patients with OAB. Published estimates of the risk of falls or fractures associated with OAB or its symptoms vary, ranging from 17.7% (for injurious falls from a large US survey of predominantly females, aged 54 years of age and older) [8] to up to 43.2% per year (in a small study of older Japanese women) [9]. Variability across studies is likely due to the design features of the studies, as well as the risk factor profile of study participants. Regardless, the available evidence suggests that there is an increased risk associated with OAB, compared to the known risk of falls or fractures among the general older adult population [2].

Chiarelli et al. explored the association between urinary incontinence and risk of falls in community-dwelling adults aged 65 years and older in a systematic review that reported that urgency urinary incontinence was associated with a 1.54-fold increased risk of falls [10]. However, this study considered only self-reported falls (rather than fractures, or falls identified from medical records) and was limited to articles up to 2008 [10]. A more recent review conducted by Noguchi et al. examined the risk of falls and fractures among community-dwelling older men with lower urinary tract symptoms (LUTS), including urgency, frequency, nocturia, and incontinence, and reported a 1.31- to 1.67-fold increased relative risk of falls [11]. Neither of these studies specifically examined the risk profile of individuals with self-reported or diagnosed OAB.

Understanding falls and fractures risk among those with OAB, compared to other causes of urinary incontinence, is important for several reasons. First, given that anticholinergic agents (some of which are the mainstay of pharmacological treatment for OAB) are associated with an increased risk of adverse health outcomes, including the risk of falls [12–16], the risk–benefit profile of OAB patients (in terms of falls and treatment) warrants examination. Second, it is conceivable that the underlying central pathophysiology contributing to OAB could also contribute to falls risk, which is supported by the systematic review conducted by Chiarelli et al. [10].

A comprehensive and formal synthesis of available evidence on the association between OAB and falls and fractures has not previously been conducted [17]. The primary objective of this study was to synthesize estimates of the risk of falls, serious or recurrent falls, and fractures among individuals with idiopathic OAB, compared to those without. As a sensitivity analysis, the same outcomes were examined among patients with OAB-related symptoms or LUTS.

METHODS

Search Strategy

To meet the study objectives, a systematic literature search was conducted in multiple databases, including Scopus, PubMed/Medline, EMBASE, and Cumulative Index to Nursing and...
Allied Health Literature. The design and implementation of the subsequent systematic literature review was guided by PICOS (Population, Interventions/Comparators, Outcomes, Study design) criteria to identify observational studies reporting rates of falls, recurrent falls, serious falls, or fractures among adults with OAB (Supplementary Table 1) published between January 1985 and February 2018 (Supplementary Table 2). The databases were also searched for the most recent year’s conference abstracts. Abstracts where no full manuscripts were available were similarly assessed against the PICOS criteria for inclusion. The reference lists of all included articles were searched for additional references meeting inclusion criteria.

Two researchers independently reviewed all potentially eligible abstracts and full-text publications against the PICOS criteria to identify articles for inclusion, with any discrepancies resolved through consensus. Articles that focused on individuals with diagnosed OAB (or urgency urinary incontinence) were included in the core analyses. To capture studies that reported on OAB symptoms, but that did not classify individuals with diagnosed OAB, studies of individuals with incontinence or LUTS, as a proxy for diagnosed OAB, were included in sensitivity analyses. Articles that reported non-OAB comparison groups were also included. Articles and abstracts were excluded if the sample was restricted to those with a specific non-urological diagnosis (e.g., cancer), non-idiopathic OAB, or institutionalized individuals (where comorbidity burdens would differ from the community-dwelling population).

Data Extraction

Data from eligible articles underwent double data extraction, performed using a customized Microsoft® Excel® workbook. Study characteristics included authors, year, study design, as well as inclusion and exclusion criteria and follow-up period. Patient characteristics included age, sex, treatment status (if available), and the number (%) experiencing falls or fractures.

On the basis of data provided in the original publications, persons who had fallen were categorized according to whether they experienced any fall (at least one fall), recurrent falls (at least two falls), or serious falls (falls that were injurious or required medical attention) over the follow-up period.

Study quality was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for observational studies [18]. A summary of the STROBE assessment is in Supplementary Table 3.

Data Analysis and Evidence Synthesis

Fall and fracture risk estimates from those with diagnosed OAB or from the non-OAB comparison samples were graphed and visually compared. Adjusted and unadjusted risk estimates were summarized by ranges and scatterplots to explore between-study variability and stratified by mean age and sex distribution of the sample. Note, as individual fall risk factors except age and sex were inconsistently reported across studies, only age and sex were used as stratification variables in the analyses.

Estimates of increased risk of falls or fractures, as the unadjusted percent attributable risk (PAR), were calculated by subtracting the percentage without OAB who experienced a fall from the percentage with OAB who experienced a fall from the same studies. Unadjusted PARs were summarized graphically.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Search Results

Of 783 unique, potentially relevant studies identified, 690 were excluded at abstract review (88.1%; Fig. 1), and 59 of the remaining 93 (63.4%) were excluded in full-text review. Nine additional references were identified from hand-searching, resulting in 43 eligible studies. Of these, 15 contributed estimates for the core...
analyses of OAB patients [6, 8, 9, 12, 19–29], and the additional 28 studies contributed only to the sensitivity analyses of individuals with incontinence or LUTS [1, 7, 30–54]. Overall, the included studies were in line with the STROBE criteria reporting recommendations; however, few studies provided details on how the sample sizes were determined, potential biases, or the generalizability of the findings (Supplementary Table 3).

Study Characteristics

Of the 15 studies contributing data for the core analysis, nine (60.0%) reported outcomes among participants with OAB, and six (40.0%) among those with urgency incontinence (Supplementary Table 4). Nine studies (60.0%) measured falls and fractures prospectively, and six (40.0%) measured these retrospectively. Five studies reported on samples from the USA; two studies each from Finland, Japan, and Australia; and one study each from Canada, the UK, Taiwan, and Korea. While 12 studies estimated risks of falls or fractures among OAB vs. non-OAB samples, three compared outcomes within treated OAB samples. Duration of follow-up ranged from 1 month to 3 years. Among the 28 studies included in the sensitivity analysis, 14 (50.0%) measured falls and fractures prospectively, and 14 (50.0%) measured these retrospectively. Additional characteristics of studies included in the sensitivity analysis are presented in Supplementary Table 5.

Risk of Falls or Fractures

Nine studies reported unadjusted estimates of the risk of any fall, or serious or recurrent falls, among those with OAB compared to those without OAB, and one of those studies [9] reported two sets of estimates (for any fall and for recurrent falls) [6, 8, 9, 12, 19, 23–25, 29]. The absolute risk of falls in OAB patients was generally higher among samples of OAB patients who were older, or included a higher proportion of women, and from studies reporting on any fall rather than serious or recurrent falls (Fig. 2). Estimates of the percentage experiencing any fall over a year ranged from 18.9% from a cross-sectional study of 941 Japanese residents 40 years of age and older residing in two municipalities [6] to 50.0% among community-dwelling women attending a geriatric health facility in Japan [9]. Estimates of the percentage experiencing recurrent or serious falls ranged from 11.3% in a sample of Medicare enrollees (mean age, 78 years; 57.4% female) over 3 years for serious falls [29] to 56.0% from a US-based retrospective claims analysis of patients with at least 1 year of follow-up and a mean age of 73 years [12]. Unadjusted PAR for any fall associated with OAB ranged from 3.7% to 15.5% (both over 1 year), and for recurrent or serious falls it ranged from 4.4% to 8.8% (Fig. 3).

Two studies estimated the risk of falls or fractures associated with OAB treatment. One study by Gomes et al. reported that the risk of serious falls among individuals with OAB treated with two different antimuscarinics was similar (0.8% for tolterodine vs. 0.7% for oxybutynin) [20]. In the other study, the unadjusted PAR for any
A fracture was slightly higher among individuals with OAB who had been prescribed an antimuscarinic (3.01) compared to those who had not been prescribed an antimuscarinic (2.77) [28].

Ten studies reported adjusted estimates of the risk of any fall, or serious or recurrent falls, among those with OAB compared to those without OAB; and again, one of those studies [9] reported two sets of estimates (for at least one

Fig. 2 Unadjusted estimates of the risk of falls among those with OAB, according to mean age and the percentage male of the sample.

Fig. 3 Unadjusted estimates of the percent attributable risk of falls associated with OAB, by mean age and the percentage male of the sample.
fall and for recurrent [two or more] falls) [8, 9, 12, 19, 21, 24–26, 29]. While studies consistently adjusted for age and sex, other significant risk factors varied across studies. Of the studies reporting adjusted risk of any falls, there was an increased risk associated with OAB, with estimates ranging from a 1.3- to 2.3-fold. One study did not show an increased risk, but had a very small sample size (n = 26; Fig. 4) [9]. Two studies reporting on serious or recurrent falls showed a 40–60% increased risk associated with OAB. Two studies, one of which was by Gomes et al., looked specifically at the impact of OAB treatment on risk of falls. No difference in risk of serious falls was observed over 3 months between patients with OAB treated with tolterodine vs. oxybutynin (odds ratio [OR] 1.04 [0.95, 1.14]) [20]; and OAB therapy may be slightly protective of the risk of falls (OR 0.88 [0.80, 0.98]) vs. not receiving OAB treatment [29].

Only one study reported unadjusted risk of fractures among those with OAB compared to those without OAB. That study, based on self-reported fractures in the preceding year, reported a 5% risk of any fracture among those with OAB versus a 2.7% risk of any fracture in the non-OAB group, resulting in an unadjusted PAR of any fracture over 1 year of 2.3% [8].

Three studies reported adjusted risk of fractures among those with OAB compared to those without OAB. While point estimates of risk were consistently above 1.0 (range 1.3–1.5), estimates of increased risk were not significant for two of three studies (Fig. 4) [8, 22, 27]. No difference in risk of fractures was observed in either study that examined the impact of treatment [20, 28].

| Author                | Predictor                                    | OR (95% CI)                          |
|-----------------------|----------------------------------------------|--------------------------------------|
| **Falls, Prospective**|                                              |                                      |
| Darkow, 2005a         | OAB                                          | 1.7 (1.6, 1.8)                       |
| Takazawa, 2005        | Urge incontinence                            | 0.6 (NR, NR)                         |
| Brown, 2000           | Urge incontinence                            | 1.3 (1.1, 1.4)                       |
| Noguchi, 2016*        | Urge incontinence                            | 1.9 (1.2, 3.0)                       |
| **Falls, Retrospective**|                                              |                                      |
| Wagner, 2002          | OAB                                          | 2.3 (1.5, 3.5)                       |
| Moon, 2011            | OAB                                          | 1.8 (1.0, 3.1)                       |
| Teo, 2006             | Urge incontinence                            | 1.8 (1.3, 2.4)                       |
| **Falls, Impact of treatment**|                                              |                                      |
| Gomes, 2011**         | Tolterodine vs. oxybutynin                   | 1.0 (0.9, 1.1)                       |
| Jayadevappa, 2018     | OAB treatment vs. no treatment               | 0.9 (0.8, 1.0)                       |
| **Recurrent/serious falls, Prospective**|                                              |                                      |
| Luukinen, 1996        | Urinary urgency                              | 1.6 (1.0, 2.6)                       |
| Jayadevappa, 2018     | OAB or its symptoms                          | 1.6 (1.5, 1.7)                       |
| Yehoshua, 2016        | OAB                                          | 1.5 (1.2, 1.8)                       |
| **Any fracture**      |                                              |                                      |
| Brown, 2000**         | Urge Incontinence                            | 1.3 (1.1, 1.7)                       |
| Wagner, 2002          | OAB                                          | 1.5 (0.7, 3.2)                       |
| Luukinen, 1997        | Urinary urgency                              | 1.5 (0.8, 2.8)                       |
| **Any fracture, Tolterodine vs. oxybutynin**|                                              |                                      |
| Gomes, 2011**         | OAB treatment                                | 1.0 (0.8, 1.2)                       |
| Kao, 2018**           | OAB treatment vs. no treatment               | 1.1 (1.0, 1.3)                       |

Fig. 4 Adjusted estimates of the risk of falls or fractures among those with OAB. *Presented incidence rate ratios rather than odds ratios. **Presented hazard ratios rather than odds ratios
Sensitivity Analysis

In sensitivity analyses, the population was broadened to include any incontinence or LUTS, comprising a wider range of symptoms related to OAB but that may not have been classified as OAB. In this population, unadjusted estimates of the risk of falls among those with incontinence or LUTS were elevated, but less than that observed among those with OAB. Overall, estimates were higher among samples that included older patients or had a higher percentage of women (Supplementary Fig. 1). Adjusted estimates continued to demonstrate an increased risk of falls associated with incontinence or LUTS, although less consistently than for OAB (Supplementary Fig. 2). For fractures, while point estimates from adjusted analyses generally suggested an increased risk associated with incontinence or LUTS, most confidence intervals spanned 1.0 (Supplementary Fig. 2).

DISCUSSION

While OAB and its constituent symptoms, particularly urgency and nocturia, are known risk factors for falls and fractures, the strength of the association is unclear because of variability in the designs and populations of studies contributing estimates of risk. This systematic review and synthesis of published estimates was performed to understand the range of estimates of falls and fractures associated with OAB, and the impact of other factors on that risk. Samples with OAB had consistently elevated risks of falls and fractures compared to non-OAB samples; and the risk among those with OAB was higher with increasing age and proportion of women in the sample. Approximately one-quarter to one-half of patients with OAB were observed to fall annually, and adjusted estimates indicate a 1.3- to 2.3-fold increased risk of falls compared to non-OAB samples. Analysis of serious and recurrent falls showed similar trends, but the magnitude of risk was less. While analysis of fractures showed elevated risk in terms of the point estimates, most studies were designed to estimate falls and were underpowered to detect significant differences in fractures. The sensitivity analyses of incontinence and LUTS showed consistent trends, but with greater variability in estimates, reflecting the greater variability in symptoms and sample characteristics within those studies. These findings extend beyond older systematic reviews that considered a more limited range of fall-related outcomes [10], or urinary symptoms, and did not specifically focus on OAB or its treatments [11], which consistently reported increased risks of falls and fractures among those with other urinary symptoms [10, 11].

The findings from this study highlight both the strength of the relationship between OAB and falls and fractures, and the limited evidence of the impact of any treatment on that risk. In the core analysis, only two studies reported treatment status among cohorts examined for falls and fractures. One compared outcomes over 3 months and found no difference in serious falls among those initiating tolterodine vs. oxybutynin [20], although the time horizon was too short to observe serious falls or fractures and an untreated cohort was not included. The other study noted a slightly protective effect of OAB treatment on falls [OR 0.88 (0.80, 0.98)], but the exact nature of the OAB treatment was unspecified [29]. In the included study by Yehoshua et al. which compared outcomes among non-OAB patients and OAB patients who had initiated treated with anticholinergics, it was reported that the OAB patients were at 46% higher adjusted risk of falls or fractures, and a higher economic burden resulted; because all OAB patients in this study were receiving treatment, it was not possible to isolate the effects of treatment from the effects of OAB, although it is notable that the increased risk of falls or fractures persisted following any symptom control conferred by the antimuscarinic treatment [12].

A recent systematic review of the impact of continence management strategies, including pharmacotherapy for OAB, on falls risk also identified little evidence that such strategies reduce falls, and acknowledged that the increased falls risk associated with anticholinergic medications could counter any observed benefits of continence management strategies in decreasing falls in this population [55].
While the findings of this review support the significant association between OAB and falls and fractures, substantial variability in estimates of risk was observed even after adjustment for other known risk factors. Risk varied according to age and sex of the sample but would have also varied according to the comorbidity burden or presence of other risk factors for falls, which were reported inconsistently across studies. The range in estimates observed highlight the challenges of disentangling the impact of OAB from that of other comorbid conditions and age. While estimates varied considerably by age and sex, the unadjusted PAR estimates were fairly consistent across studies, suggesting that while fall and fracture rates rise with older age and the proportion of the sample that is female, the additive effect of OAB remains constant across age and sex categories.

Strengths and Limitations

Strengths of this study included the application of rigorous systematic review methods to gathering the evidence base. While the core analysis was restricted to those with diagnosed OAB, the sensitivity analysis allowed the inclusion of individuals with a wider range of OAB-related symptoms. Multiple measures of falls and fractures were considered, as were multiple types of estimates of risk. This study has limitations, largely dictated by the quality of the design and extent of reporting of the original articles. As a result of the nature of the research question, the present study was limited to observational studies, which are subject to various biases and different methods of defining OAB cases and/or outcome assessment. Despite being limited by variability across study designs, after assessing the quality of the included studies, the overall quality was considered to be good, with most studies fulfilling more than 50% of the STROBE criteria. Other risk factors for falls and fractures were inconsistently reported across studies, and hampered both the comparison of estimates and the isolation of specific impacts due to OAB from other comorbid conditions. Heterogeneity in study designs and sample characteristics prevented a meta-analysis of falls risk. Variable time horizons were employed across studies and fall and fracture rates could not be annualized. While every effort was made to identify all relevant publications, there may be some published data describing the risk of falls or fractures in OAB patients that were not identified and thus not included in the analysis. Although not examined here, as there is evidence that OAB is associated with frailty in older adults [56], and that frailty may be a risk factor for falls [57], an examination of the role of frailty status as a predictor of falls and fractures may be warranted. Unfortunately, as previously mentioned, as a result of inconsistent reporting of risk factors across included studies, this was not examined in the present study.

CONCLUSION

With the growing number of older adults worldwide, the clinical and economic impact of serious falls and fractures will likely continue to grow. Understanding the contribution of modifiable risk factors therefore becomes crucial. Even after adjustment for other risk factors, OAB remains an important and potentially modifiable risk factor. However, the risk directly attributable to OAB and the impact of medication use remains unclear. Evidence from the published literature clearly demonstrates the importance of OAB and its symptoms as risk factors for falls and fractures.

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**Authorship Contributions.** All others contributed to the study concept and design. Shelagh M. Szabo and Karissa M. Johnston were responsible for the acquisition of data. All authors contributed to the analysis and interpretation of data. Shelagh M. Szabo was responsible for the drafting of the manuscript. All authors contributed to the critical review and editing of the manuscript.

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**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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