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NSAIDs and the Risk of Accidental Falls in the Elderly

A Systematic Review

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Abstract

Accidental falls, especially those occurring in the elderly, are a major health and research topic nowadays. Besides environmental hazards and the physiological changes associated with aging, medication use (e.g. benzodiazepines, vasodilators and antidepressants) and polypharmacy are significant risk factors for falling as well. Exposure to NSAIDs has been associated with accidental falls too, although information on this area is less consistent. Therefore, the main goal of this review is to provide an updated overview of all the evidence published on the risk of falling due to NSAID use thus far. A systematic literature search for material published between 1966 and March 2008 in PubMed, EMBASE, the Cochrane Database of Systematic Reviews, Exerpta Medica, Current Contents and Science Citation Index was combined with a check of the reference lists of all the retrieved articles. Validity and data extraction of the eligible articles was assessed by adapted criteria, based on checklists that were originally developed to assess case-control or cohort studies. From the 16 selected articles, two studies were rejected because of clustering of data and one article was excluded because

it contained the same data as that in one of the included articles. None of the articles retrieved included a randomized controlled trial. The remaining 13 studies all showed some lack in completeness of their statistical methods, and much variation in reporting of effects. The overall mean age was high in the study populations, leaving the results to be poorly generalizable to a larger population and other age categories. Despite these imperfections, all studies showed an increased risk of falling due to NSAID use (four significant, nine non-significant), and a tendency towards an increased fall risk with NSAID exposure could be noted. The results shown in the present review suggest that an increased risk for accidental falls is probable when elderly individuals are exposed to NSAIDs. The studies with the highest quality show that the community-dwelling elderly in particular appear to be at higher risk. This review can serve as a comprehensive overview of the published evidence on fall risk of elderly individuals attributable to the use of NSAIDs, and as an inducement for future research.

1. Accidental Falls

With the number of elderly steadily increasing, and their mean age rising, the (physical) problems that come with age will need more and more attention. Accidental falls, for example, have become a major health and research topic in terms of causes, consequences and prevention, and 400 potential risk factors have already been identified.[1-5] A crude way to classify these risk factors is the segmentation into intrinsic and extrinsic factors.[6,7] Since this segmentation is still more or less ambiguous, the Effective Health Care Bulletin[1] managed to classify potential risk factors for falls and injury into five classes: medication related factors, changes and medical conditions associated with aging, environmental hazards, lack of exercise and nutrition.

1.1 Medication-Related Risk Factors for Accidental Falls

Medication-related factors comprise the use of drugs such as benzodiazepines, vasodilators, antidepressants, NSAIDs and polypharmacy.[8-12] A Canadian study showed that 27% of elderly individuals (>65 years of age) hold a current or recent NSAID prescription.[13] Common adverse effects of NSAIDs include gastrointestinal and central nervous system problems. The latter consist of dizziness, headaches, mood alteration and confusion,[14] consequently putting elderly individuals at a greater risk for accidental falls. The focus of this review will be on NSAID exposure as a risk factor for falls in particular.

Many researchers have studied the risk factors associated with medication-related falls.[5,13,15] Russell et al.,[11] for instance, studied 300 community-dwelling individuals and identified polypharmacy as a risk factor for falls in 79% of the admissions to the emergency department. However, Ziere et al.[16] showed that polypharmacy itself is not a risk factor for falling unless a drug known to increase the risk of falls is part of the drug regimen. In fact, the odds of falling increased when drugs known to increase fall risk (e.g. benzodiazepines) were used; from 1.3-fold when one such drug was used, to 2.5-fold when two such drugs were used concomitantly, compared with the fall risk when no drugs known to increase fall risk were used.

The NSAIDs were not considered to be a drug class associated with an increased fall risk. Nevertheless, there have been a few attempts to study the relationship between other specific drug classes and falls, including some on NSAIDs. In 1999, Leipzig et al.[17] published a systematic review and meta-analysis on cardiac and analgesic drugs. The authors found a slight non-significant increase in fall risk in elderly individuals exposed to NSAIDs. However, since then, several new studies have appeared and therefore there is a

need for an updated version. Our goal is to provide an updated systematic review of all studies published thus far that present odds ratios (ORs) for the risk of falls due to NSAID use.

2. Study Identification and Selection

Medical subject headings and text words were used to perform a systematic search for material published between 1966 and 31 March 2008. Our core search terms were 'accidental falls' or 'falls', combined with 'anti-inflammatory non-steroidal agents/drugs' or 'NSAIDs' or 'drugs'. This way, a total of 995 articles were retrieved from the electronic databases PubMed and EMBASE, which we used as the primary databases for our search. The Cochrane Database of Systematic Reviews as well as the databases Excerpta Medica, Current Contents and Science Citation Index were secondary databases and revealed no new material.

Studies were eligible for inclusion if they were published in English, German or Dutch. They also had to involve NSAIDs and present an odds ratio (OR) for accidental falls, or percentages or numbers of those who had experienced falls with NSAID exposure. Two reviewers independently screened titles and abstracts on these inclusion criteria. After administration of these criteria, full-text copies of the remaining studies were obtained. In case a study was included but lacked relevant data, first authors were asked to provide the raw data on numbers of those who had and had not experienced falls with and without the use of NSAIDs.

Amongst the 995 articles retrieved, there were no randomized controlled trials, controlled trials or highly controlled trials, controlled before-and-after studies or interrupted time-series studies. Only one systematic review and meta-analysis on cardiac and analgesic drugs was found,[17] and its references were used to check suitability for our review.

3. Methodological Evaluation

Based on checklists that were originally developed to assess case-control or cohort studies, we formulated adapted criteria as described in the following two sections. [18,19] Validity and data extraction of the articles were assessed by means of these criteria, and were scored according to four levels: sufficient [++]; moderate [+]; insufficient [–]; or inapplicable [o].

3.1 Criteria for Validity Assessment

V1: This criterion tested whether there was sufficient controlling for possible confounders. Confounders had to be identified in the article, and the results had to be adjusted for them. For this review, relevant possible confounders were age, gender and co-morbidity.

V2: The selection criteria for cases and the rationale for controls were tested. Cases were persons who had experienced one or more accidental fall. Controls were defined as persons who had not experienced an accidental fall.

V3: We judged the selected study design in relation to the study aim. A cohort study (prospective/historical) was considered appropriate when all persons who were using NSAIDs were included and, thereupon, for a fixed period of time, the number of accidental falls was observed and counted. A case-control study was considered suitable when NSAID exposure was checked after all accidental falls were counted in a defined period of time.

V4: This criterion tested whether appropriate measures were taken to address potential sources of bias. The sources of bias can be defined as a distortion of evidence or data that arise from the way that the data are collected. Sources that were considered relevant for this review were selection bias and information bias. Selection bias was defined as the composition of the study groups showing failures. Information bias was defined as weakness in the measurement of the medication exposure in the study groups.

V5: Statistical methods related to study design were evaluated. The emphasis was on matching, group comparison, control for confounding and handling of missing data. Logistic regression, Mantel Haenszel technique or stratification of the OR were considered adequate statistical methods.

3.2 Criteria for Data Extraction

D1: This criterion assessed whether the inclusion and exclusion criteria were described.

Whether the base population from which the study groups were selected was described properly was also assessed.

D2: Appropriate reporting of effects in terms of statistical (ORs with 95% confidence intervals [CIs]) as well as quantitative measures (e.g. number of cases and controls) were assessed in this criterion.

D3: It was judged if control for confounding was applied to the data by means of showing stratified adjusted odds ratios.

D4: Description of the exposure was assessed in this criterion. We defined two levels of description. First, extensive description (E): mention of specific drugs with their dose. Second, simple description (S): NSAIDs only mentioned as a group, without any information on dose.

D5: This criterion tested whether the results of the study could be generalized to a larger population, including different age categories.

Two reviewers (JH and BvdB) independently evaluated the quality of the selected articles using the structured checklist and a data-collection form. To extract corresponding data, NSAIDs were defined not to be equivalent to analgesics or aspirin (acetylsalicylic acid). The definition for an accidental fall used was the one provided by the Prevention of Falls Network Europe, i.e. "an unexpected event in which the participant comes to rest on the ground, floor or lower level".[6]

First-round agreement was achieved in six articles. The rest were reassessed until both reviewers reached consensus.

4. Overview of Research on NSAIDs and Accidental Falls

The initial 995 studies that were retrieved from the electronic databases were reduced to 15 articles that met our inclusion criteria for detailed data abstraction (figure 1). We divided this selection into two groups: observational studies (n = 14); and systematic reviews (n = 1). The studies used in the systematic review revealed no new articles compared with those already retrieved, whereas checking the references of the 14 regular studies yielded another 2 articles that met the inclusion criteria for our review. From this total of 16 selected articles, 3 studies were rejected. This was because of the clustering of data on analgesics together with NSAIDs in two articles,[20,21] and one was excluded because it contained the same data as that in one of the included articles.[22] All together, these rejections resulted in 13 studies[23-35] eligible for our review.

Table I identifies differences in settings, sample size and characteristics of the populations and study designs. What is most striking is the large variety in sample sizes and the overall high mean age. In all studies, over 50% of those who had experienced falls were female. In two studies,[24,28] significantly more of the cases were females than in the control group; in one of these studies,[24] the cases were significantly older than the control group as well. Of the 13 eligible studies, there were 9 case-control studies, 3 prospective studies and 1 cross-sectional study. Six studies involved

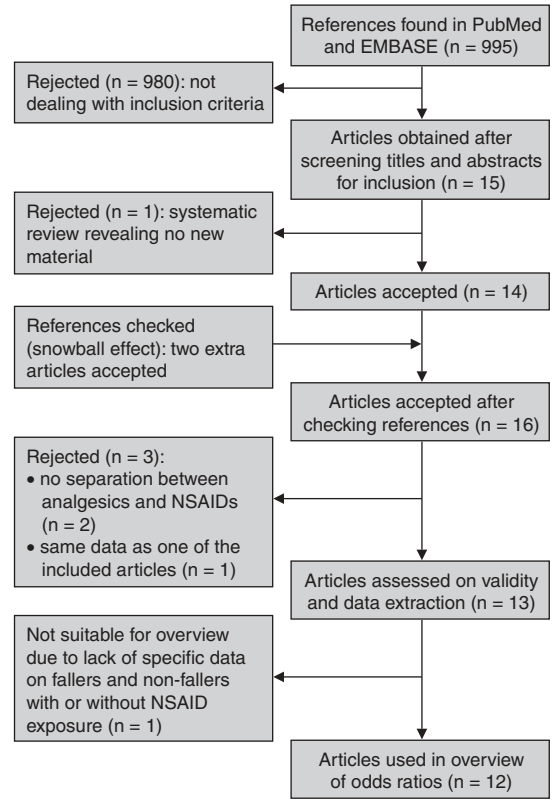

Fig. 1. Flowchart of the selection and inclusion of articles.

Table I. Differences in settings, sample size and characteristics of the populations and study designs

Study (y)	Study design	Study setting	Sample size	NSAID use	Mean age (y)	% Female	Confounders[a]
Kerman and Mulvihill[25] (1990)	Case-control	LTC	Ca: 57 Co: 90	Ca: 30 Co: 32	Ca: 87.2 Co: 85.5	Ca: 79 Co: 87	
Lipsitz et al.[28] (1991)	Case-control	LTC	Ca: 70 Co: 56	Ca: 21 Co: 13	Ca: 87.0 Co: 87.0	Ca: 73[b] Co: 48	Age, gender, co-morbidity
Myers et al.[31] (1991)	Case-control	LTC	Ca: 184 Co: 184	Ca: 22 Co: 9	Ca: 83.0 Co: 80.7	Ca: 68 Co: 76	
Ryynänen et al.[33] (1993)	Case-control	CD Ca: 83% Co: 97%	Ca: 380 Co: 342	Ca: 126 Co: 51	Ca: 79.1[b] Co: 73.8	Ca: 77 Co: 72	Age, co-morbidity
Yip and Cumming[35] (1994)	Case-control	LTC	Ca: 71 Co: 55	Ca: 15 Co: 7	Ca: 82.3 Co: 81.7	Ca: 66 Co: 65	Age, gender, co-morbidity
Lord et al.[29] (1995)	Prospective	CD	362 Ca: 73 Co: 289	 Ca: 24 Co: 65	74.0	100	Age, co-morbidity
Koski et al.[26] (1996)	Prospective	CD	979		>70.0	62	Age, gender
Mustard and Mayer[30] (1997)	Matched case-control	LTC	Ca: 1486 Co: 1486	Ca: 260 Co: 234	Ca: >75.0 Co: >75.0	Ca: 78 Co: 78	Age, gender, co-morbidity
Nikolaus et al.[32] (1999)	Prospective	CD	279 Ca: 120 Co: 159	 Ca: 29 Co: 91	81.6	73	
Kelly et al.[24] (2003)	Case-control	CD	Ca: 2278 Co: 9112	Ca: 159 Co: 547	Ca: 78.5[b] Co: 74.5	Ca: 69[b] Co: 57	Age, gender, co-morbidity
Kallin et al.[23] (2004)	Case-control	LTC	Ca: 301 Co: 3303	Ca: 26 Co: 187	Ca: 83.1 Co: 83.3	Ca: 66 Co: 68	Age, gender
Walker et al.[34] (2005)	Case-control	LTC	Ca: 62 Co: 62	Ca: 30 Co: 11	Ca: 74.9 Co: 74.5	Ca: 52 Co: 50	
Lee et al.[27] (2006)	Cross-sectional	CD	4000 Ca: 1024 Co: 2976	 Ca: 61 Co: 112	72.5	60	Age, gender

a Odds ratio adjusted for these potential confounders.

b Significant difference between cases and controls.

Ca = cases; **Co** = controls; **CD** = community dwelling; **LTC** = long-term care facility.

community-dwelling persons; the remaining studies investigated accidental falls in persons living in a long-term care facility.

The outcomes of the assessment of validity and data extraction are presented in table II. None of the studies complied with all ten criteria used in this assessment. From the aspect of validity, all studies show some lack in completeness of their statistical methods; correction for possible confounders was sufficiently carried out in only four studies. The selection of cases and controls, and the selected study design were adequate in all but one study.

Data extraction showed more inconsistencies; in particular, the specification of the base population and the inclusion and exclusion criteria, and adequate reporting of effects varied greatly. Only one study presented an extensive description of the medication exposure. The results of most studies were judged to be difficult to generalize to a larger population and different age categories. This was mostly as a result of the overall high mean age of the study populations.

Figure 2 shows an overview of the ORs of 12 studies with their 95% CI and was created with the benefit of StatsDirect statistical

Table II. Outcomes of the assessment of validity and data extraction of the eligible articles[a]

Study (y)	V1	V2	V3	V4	V5	D1	D2	D3	D4	D5
Kerman and Mulvihill[25] (1990)	–	++	++	+	–	+	–	–	S	–
Lipsitz et al.[28] (1991)	+	++	++	+	+	++	++	+	S	+
Myers et al.[31] (1991)	+	++	++	++	+	+	+	+	S	+
Ryynänen et al.[33] (1993)	+	++	++	++	+	+	+	–	S	+
Yip and Cumming[35] (1994)	++	++	++	++	+	++	++	++	S	+
Lord et al.[29] (1995)	+	++	++	+	+	++	+	+	S	+
Koski et al.[26] (1996)	+	++	++	++	+	++	+	+	S	+
Mustard and Mayer[30] (1997)	++	++	++	++	+	+	++	+	S	+
Nikolaus et al.[32] (1999)	–	++	++	++	+	+	++	–	S	–
Kelly et al.[24] (2003)	++	++	++	++	+	++	++	++	S	++
Kallin et al.[23] (2004)	+	++	++	+	+	++	++	–	S	+
Walker et al.[34] (2005)	–	++	++	+	+	++	++	–	E	+
Lee et al.[27] (2006)	+	++	+	+	+	++	++	++	S	++

a Four scoring levels were used: sufficient [++], moderate [+], insufficient [–], or inapplicable.

V1 = possible confounders; **V2** = selection criteria cases and controls; **V3** = study design related to study aim; **V4** = address of potential sources of bias; **V5** = statistical methods related to study design. **D1** = description inclusion and exclusion criteria; **D2** = reporting of effects; **D3** = control for confounding; **D4** = description of medication exposure (**E** = extensive, **S** = simple); **D5** = generalizability. See section 3 for a more detailed explanation of symbols.

software© (version 2.6.7 [13 May 2008]; StatsDirect Ltd, Cheshire, UK). One study is not included in this final overview. It presented an OR of 1.7 (95% CI 0.95, 3.10); however, it was impossible to retrieve the raw data needed.[26] The ORs calculated in figure 2 are based on raw data on those who had experienced falls and those who had not, with and without NSAID exposure. Again, a large variety between the studies is observed; ORs, 95% CIs, as well as sample sizes show vast differences. In this figure, with four studies presenting a significantly increased OR and eight studies presenting a non-significantly increased OR, a tendency towards an increased fall risk with NSAID exposure is suggested.

5. Comparison with Other Drug Classes

The main goal of this study was to provide an updated overview of all evidence published on ORs and falls due to NSAID use. Thirteen studies turned out to be eligible to reach this goal; none of them were randomized clinical trials. Several studies presented an OR between 1 and 2. This is in the range of the OR for accidental falls for benzodiazepines – a drug class known to increase the risk of falls – identified by Ziere et al.[16] (OR 1.3; 95% CI 1.0, 1.9). In line with this finding, Leipzig et al.[36] presented an OR for accidental falls of 1.48 (95% CI 1.23, 1.77) in elderly people exposed to benzodiazepines. Moreover, Ensrud et al.[37] found a 51% increased risk for falling in older women using benzodiazepines. These findings imply that elderly individuals taking NSAIDs can indeed be at a higher risk of accidental falls, even at a similar level as those taking drugs already well known to increase the risk of falls.

In 1999, Leipzig et al.[36] conducted a systematic review and meta-analysis on psychotropic drugs to evaluate the evidence linking these risk drugs with accidental falls in older people. They found a small association between the use of most classes of psychotropic drugs and falls, but the evidence was methodologically similar to the findings in the present review. Even though there is more knowledge about evidential value in studies nowadays, heterogeneous methodology and therefore the lack of univocal results is still a common phenomenon.

6. Effects of Variability in Methodology

For the present review, it was clear that there was a large variability in the studies selected. This

finding is concordant with the conclusion of Leipzig et al.[17] in their review on cardiac and analgesic drugs. The two elements all studies had in common were that they were solely based on observational data and the high mean age of the study population (on average >75 years). Moreover, the heterogeneous methodology and diversity on many aspects of the studies was striking. Major aspects such as correction for possible confounders, sample size and possible generalization of the outcomes to a larger population varied widely. Even the kind of populations and falls that were included showed dissimilarities. No single definition of an accidental fall was used as a designated standard. One study comprised injurious falls only, thereby very likely biasing the OR, since injurious falls represent only a minority of all falls in elderly populations.[33] Nevertheless, all included studies present an increased OR, and their results imply that there is a tendency towards an increased risk of accidental falls when elderly individuals are using NSAIDs.

6.1 Selection Bias and Information Bias

One of our validity criteria involved the assessment of selection bias and information bias. After assessing all eligible articles, more possible sources of bias were apparent, but they did not concern all studies. First, is the problem of recall bias regarding falls. There is published evidence that retrospective reporting of falls in older people is an aspect that biases the estimated risk of an accidental fall.[38,39] Consistent with Ganz et al.,[38] Mackenzie et al.[39] concluded that retrospective self-reporting of falls is less accurate than prospective calendar-recorded fall data. They also found that an injurious fall does not, by definition, result in a better recall of falls. This is in contrast to Ganz et al.,[38] whose systematic literature review showed that patients with injurious falls were more likely to recall their falls. In addition to self-reported falls, caregivers can report falls as well. The question arises whether this method of reporting is free of bias. It is likely that an accidental fall in dependent frail elderly will be remembered and reported more easily compared with a fall in more independent elderly. Bearing this in mind, the chances are that the actual number of accidental falls is higher, thereby leaving the interpretation of the results presented in the selected studies with some uncertainties.

6.2 Recall of Medication Use

Second, is the recall of medication use. Accurate identification of medication exposure by retrospective (self) reporting showed inconsistencies as well. Misclassification of medication exposure can either be due to medicines that are only provided or used when needed, or to a single

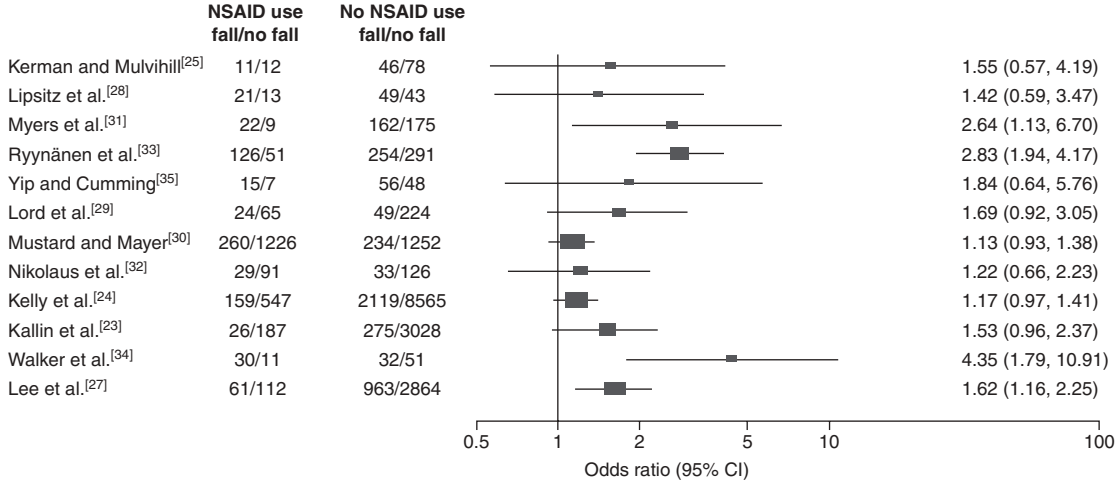

Fig. 2. Forest plot of the odds ratios (and 95% CIs) presented in each of the 12 studies. The black squares represent the sample sizes.

measurement of exposure, which does not provide for the most up-to-date exposure.[23,30,40] Another aspect that interferes with accurate identification of medication exposure is the use of over-the-counter (OTC) drugs. Non-aspirin NSAIDs in particular are often used as OTC drugs. Use of these drugs is usually poorly recalled.[41] Lewis et al.[41] studied the use of non-aspirin NSAIDs in 1889 subjects (median age 54 years) over an 8-week period. In this period, 17.5% used prescribed non-aspirin NSAIDs, and more than twice this number (44.2%) used OTC non-aspirin NSAIDs. In line with this finding, Sawyer et al.[42] showed that taking OTC pain medication was associated with lower odds for taking prescribed pain medication (OR 0.50; 95% CI 0.4, 0.7). Since in this current review none of the assessed articles showed data on OTC medication, it remains unclear in what way possible use of OTC medication might have influenced the results. In future studies, researchers should take this possible influence into account.

7. More Complications in Fall Risk Assessment

Another factor that complicates fall risk assessment is the use of medications in general. Up to 80% of elderly individuals suffer from chronic diseases,[5,43,44] and the oldest individuals in particular usually require long-term medical treatment and several medications. Deterioration of physical and mental health status, and increasing age were found to be associated with the use of more medications.[45-47] Nevertheless, there are numerous studies that have consistently found that polypharmacy or just an increase in the number of medications used by a patient can result in up to a tripling of the risk of falling.[21,28,32] Yet, Lawlor et al.[44] showed that chronic diseases and multiple pathology were more important predictors for falling than polypharmacy. They found a strong linear association between the number of drugs taken and the individual experiencing an accidental fall. However, after adjusting for chronic diseases and other potential confounding factors, this association turned out to be non-significant. Similarly, NSAIDs are mostly prescribed for (chronic) diseases of the locomotor apparatus, which themselves are a risk factor for falls.[44,48,49] Given that correction for possible confounders is generally poor in most (observational) studies on medication use and the assessment of fall risk, confounding by indication is very likely to be the backdrop of the fall risks presented.

8. Conclusions

The results shown in the present systematic review suggest that an increased risk for accidental falls is probable when elderly individuals are exposed to NSAIDs. Given that correction for possible confounders is generally poor in most (observational) studies on medication use and the assessment of fall risk, confounding by indication is very likely to be the backdrop of the fall risks presented. Bearing this in mind and considering the high incidence of co-morbidity in the elderly, caution should be exerted when interpreting the results of studies about medication use and fall risk. Nevertheless, this review can serve as a comprehensive overview of the published evidence on fall risk of elderly individuals due to the use of NSAIDs thus far, and as an inducement for future research with more evidential value. Taking the incidence of falls and their consequences in the growing population of elderly individuals, exemplary future research should comprise large randomized controlled trials, along with improved prospective and extensive measuring of falls and medication use.

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