

# Falls and medications in the elderly

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## INTRODUCTION

Falls are common in the elderly and contribute to morbidity and mortality. Elderly people are often on a variety of medications as well, and this suggests a causative relation between use of medicine and falls. However, the evidence available to support this assumed relationship is not very robust. In this article, we will discuss specifically the medications that are presumed to be associated with falls. Falls in older people are a major public health problem with significant consequences for individuals, their families, and healthcare providers. The incidence of hip fractures increases with age. In the over 65 year olds, the rate of hospital admissions due to fractures from falls is increasing.<sup>1</sup> There has been a doubling of the hospital admission rate for patients >65 years with a hip fracture in the Netherlands during the last 20 years.<sup>2-4</sup> This has resulted in an enormous increase in the costs of intramural and extramural healthcare. In addition to an influence on morbidity and mortality, falls have a negative effect on daily life activities and quality of life. This is especially so when the fear of falling leads to avoidance behaviour, which promotes inactivity with a further deconditioning of musculoskeletal function, propensity to inactivity and social isolation, all facilitating new falls.<sup>5</sup> In the elderly, falls represent a multifactorial problem which should be regarded as the result of complex interactions between intrinsic factors and factors relating to environment and the specific situation. Judicious application of medications that enhance the likelihood of falling probably contributes to prevention of an important cause of morbidity in the elderly.<sup>6</sup> Recent data from the Dutch Foundation for Pharmaceutical Statistics (SFK) have revealed that salicylates used as an antiplatelet agent,

temazepam, furosemide and oxazepam (also see: [www.sfk.nl](http://www.sfk.nl)) are among the medicines most frequently taken by elderly patients (>65 years).

Pathophysiology of orthostatic hypotension is discussed and changes in the pharmacokinetics and pharmacodynamics due to ageing are addressed. A focus will be on the evidence currently available on medication as a risk factor for the occurrence of dizziness and falls. Osteoporosis and effects of medications on reaction time are beyond the scope of this review.

## DEFINING THE PROBLEM

For elderly people aged >65 years who live in the community, the risk of falling varies from 25 to 40% a year,<sup>2,3,7,8</sup> while for the institutionalised elderly this can be as high as 70%.<sup>9</sup> The incidence of falls increases with age and is greater in women.<sup>10-12</sup>

At least 5% of community-dwelling elderly >65 years will suffer from a fracture related to a fall. Especially fractures of the hip result in hospital admission<sup>4</sup> with a death rate within the following year of 20 to 30%.<sup>13-15</sup> The same percentage of elderly people is admitted to a nursing home because of remaining disability.<sup>13,14</sup>

## PATHOPHYSIOLOGY OF ORTHOSTASIS

Normovolaemia may be defined as the effectively circulating volume of a healthy person in the supine position.<sup>17</sup> A change in posture to the upright position elicits a shift of

~300 to 800 ml of blood from the chest to the lower parts of the body. To maintain cardiac output, the consequent fall in ventricular filling volume must be met by continuous adjustment of arterial and venomotor tone and by regulating cardiac contractility and chronotropy.<sup>18</sup> Humans can stand upright for long periods of time. Their orthostatic circulatory adaptation is provided by the evolution of an effective set of neuromuscular and circulatory mechanisms that are largely involuntary or autonomic, aiming to preserve arterial pressure as the controlled variable, independent of gravity. The arterial baroreflex is the well-known example of short-term control acting within the single heartbeat, while the more slowly acting but extremely powerful humoral-cardiovascular-renal system secures body fluid control, provided the fluid intake is normal.<sup>19,20</sup>

Orthostatic stress affects cerebral perfusion pressure and the cerebral autoregulatory system aims to limit the postural reduction in perfusion of the brain. Nevertheless assumption of the sitting or standing position affects cerebral perfusion and regional cerebral oxygenation in healthy humans.<sup>21-23</sup>

#### Age-related changes

Although function and efficacy of cardiovascular reflex activity change with increasing age,<sup>24,25</sup> arterial pressure in the upright position is usually well maintained.<sup>26</sup> In addition, the magnitude of the blood volume declines with age but its possibly disadvantageous effects are offset at least in part by the concurrent decline in venous compliance limiting the volume of blood pooled. This explains the increased susceptibility of elderly patients for diuretic treatment interfering with the maintenance of blood volume and thus orthostatic tolerance.<sup>27,28</sup>

Postural stress affects cerebral oxygenation in the elderly<sup>29</sup> but it is as yet uncertain whether this is related to a decline in autoregulatory capacity.<sup>30</sup> Orthostatic tolerance in the elderly is reduced,<sup>31</sup> and blood pressure and cerebral perfusion are affected further for at least for ~45 to 60 minutes following a meal.<sup>32-36</sup> Postprandial hypotension is defined as a >20 mmHg postural drop in systolic blood pressure but this cut-off point should be regarded as less relevant with respect to the development of orthostatic symptoms.<sup>16</sup> Especially in elderly people with hypertension a limited reduction in blood pressure may already elicit symptoms of cerebral incompetence.<sup>37</sup> Following a meal, instead of resting, walking may benefit postprandial blood pressure and development of symptoms.<sup>38</sup> Moderate exercise training expands plasma volume and enhances leg muscle tone limiting orthostatic venous pooling and supporting orthostatic tolerance.<sup>39</sup> In the elderly the use of medicines and time of a meal may interfere with orthostatic tolerance in a complex way.

## AGE-RELATED CHANGES OF PHARMACOKINETICS AND PHARMACODYNAMICS

In the elderly, the rate of absorption of most drugs administered orally is almost identical to that of younger people, but with ageing marked changes in body components affect the distribution. Body fat as a proportion of body weight increases by over 35% from the age of 20 to 70 years. There is a concurrent decrease in plasma volume of 8% with normal ageing; lean body mass and total body water decrease approximately 17%<sup>40</sup> with an increased rate of adverse effects of both lipophilic (for example diazepam: large volume of distribution) and hydrophilic medications (high plasma concentration). Also the metabolism of many medicines changes with ageing. Hepatic biotransformation is a prerequisite for drugs with limited renal clearance. There is a modest decrease in the efficiency of phase I reactions (oxidative and hydroxylation processes), reactions generally mediated by the mixed-function monooxygenase system (cytochrome P-450 system). In contrast, phase II reactions (by conjugation enzymes and transferases) are generally unaffected and in older vs younger patients drugs metabolised by phase II processes only are preferable. Drugs known to have a strong 'first pass' effect, such as metoclopramide and opiates, should be used in low doses. Renal drug excretion includes glomerular filtration, tubular secretion, and in a varying degree, tubular reabsorption as well. The half-life of a drug is directly related to the volume of distribution and inversely related to its clearance (metabolism and excretion). In the majority of elderly people renal function is diminished due to a reduction in both renal blood flow and number of functional nephrons with an increased half-life for drugs that depend on renal function for elimination.<sup>41</sup> Insight into the effects of ageing on pharmacodynamics, probably through disease-related changes in target organs, diminished reserve capacity and changes in receptor function of end organs, is limited.<sup>42</sup> As an example, the plasma concentration of diazepam required to achieve a certain level of sedation is much lower in the elderly than in subjects aged 30 to 50 years. An increased sensitivity has also been shown for opiates, anticholinergic and antihypertensive drugs and dopamine agonists. In contrast, the susceptibility of older vs younger patients for  $\beta$ -blockade and insulin<sup>40</sup> is reduced. From this viewpoint, data from literature concerning antipsychotics, (tri)cyclic antidepressants, anticonvulsive and cardiovascular medications are discussed.

## MEDICAL CAUSES AND RISK FACTORS FOR DIZZINESS AND FALLS

Theoretically, randomised controlled trials are likely to provide the evidence to prove the causal relationship between medication use and falls. When addressing the

specific cause of falls, the rate of falls must be known both in the intervention and the control group but such evidence is only rarely available. Data on the relationship between drugs and falls are usually derived from observational studies, for instance from cohort or patient-controlled studies, rendering interpretation of results difficult. The majority of studies and reports available suggest a relationship between number of medications and the risk of falls.<sup>9,40,43-53</sup> Also a recent change in dosage of drugs is associated with an increased risk of falls. The use of psychotropic medication is regarded as a risk factor for falls.<sup>40,54,55</sup> Psychoactive medication likely contributes to the occurrence of falls by affecting balance, partly because of the extrapyramidal side effects, dizziness and postural hypotension<sup>56</sup> in addition to a delayed reaction time, with a higher incidence if combinations of medications are used. A fall resulting in hospital admission in the elderly is likely to be regarded as a side effect of drug treatment.<sup>57</sup> The risk of falls in the elderly is increased with postural instability, regardless of the cause which can range from acute illness with fever and dehydration, the use of a specific drug affecting plasma volume or the reaction time to floor covering. The risk of a second fall within one year is increased especially in elderly individuals on benzodiazepines, neuroleptics or anticonvulsants.<sup>58</sup> Tables 1 and 2 give the odds ratios of psychoactive agents and falls.

**Table 1**  
*Pooled OR for associations between use of various psychotropic medications from 40 nonrandomised controlled trial<sup>46,63</sup>*

<b>Benzodiazepines</b>	OR 1.48 (95% CI 1.23-1.77)
Short-acting	OR 1.44 (95% CI 1.09-1.90)
Long-acting	OR 1.32 (95% CI 0.98-1.77)
<b>Antidepressants</b>	OR 1.66 (95% CI 1.38-2.00)
TCA's	OR 1.51 (95% CI 1.14-2.00)
SSRIs: low dose	OR 1.50 (95% CI 1.30-1.70)
high dose	OR 2.40 (95% CI 1.70-2.20)
<b>Neuroleptics</b>	OR 1.50 (95% CI 1.25-1.79)

OR = odds ratio; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor.

**Table 2**  
*Psychotropic medication from nonrandomised controlled trials<sup>46,63</sup>*

<b>Benzodiazepines</b>	
Short-acting	Lorazepam, oxazepam, temazepam, alprazolam, triazolam, bromazepam
Long-acting	Flurazepam, chlordiazepoxide, clonazepam, clorazepate, diazepam, prazepam
<b>Antidepressants</b>	Tricyclic antidepressants, selective serotonin reuptake inhibitors
<b>Neuroleptics</b>	Phenothiazines, butyrofenones

## PROBLEMS CONCERNING RESEARCH OF FALLS AND MEDICATIONS

The available data from studies on risks of falls are difficult to compare because of the different definitions used for falls, the nature of the analysed risks, and the populations interrogated. Confounding by indication remains a most important consideration in pharmacoepidemiology.

Polypharmacy in the elderly is associated with an increased risk of falling, but it is equally likely to result from physical and mental frailty.<sup>40,52,59,60</sup> When interpreting epidemiological data it should be considered that in the majority of studies subjects in poor health were excluded from analysis, with gross underestimation of adverse drug events. In addition, the design of many studies focussed primarily on risk factors rather than on drugs.<sup>40</sup> Lumping together several groups of medications (excluding all psychoactive drugs) and poor recording of actual medication use at the time of the fall in many studies has limited the opportunity to identify specific drug classes. In addition, recall of falls and sample size to detect a moderate increase in drug risk is often insufficient, a methodological error common to many studies addressing adverse events of drugs.

### Neuroleptics

All classes of neuroleptics increase the risk of falling, but through different mechanisms, including enhancement of extrapyramidal disturbance, syncope,  $\alpha$ -blockade, sedation, postural hypotension and/or cognitive impairment.<sup>61-63</sup>

### Tricyclic antidepressants and selective serotonin reuptake inhibitors

A prerequisite for appropriately identifying falls as adverse events from the use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) is that a distinction is made between studies conducted in normal volunteers and those with symptoms of depression. When comparing drugs, the risk of falling relates to the sedative characteristics of the drug used. The risk of contracting a fractured hip is increased in elderly patients on tricyclic antidepressants, probably related both to the drug itself and to depression or confusion.<sup>47</sup> Confounding by indication can be of influence on the results of studies. In a recent study that corrected for indication by indication, an influence of prescription was no longer detected.<sup>58</sup>

In elderly patients on antidepressants, sedation with psychomotor retardation has been proposed as the most likely cause of falls.<sup>64</sup> When using TCAs, orthostatic hypotension (as a result of  $\alpha$ -blockade) and cardiac arrhythmias are the most important factors contributing to falls. When using SSRIs, the risk is comparable<sup>65-68</sup> or even larger<sup>58</sup> than the risk with TCAs.

Polypharmacy in the elderly enhances the chance of interaction between drugs. Some SSRIs are strong inhibitors of isoforms of the cytochrome P450 system with important pharmacodynamic interactions.

No pharmacokinetic interaction was reported for dopamine agonists and SSRIs. On theoretical grounds interaction between ropinirol and fluvoxamine is likely because of the inhibition of metabolism of ropinirol through CYP1A2 by fluvoxamine.<sup>62</sup>

### **Benzodiazepines**

In normal volunteers, benzodiazepines impair function in tests of postural sway, they delay reaction time, cause ataxia, reduce proprioception during the period corresponding to the drug's elimination half-life<sup>69,40</sup> but for the elderly the results are less uniform. Although in most studies a correlation between long half-life time and falls is confirmed, there is also evidence that benzodiazepines with a short half-life also lead to an increased risk of falls.<sup>58,70</sup> In one study the dose was more important than the half-life as such.<sup>71</sup> In elderly patients in general, side effects are more serious for each dose, regardless of the dosage, due to the mentioned changes in pharmacokinetics and pharmacodynamics.<sup>72</sup>

### **Anticonvulsants**

The following side effects of anticonvulsants may be related to falls: sedation, dizziness and balance disturbances. In one study the likelihood of falling ( $\geq 1$ ) for women taking anticonvulsants vs controls almost doubled, as did the rate of falling.<sup>58</sup>

### **Cardiovascular drugs**

A relationship between usage of antihypertensive agents, diuretics or nitrates and the occurrence of falls in the elderly may seem plausible but it is hard to prove. In a meta-analysis of 29 nonrandomised studies addressing the relationship between cardiovascular drugs and falls in the elderly, a weak relationship could only be found for digitalis, type 1A antiarrhythmic drugs and diuretics.

The evidence was, however, weak and based merely on observations with minimal correction for confounders, dosage or duration of treatment.<sup>45</sup> From a practical viewpoint, in the absence of firm evidence it is worthwhile to reconsider diuretic treatment in the elderly<sup>73</sup> although in a meta-analysis of randomised, cohort and patient-controlled studies no clear causal relationship between diuretic treatment and falls could be identified.<sup>74</sup> Polypharmacy is common and this is especially so in cardiovascular disease with chronic heart failure as an example, involving combination treatment with ACE inhibition,  $\beta$ -adrenergic blocking agents and often diuretics as well. The occurrence

of orthostatic hypotension is a side effect of treatment aiming at left ventricular afterload reduction. Nevertheless a meta-analysis of 15 randomised trials regarding antihypertensive treatment in  $>21,000$  subjects  $>60$  years of age for at least a year did not reveal an increased fall rate.<sup>75</sup>

## **INTERVENTIONS**

### **Reduction in total number of medications**

When starting a drug or changing its dosage, one must decide whether it is clearly indicated and also if the benefits of the prescribed drug counterbalance its possible adverse effects, especially in the case of benzodiazepines, neuroleptics, antidepressants, anticonvulsants and cardiovascular medications. If a drug is indicated, it may be an option to choose a drug from a different class. In addition, in the elderly, periodical evaluation of the indications for drug treatment and/or consideration of dosage reduction is warranted. The ultimate goal is to optimise daily functioning with a maximum of profit from drug treatment and a minimum of adverse effects, such as falls. In a single randomised double-blind trial addressing stopping of psychotropic drug treatment in institutionalised elderly patients  $>80$  years, the risk of falling was reduced by 66%.<sup>50</sup> Reducing the total number (to less than four) of medications is a real option to reduce the risk of falls.<sup>6,54,76,77</sup>

### **Information and advice**

When prescribing and delivering drugs it is important to inform the patient on the use of medication and their role in signalling side effects. The patient also has a responsibility concerning self-medication and reporting adverse events allowing timely intervention in limiting adverse events and interactions.

## **PERSPECTIVE**

The relation between usage of drugs and falls has been studied in many trials, but the majority are retrospective, uncontrolled trials. From the data of studies available it is not yet possible to reveal a causal relationship for most drugs. Data from the majority of trials suggest that the use of drugs involves an increased risk of falling, especially in the frail geriatric patient on several drugs.

When prescribing a new medication in the older patient, the indication should be considered critically without withholding of treatment. When a decision to start treatment is made, one should 'start low, go slow', with explicit attention and active search to possible adverse events.

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