



abstract

**Objective:** to review the available evidence on the causes and consequences of falls, and the possible strategies to minimize them. **Methods:** A bibliographic search was made in Trip database and Pubmed with the following key words: “falls”, “falls prevention”, and “medication.” The search was filtered by type of study (clinical guidelines, systematic reviews, meta-analysis, or clinical trials). The two authors evaluated the information and worked separately in the initial analysis; a third party was asked for collaboration in the bibliographic search. **Results and conclusions:** Falls are especially frequent at the extreme ages of life. In elderly people they usually involve important morbidity, loss in quality of life and ultimately, increase in mortality. Some medications are associated with an increase in the incidence of falls in the elderly (especially benzodiazepines, other hypnotics, antidepressants, or antipsychotics). Prudence when prescribing is paramount. Only a few interventions have proven effective in the reduction of falls. Adapted exercises for each individual, and a multifactorial approach including precautionary withdrawal of some medication should be considered.

## Multicasuality of falls and the role of drugs

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## Introduction

During the process of Evolution different species of primates developed the erect posture. Bipedation demanded structural and dynamic changes, with its costs and benefits. For example, the foot changed, the pelvis was strengthened, the spinal column presented a double curvature and the skull moved forward. To maintain balance it was necessary to coordinate weight distribution, a constant activity carried out by muscles and controlled by the central nervous system from the information captured by the semicircular channel receptors of the inner ear, the retina, and other areas like joints.

Bipedation 'frees' the hands and 'raises' the eyes in such a way that primates can walk and over time transport objects in their hands. All this occurs with a visual perspective at a height above than that possible if they were walking on their four limbs. Moreover, the development of the hand is parallel to the brain, and viceversa, such that manual skills permit delicate manipulation and the work with materials which are transformed into useful and varied objects.

It is common to say that 'the child has learnt to walk' when in reality it is innate to the species, and is achieved with myelination of axons and dendrites that transmit the nervous impulses from the brains to the muscles. No one teaches a child to walk. Walking is something natural, just as standing upright. All this seems easy and simple as it seems automatic. Responses to falls are also automatic. The human being is prepared to respond with various and quick reflexes that avoid or limit the injury caused by falls.

There are different circumstances where these mechanisms are diminished and the consequences of falls can be dramatic. For example, when we are tired, sleepy, or with greater muscle weakness. With age, the possibility of falling also increases, for various reasons like a reduction in musculature and slow reflexes. Moreover, the susceptibility to different effects of drugs increases (alterations in renal and/or liver function, greater proportion of body fat, lower water content, lower levels of serum albumin, etc.). For all these reasons, special precaution in elderly people is required, to avoid falls without conditioning their quality of life.

This paper evaluates falls, their causes within the individual, family and social context of the person, with a special focus on some drugs. The authors aim to help clinicians in the decision making process in daily practice.

## Definition of 'fall'

The necessary equilibrium to stand up at rest and during movement is so very delicate that falling is nearly inevitable. Examples include when walking in the dark, or when under the effects of alcohol, or walking over ice, or in response to emergency situations or anguish, or when walking distractedly, etc. Falls are more frequent in early childhood (when 'learning' to walk) and at elderly ages, such that the incidence draws a typical 'U' form.

To maintain balance at rest and while moving, perfect functioning of the whole organism is necessary. We talk of falls when there is an abrupt, unexpected and involuntary loss of the erect position. Falls can also occur from the rest position (for example from a bed, or a chair) and one can fall without losing the erect position, for example after slipping while walking on the border of a height. In any case, falls are typically abrupt, involuntary and unexpected. The WHO defines 'fall' as an event which results in a person coming to rest inadvertently on the ground or floor or other lower level.<sup>1</sup>

## Consequences of falls

Falls are usually associated with fractures and senility, and studies focus on these aspects. However, falls occur at all ages, and many times the most severe consequences do not depend on fractures. Here are three clinical cases to illustrate the global impact of falls:

### Case 1

An 82 year old woman with mild cognitive impairment related to initial phases of Alzheimer's disease lives with her 85 year-old husband, who is healthy. He assists her with the help of a care giver (two hours a day). Their four children do not agree on home based-care and continually insist on admitting their mother to a nursing home because they believe that elderly people do not eat well, do little exercise and gradually isolate themselves. One night, the first time she took a neuroleptic agent prescribed by her doctor who said that it was 'so she and her husband could rest' she fell down in the hallway as she went to the bathroom. Her husband was unable to lift her up, as she was trapped between the wall and a shelf. The old man called one of his sons, who came over to the house and resolved the problem three hours after the fall.

The patient presented urinary and fecal incontinence during this period. After one week the couple left their home and went to a nursing home. She has a decubitus pressure ulcer in the sacral region after the fall and three hours in an immobile position (with urine and faeces). At the nursing home the elderly woman spends her day in front of a TV set with retention system applied to her. Her husband becomes desperate as he can no longer take a walk with her, because he has been forewarned that 'she could fall and break her hip.'

His wife got a common cold that became worse and she developed pneumonia. She died a month after admission to the nursing home. Her husband stayed in the nursing home for a year until he died of 'pity'.

### Case 2

A 19 year-old woman was healthy until she got her vaccination for human papilloma virus. While getting the first dose she collapsed and fell abruptly causing injury to her left cheek that required 6 sutures. After second dose, she suffered from a seizure and fell down again, and later required admission to a hospital. The episode resolved with anticonvulsant therapy that requires periodic follow-ups by a neurologist. Since then her life has changed. Due to the adverse effects of the drug (she refers to herself as being at a 'standstill') she has to live with certain restrictions regarding her social and night life and the consumption of alcohol at parties and at weekends. Finally after three years, with no history of seizures and in agreement with the family physician she gradually withdrew anticonvulsant therapy.

### Case 3

A 52 year-old unemployed man. After a argument with his wife, he abandons his home slamming the door and as he walks down the stairs, he slips and falls, and after receiving a strong blow to his neck he dies instantly.

These three cases did not cause any fracture. The second case involved an adolescent. No age is free from falls and their consequences.

Falls can cause:<sup>2,3,4,5</sup>

- **Injuries:** fractures, dislocations, sprains, lesions, bleeding, harm to internal organs (brain, spleen, etc) or death.
- **Prolonged immobilisation on the floor:** dehydration, rhabdomyolysis, pressure ulcers, hypothermia, pneumonia, death, etc.
- **Greater use of health and social services in the short and long term:** attention at home, at the emergency room, admission to hospital, rehabilitation, etc.
- **Loss of confidence and self-esteem:** perception of vulnerability, fear of repetition and fear in general,

*Falls are the major risk factor for fracture*

restriction of movements, obligatory need for help in ordinary daily activities.

- **Changes in lifestyle:** limitations in social life, admission with variable willingness to a more 'secure' nursing home, transitory and permanent disability, etc.

### What causes a fall?

Avoiding falls is fundamental, especially with regard to patients at high risk, those who can suffer severe consequences, and those who present limitations in movement and maintaining balance.

These limitations can become the nitty-gritty of the problem, for example, vertigo in a patient with Menière's disease or seizures in patients suffering from epilepsy. In other cases, the limitations are consequences of a health problem, for instance blind patients, children with brain palsy, an adolescent treated with a cast after a tibial or peroneal fracture after a traffic accident, or an elderly person with cognitive impairment due to Alzheimer's disease. Sometimes, the limitation may be due to a temporary condition, like the use of chemical products that alter the body homeostasis. Examples include the already mentioned alcohol intoxication, orthostatic hypotension provoked by antihypertensive agents, coma induced by excessive insulin dose, and unbalance caused by benzodiazepines.

Other factors can add to the limitations associated with health problems that may 'provoke' a fall. In most cases falls produced by different causes have a multifactorial origin. In order to help identify rationally when and where to intervene when managing patients at risk of falls, a Haddons matrix can be useful in the analysis of multiple causes.<sup>6</sup> Three phases are (before, during and after) and three factors are considered, person, agent, and environment (table 1).

As this example illustrates, the agent was a key factor, but only a part of a number of factors that led to a rupture of the married couple's routine, and finally the death of the couple in an environment they had always rejected.

### Falls and drugs

Numerous drugs can increase the risk of falling given the effects on different body systems. Thus, insulin

**Table 1.** Multi-causal analysis of the fall described in Case 1.

	BEFORE	DURING	AFTER
<b>Person</b>	<b>Intrinsic conditions (not modifiable):</b> <ul style="list-style-type: none"> <li>· senility and consequent reduction in liver and renal function.</li> <li>· muscular weakness, etc.</li> </ul> <b>Extrinsic conditions (modifiable):</b> <ul style="list-style-type: none"> <li>· malnutrition</li> <li>· inadequate hydration</li> <li>· sedentarism</li> </ul>	<b>Intrinsic factors</b> <ul style="list-style-type: none"> <li>· reduction of muscular mass and gluteus fat</li> <li>· inability to help oneself to recover or get up after a fall.</li> </ul> <b>Extrinsic factors</b> <ul style="list-style-type: none"> <li>· no external protection employed against contusions.</li> <li>· rejection of non-pharmacological means to treat insomnia.</li> </ul>	Development of pressure ulcers Atrocious fear of falling. Increase in sedentarism, loss of personal autonomy and self-esteem Submissive attitude to the suggestions from physicians and children to be admitted to a 'nursing home'.
<b>Agent</b>	Prescription and intake of a neuroleptic agent: modifiable by either indication or dose.	Long half life of a neuroleptic agent and adverse effects, such as urinary and faecal incontinence.	Withdrawal of medication, substituted by the 'strict' medical recommendation to change one's home for a nursing home for the elderly.
<b>Environment</b>	Does not use a potty at night to avoid leaving the bedroom to urinate. Absence of a personal warning system to alert in case of falls. Absence of an employed care giver, etc.	Lack of skills and training of the spouse to lift up the victim from the floor. Absence of physical supports to aid in getting up or lifting oneself up. Delays in obtaining help, etc.	Renouncing improvements at home and in the management of the patient (and the couple as a whole), to avoid shame or loss of pride of the elderly person. Admission and confinement in a nursing home.

**Table 2.** Risk of falling in elderly patients in relation to the different classes of drugs.

TYPE OF DRUG	OR (95%CI)
Antipsychotics	1.50 (1.25-1.79)
Hipnotic agents and sedatives	1.54 (1.40-1.70)
Antidepressants	1.66 (1.40-1.95)
Benzodiazepines	1.48 (1.23-1.77)
Group 1 antiarrhythmic agents (Quinidine and procainamide)*	1.59 (1.02-2.48)
Diuretic agents	1.08 (1.02-1.16)
Digoxin	1.22 (1.05-1.42)

(\*) These drugs prolong the QT interval.

can cause hypoglycaemia or antihypertensive drugs can cause orthostatic hypotension which increases the risk of falling. Other drugs such as benzodiazepines, produce somnolence or reduce motor coordination. Some medications, like anticonvulsants, can either avoid or provoke falls.

The elderly are a very susceptible group. In 1999, two meta-analyses<sup>7,8</sup> reviewed the relationship between pharmacological treatment and the risk of falling in patients over 60 years. In one of them psychotropic drugs were evaluated, and in the other, the use of analgesics and cardiovascular drugs was analysed. Only transversal, cohort, and case-control studies were included, as no randomised clinical trial was found in which the primary endpoint was the incidence of falls.

In these meta-analyses, a higher risk of falls in individuals under psychotics was observed, OR = 1.73 (95%CI, 1.52-1.97). Table 2 outlines the different risks found in relation to the type of medication.

It was also observed that those patients under three or more drugs presented a higher risk of falls.<sup>8</sup>

Later on, two new meta-analyses were carried out to evaluate the risk of falling. In one of them<sup>9</sup> a Bayesian approach was employed and just like before, a higher risk of falling was found with antipsychotics, antidepressants, anxiolytic agents, sedatives and benzodiazepines. With another approach, the other meta-analysis<sup>10</sup> found the same relative risk with antipsychotics. In addition, a higher risk was also found with NSAIDs, (OR = 1.21; 95%CI 1.01-1.44)

and opioids (OR = 1.38; 95%CI 1.23-1.56). In 2006, a case-control<sup>11</sup> study was published in which an increase in the incidence of hip fractures was observed in relationship with the use of opioids.

These findings could be explained, at least in part, by an indication bias.<sup>12</sup> Patients with a worse health status will probably be prescribed more drugs, but the higher risk of falls could be attributed to the poor health status rather than drugs. In order to minimize the risk of bias, new epidemiological studies employ the same subjects as controls during periods without treatment. In one cross-over study<sup>13</sup> in a nursing home a 66% (OR = 1.66, 95%CI 1.45-1.90) increase in the risk of suffering a hip fracture was found in elderly patients who were under treatment with non-benzodiazepine sedative agents (zolpide, zopiclone, or zaleplon). These new designs have also served to clarify the risk of falling in relation to antihypertensives. Thus, in one study involving a cohort of elderly people in Canada<sup>14</sup>, a 43% increase (ratio of incidence rates, 1.43; 95%CI, 1.19-1.72) was found in the risk of suffering a hip fracture when initiating antihypertensive treatment. For this reason, this initial period is considered highly critical.

Currently we lack studies on the risk of falling when starting treatments (or when modifying doses, and regimens of treatment). Nor are there studies on the accumulative effects of different drugs and their interaction when acute ailments occur and/or in cases of destabilization of chronic diseases. Furthermore, there is no information on the effect of different products related to phytotherapy, which are increasingly consumed by the population. Some of them can produce interactions in patients with cardiovascular disease.<sup>15</sup> For instance, grapefruit juice or St John's wort have important effects on the pharmacokinetics of numerous drugs and other products such as horsetail plant and whitethorn that have diuretic and cardiovascular effects.

With all their limitations, the above cited meta-analyses can help in making decisions on improving the use of drugs in elderly patients, but it seems that these papers hardly have any influence on physicians when prescribing. We lack evidence-based information on how to achieve the necessary changes of the physicians' routines.

### **How to help the patient reduce the probability of falling**

There are many proposals to reduce the incidence of falls, especially in the case of the elderly. Some have proven efficacy in people who are not institutionalized. Clear evidence has been found for physical exercise carried out in groups or individual programs at home, which usually include exercises that strengthen musculature and re-train patients on maintaining balance. Nevertheless, the information is limited, for example, with regard to the type and

*The main cause of fracture is not osteoporosis but age*

duration of exercise, intensity and adequacy for each individual, etc.

Efficacy has been shown from some trials with small sample sizes that the gradual and prudent withdrawal of psychotropic agents, administration of vitamin D supplement in cases of deficiency (not in all the population) and interventions to reduce potential risks within the home.<sup>16</sup>

It should be taken into account that the studies are focused on the efficacy of the measures, but not on the efficacy of medical advice in modifying patient's habits. For example, in the case of the recommended physical exercise, one thing is the efficacy of the measure, and another is whether the advice to carry out this measure is effective. It may happen that although exercise is an effective measure in reducing falls, the medical advice may fail to make the patient exercise more.

Yet still, there is less evidence that there is any efficient measure for patients living in care facilities and nursing homes,<sup>17</sup> including situations clearly associated with falls such as the case of stroke victims.<sup>18</sup>

Moreover, there is no evidence showing that the reduction in the incidence of falls is followed by less severity of complications, greater survival and a higher quality of life. What matters is to avoid falls, obviously, but above all to obtain a lower impact of falls. In any case, studies on efficacy do not recommend routine evaluations of all the elderly (clinical screening) to study the opportunities for intervention with respect to falls. The time employed in this 'clinical measure' yields very little.<sup>19</sup>

Many drugs are associated with an increase in the incidence of falls, and logically their use should be limited to strictly necessary cases, and in these occasions with additional measures to palliate the possibility of falling. Among the drugs, we have benzodiazepines (short and long acting), Z analogues (zopiclone, zolpidem), antipsychotics (including the atypical agents) and antidepressants (including SSRIs) either taken in monotherapy or potentiated by other drugs which also can provoke falls, such as antihypertensive agents, antiarrhythmics, and other cardiovascular drugs in general.<sup>20,21</sup> Several studies show that dose reductions or the withdrawal

of psychotropic agents can reduce the incidence of falls and other adverse effects.<sup>22</sup>

There are at least two clinical queries that remain unanswered:

- Up to what point can the use of these drugs be avoided when considering the probability of the harmful effects and potential benefits of their use in clinical practice and daily life?
- What drugs are associated with severe consequences of falling (cause hospital admission and/or death, for example) which would lead to their withdrawal or not prescribing them?

Unfortunately, most studies evaluate the association between the use of drugs and the increase in falls (number of falls, but not their severity). However, neither the severity of falls nor the benefit-risk balance of starting or withdrawing treatment has been evaluated.

There are other non-pharmacological recommendations of variable efficacy such as the elimination of rugs at home, the use of adequate footwear and other measures<sup>23</sup>. In general, the most effective measures are multifactorial, that is, those that act upon various causes.<sup>24</sup>

How can the clinicians select patients that will most benefit from multifactorial interventions? In clinical practice an evaluation of risk factors for falling has been proposed including age, previous history of falls, orthostatic hypotension, visual defects, balance and/or walking disorders, use of certain medications, instrumental limitations in daily life activities and cognitive impairment. Such factors have been evaluated according to their relative risk in observational studies, and therefore offer very little in the process of deciding on the management of individual patients.

It is useful to measure the probability of one event in an examined patient. Using this method, patients can be selected with two parameters:

- Previous history of falls (during the last year, and especially in the last month);
- Presence of gait and/or balance disorders.

These patients present a 50% probability of falling in the following year and a multifactorial approach to their management is worthwhile, which should include clinical and pharmacological review.<sup>25</sup>

### Falls, osteoporosis, fractures and drugs

Hip (femoral neck) fractures are the most relevant ones in terms of morbimortality. It is estimated that a hip fracture is produced in 1% of all falls, and that 90% of these fractures are caused by falls.

*Management should not focus on treating osteoporosis pharmacologically but on fall prevention*

Hip fractures have not decreased over time, despite the intense use of drugs in the management of osteoporosis. Nor has a reduction been observed in mortality resulting from hip fracture, despite advances in surgical treatment.

In Spain, the incidence of hip fractures increased by 36% between 1997 and 2008 (from 34,876 to 47,308), while there was also an increase in the average age of patients, from 78 to 80 years, and in mortality (from 4.71% in 1997 to 5.5% in 2008).<sup>26</sup> Likewise, no reduction in mortality has been observed in the United Kingdom, where the mortality is greater among patients belonging to lower classes and with increasing age (up to 31% in patients over 90 years).<sup>27</sup>

The incidence of hip fractures in Spain is low in comparison to countries in the North of Europe (Denmark and Sweden have a standard incidence rate per 100,000 person-years of 439 and 401, respectively, compared to 164 in Spain). This coincides with the data from epidemiological studies, where a lower risk of osteoporosis-related fractures is observed in Spain in comparison to other European and Anglo Saxon countries.<sup>28</sup> However, Spain is the world leader in the consumption of osteoporosis drugs and their use increased 6 times between 2000 and 2009.<sup>29</sup> The risk of fracture significantly increases in women and men over 70 and 75 years respectively. However, reiterative use of drugs and bone densitometry scanning in younger patients with low risk of fracture is observed in Spain. In women, risk

*Patients with higher risk have a history of previous falls, and gait or balance alterations*

factors for hip fracture include falls, sedentarism, and previous history of fractures. In men, scarce calcium intake, smoking, falls and sedentarism.<sup>30</sup>

The phrase ‘the patient does not fracture due to osteoporosis, but because of age’ summarizes the multifactorial causality with regard to hip fractures, frequent in fragile and elderly people, with diverse range of morbidity and polypharmacy, and always in relation to trauma (generally a fall) and with mental and/or physical limitations.<sup>31</sup> Hip fractures carry the risk of different complications, admission to hospital and major surgery. The post-surgical period is complicated, just like rehabilitation and reintegration into daily activities as before. Death in many cases is the end, especially in elderly patients over 90 years.

Falls, and not osteoporosis, is the main risk factor in the elderly. Given that some interventions have proven effective in reducing falls, it is time to focus on the prevention of falls and emphasize the key role of primary care physicians.<sup>32</sup> For example, in a study carried out in Norway, 5% of hip fractures were attributed to the use of antidepressants.<sup>33</sup> Thereby reducing the use of antidepressants could have a higher impact in decreasing fractures than the theoretical benefits, if any, of osteoporosis drugs.

#### Acknowledgments

To Ernesto Barrera, for his help in the bibliographic search. We thank Dr Clint Jean Louis, of the Emergency Department of the Navarre Regional Health Service in Spain, for translating the original manuscript into English

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#### Conclusions

Falls cause important morbidity and mortality in elderly people, but can occur at any age.

They can be caused by various concurrent causes. Psychotropic agents such as benzodiazepines and other hipnotic drugs, antidepressants, antipsychotics and opioids have been associated with a higher incidence of falls.

Other drugs such as antihypertensives or hypoglycaemic agents also increase the risk of falls.

There are important gaps in current evidence on the efficacy of interventions to reduce the frequency and severity of falls.

Exercise, multifactorial interventions and psychotropic drug withdrawal programs have proven effective in reducing the incidence of falling in elderly patients.

In clinical practice, family doctors should focus on patients with a high probability of falling. That is, those who present a previous history of falls (during the last year and especially in the last month) and the presence of any alterations affecting the patient's balance and/or gait.

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#### ISSN

1138-1043

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