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Falls at the interface between geriatric and psychiatric patients: a critical review from a psychopharmacological perspective

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Summary. Falls in the elderly represent one of the major clinical problems as they are serious events that often result in high residual disability and mortality rates. Knowledge on the subject derives mainly from geriatric and gerontopsychiatric research. However, gerontopsychiatric patients differ from geriatric patients not only for the psychiatric and neurological comorbidities, which are often not sufficiently taken into account in the scientific context, but also for the intake of psychotropic drugs, notoriously described as one of the main risk factors for falls. Such drugs are widely prescribed in this group of patients, often even off-label. Clinicians therefore should pay particular attention to falls, since various comorbidities and polypharmacy as a prescribing issue can have important consequences for clinical management. Falls have not been sufficiently investigated yet in a purely psychiatric context.

Key words. Confounding, falls, gerontopsychiatry, psychiatry, psychotropic drugs.

Le cadute nei pazienti geriatrici e psichiatrici: una revisione critica dalla prospettiva psicofarmacologica.

Riassunto. Le cadute nel paziente anziano rappresentano un problema clinico di grande rilevanza poiché esitano spesso in disabilità e mortalità molto elevate. Le conoscenze sull'argomento sono prevalentemente derivanti dall'ambito geriatrico e psicogeriatrico. Tuttavia questo secondo gruppo di pazienti si differenzia dal primo per la comorbilità psichiatria e/o neurologica, che spesso non viene sufficientemente presa in considerazione nel contesto scientifico, e per l'assunzione di farmaci psicotropi, notoriamente descritti come uno dei principali fattori di rischio per le cadute. Tali farmaci vengono spesso prescritti nella categoria di pazienti in questione, talvolta anche off-label. Risulta pertanto evidente quanto sia fondamentale considerare adeguatamente le cadute nelle categorie di pazienti sopracitate, sia per le comorbilità sia per le polifarmacoterapie assunte da questi ultimi. A oggi le cadute non vengono adeguatamente approfondite in un contesto puramente psichiatrico.

Parole chiave. Cadute, confounding, gerontopsichiatria, psichiatria, psicofarmaci.

Introduction

According to the literature, falls are a frequent and serious problem in the elderly population as they often lead to a deterioration in the quality of life and a reduction in the self-sufficiency of the elderly person[1,2]. 30% of people over 65 years of age and 50% of people over 80 years of age fall at least once; older people who have already fallen once have a 2-3 times greater likelihood of falling again within 12 months[3,4].

60% of elderly persons fall at home, 30% in public places and the remaining 10% fall in a nursing home or hospital; in 10-25 % of cases falls lead to fractures or serious injuries.

In most studies, fall incidence rates vary between 1.6 and 17 falls per 1000 patient days (pd). In one of the largest studies conducted in the United States with 315 817 falls included, the total fall rate was 3.56 falls per 1000 pd[5]. In psychiatric wards, fall rates ranged from 4.1 to 6.4 falls per 1000 pd, which is higher than the average fall rate of 3.56 referring to hospitalized patients. The highest fall rates, from 9.1 to 17 falls per 1000 pd, were found in geriatric or psychogeriatric wards. The fall rate is up to three times higher in institutions such as hospitals or nursing homes than at home[6-8].

Last but not least, falls are also an economic problem. Prolonged hospital stays of patients admitted for falls, increase the costs of treatment and constrain resources[9,10]. The costs of the treatment for fall injuries vary between 2,000 and 42,000 US dollars[11].

Psychotropic drugs are often highlighted as a major cause of falls. Antipsychotics, antidepressants, benzodiazepines and Z-drugs increased the likelihood of falls in elderly patient groups[12-14]. Side effects of medication such as reduced cognitive ability, attention, visual acuity, sedation and orthostasis are often reported as causes of falls[15-18]. But also age by itself inevitably leads to a deterioration of cognitive and physical functions, so the task of finding risk factors for falls remains often multifactorial[4].

As far as the current context of psychiatric research is concerned, the subject of falls has been barely studied and convincing data are still missing.

With increasing age of patients, there is often an overlap between geriatric and psychiatric clinical conditions. Thus, on the one hand, psychiatric comorbidities increase in geriatric patients and, on the other hand, we are confronted with the natural ageing process in the psychiatric patient population[19]. The relevance of geriatric syndromes, such as falls, in the context of the pressing polypharmacy prescribing issue is therefore gaining more and more importance[6,8,20].

The aim of this review is to present the problem of falls in the intersection between geriatric and psychiatric conditions and to summarize the current literature on mostly pharmacological risk factors highlighting the multiple difficulties of prescribing in elderly patients.

Methods

While this article is by no means a complete review of fall studies, the goal is to familiarize the reader with the strengths and limitations of the types of research often used to examine falls and its risk factors in psychiatric and geriatric patients. Bias and confounding are common problems affecting fall studies. We therefore chose a quality criterion by which we selected only studies with a methodology that tried to reduce the effects of bias and confounding, such as multivariate logistic regression analysis. We performed a PubMed/MEDLINE, Scopus and PsycINFO search to identify all articles within the last 10 years until 2021. The following terms were cross-referenced with falls in the search: "polypharmacy"; "antidepressants"; "antipsychotics"; "anticonvulsants"; "benzodiazepines"; "non-benzodiazepines"; "Z-drugs". The resulting reference list of the article was first auto-searched using Boolean operators ("AND", "OR") as well as filters. The resulting list was hand-checked to eliminate duplicates (figure 1). 249 articles were identified of which 57 met our inclusion criteria. We further classified the resulting medications based on high odds-ratios or relative risk scores in the primary research or review articles in high or low risk categories. To provide information on connected topics like "side effects"; "hyponatremia"; "cognitive function"; "aging"; "fractures"; "sarcopenia", "pharmacokinetics"; "pharmacodynamics"; "pharmaco-interactions" and "confounding" we selected 80 key articles independently of publication date. All original articles found through the resulting literature search were read.

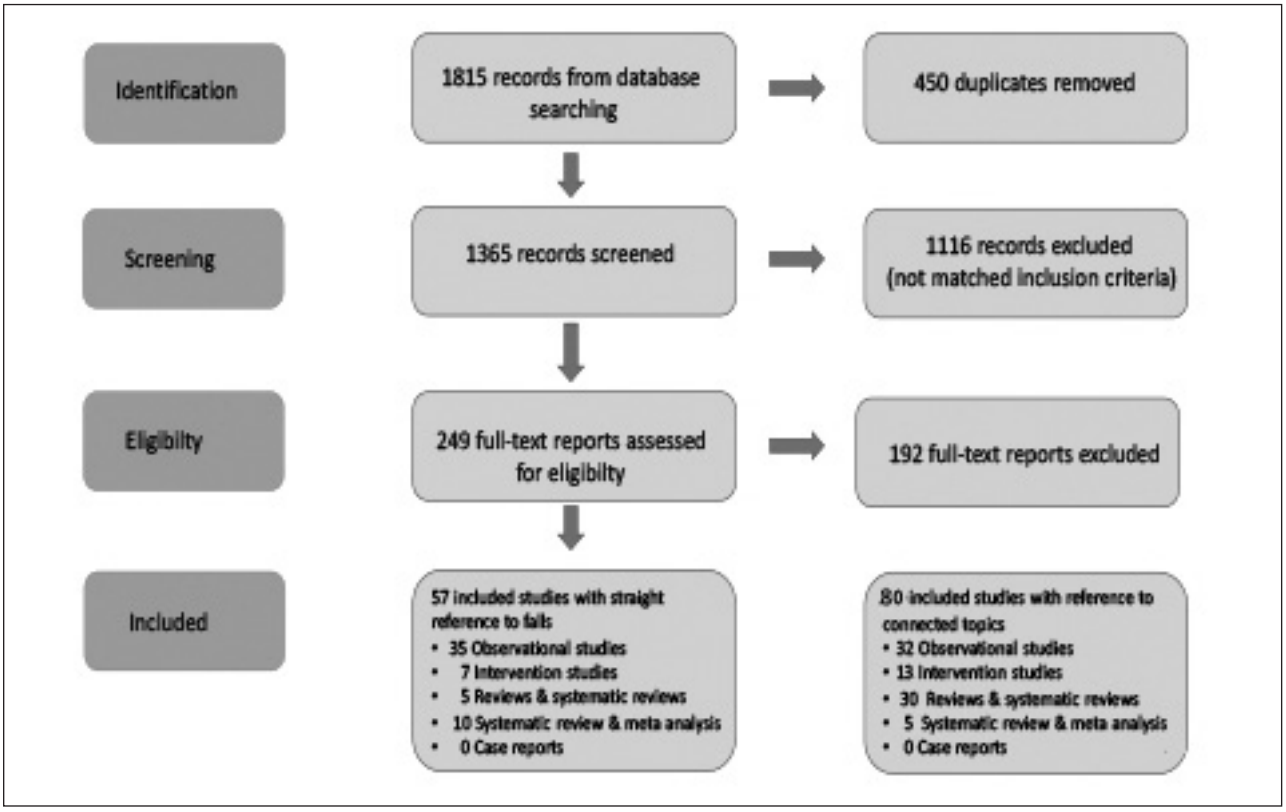

Figure 1. Criteria for inclusion of the examined articles.

The following criteria were used to exclude articles:

- studies/articles whose material is incomplete or whose content does not concern our research topic;
- studies/articles that do not clearly demonstrate a link between pharmacy and falls;
- studies that do not report for important confounders, report unclear methodology or reported results of univariate analysis only;
- studies/articles published before 2010.

All resulting listed articles in English and German were reviewed.

Results

A total of 137 articles were included in our review. No case reports were found that specifically addressed the topic. There are 5 main reviews, which include almost all studies that examined fall risk factors up to 2018. Leipzig et al. were the first to include in their review 43 studies investigating risk factors in nursing homes, hospitals and home environment[12-14,21,22]. Other authors were supplementing these findings with more recent studies on classes of drugs that had not been studied so far. However, these studies mainly represent studies in nursing homes and in the home environment. Studies on fall risk factors in the inpatient setting are represented by Leipzig et al. with only 5 studies. This also applies to the other reviews. Some classes of medication were more frequently associated with an increased risk of falls in the elderly. The investigations focus in particular on certain groups of psychoactive substances (table 1)[23-64]. These include: benzodiazepines, antipsychotics, antidepressants, Z-drugs, anticonvulsants and polypharmacy.

Benzodiazepines

Many studies associate benzodiazepines with an increased risk of falls[23-28]. However, data regarding the risk of falls for various preparations with different elimination half-life are still inconsistent[14,21,22,28]. Preparations with long and short half-life have been both associated with falls[14,23,25,28-30,65,66]. Higher doses were more likely to be associated with falls than lower doses[14,29,67]. Seppala et al.[14] in their meta-analysis found long acting benzodiazepines 1,81 OR (95%, CI 1.05-3.16) associated with a higher fall risk then short acting benzodiazepines 1,27 OR (95%, CI 1.04-1.56). These results were replicated also by other authors[31].

As early as 1978, Reidenberg et al. were able to demonstrate that the plasma concentration depends not only on the administered dose, but also on the

Table 1. Drugs associated with falls.

Drug	Association with falls
Benzodiazepines	*High risk*. Preparations with short half-life as well as long half-life have been associated with an increased risk of falling. It remains preferable to use benzodiazepines with short half-life to avoid cumulative effects over time that predispose to side effects, like falls. There is evidence of a dose-adverse events relationship. Higher doses should be avoided[23-31].
Z-Drugs	*High risk*. Several studies have reported similar effects to benzodiazepines. There is increasing evidence regarding the risk of falls and fractures[23,32-37].
Antipsychotics	*Low risk*. There is little evidence for an increased risk of falling. So far, no significant differences emerged between typical and atypical. In the psychiatric population the use of antipsychotics has been shown to be a protective factor reducing the risk of falls[38-43].
SSRI	*Low risk*. SSRIs showed in several studies a significant association with falls. The risk appeared to be comparable to that of TCAs. A major concern in falls is the risk of fracture, and there is growing evidence that SSRIs can increase the risk of fracture by causing a reduction in bone mineral density[44-52].
SNRI	*Low risk*. The risk appeared to be increased, but convincing data is missing[12,13,15,48,53,54].
TCA	*Low risk*. Their use can be problematic in the elderly due to their various side effects (which are attributable to their effect on histaminergic and α-adrenergic receptors). All TCAs cause sedation, sleep disturbances and often orthostatic hypotension[14,21,37,55,56].
Other antidepressants (mirtazapine, trazodone)	*Low risk*. They are considered the drugs of choice in geriatric depression and insomnia, thanks to their antidepressant, sleep inducing and appetite enhancing effects[53,55-57].
Anticonvulsants	*Low risk*. Play a decisive role in the treatment of bipolar disorder, behavioral disorder and anxiety disorder. Their side effect profile could influence the risk of falling. Few studies have demonstrated a risk of falling[58-62].
Polypharmacy	*High risk*. Drug-drug interactions increased up to 80% when five or more drugs were prescribed at the same time. Falls are considered an adverse event and metabolic drug interactions should always be considered[63,64].

age of the patients[68]. The focus was mainly put on the cognitive effects, influenced by the γ-aminobutyric acid (GABA) transmission, which probably play a decisive role in the risk of falling[69].

Attention, working memory, processing speed, visual construction, recent memory and expressive language deteriorate significantly with long-term use of benzodiazepines[16]. The onset of orthostatic hypotension has also been reported following the prescription of benzodiazepines[70]. Up to now, it has not been possible to fully clarify whether there is also an increased risk of developing dementia[16,71-73].

Z-drugs

Z-drugs approved in the early 1990s, proclaimed as a safe alternative to benzodiazepines, have also been associated with falls and an increased risk of fractures[23,32-36,74]. Berry et al. conducted a study on the long-term use of Z-drugs and found an increased risk of fall-related hip fractures 1,66 OR (95% CI, 1.45-1.90) on zolpidem medication[75]. These results could subsequently be replicated by other authors[33]. Zolpidem and zopiclone have long been considered the drugs of choice for sleep disorders in old age due to their lower addictive potential compared to benzodiazepines and a lower impact on sleep architecture[76]. Like benzodiazepines, Z-drugs exert their effects through increased GABA transmission. Their pharmacokinetics are characterized by a rapid onset within 30 min and short half-life (1-7 h). However, it has been shown that the addictive potential is comparable to that of benzodiazepines[77,78]. Commonly neuropsychiatric adverse events like hallucinations, anmnesia and parasomnia have been described with Z-Drugs[33,34]. Especially the elderly were prone to elevated plasma concentrations in comparison to younger individuals which could explain the higher risk of falling[79].

Antipsychotics

Data regarding antipsychotics and falls is controversial. Although typical and atypical antipsychotics have been associated with falls, there is also evidence that they might act as protective factor in psychiatric patients[13,21,22,38,80].

Among the most important undesirable side effects are listed extrapyramidal motor disturbances that could provoke falls[81]. However, hyponatremia is also mentioned as an undesirable side effect, which is considered a separate risk factor for falls[82-84].

Low potency antipsychotics are often used in elderly patients with sleep disorders, because of their favourable side effect profile[39,85,86]. However, attention needs to paid on their anticholinergic effects that could provoke falls.

Studies regarding the fall risk have been shown an increased risk of falls and fractures, especially in long-term prescriptions[40,57,81,87-89]. Epidemiolgical studies designed to investigate antipsychotic prescription are rare[41,90].

Antidepressants

Different antidepressant classes (Tricyclic Antidepressants - TCA; Selective serotonin reuptake inhibitors - SSRI; Selective norepinephrine reuptake inhibitors - SNRI) were associated with falls in several studies[44-48,57]. The most frequently prescribed SSRI, considered as the drugs of choice in depressive and anxiety disorders, have been associated in many studies with an increased risk of falling. Above all, the risk of fracture appeared to be increased, which may be related to an increased likelihood of developing osteoporosis under treatment[49-52]. Wang et al. for instance found an adjusted OR of 3.05 (95% CI 2.73-3.42) for patients affected by osteoporosis and falls[52]. SNRIs, on the other hand, are still poorly studied with regards to their fall risk[12,13,15,48]. An association with the risk of developing orthostatic hypotension seems possible[15]. But even during treatment with SSRIs and SNRIs, a variety of unwanted side effects can occur. A new onset of sleep disorders and the frequent feeling of restlessness at the start of treatment could have contributed on increasing the risk of falls[27,91-97].

As already described in the case of antipsychotics, hyponatremia in blood examination occurs relatively frequently during treatment with antidepressants and is considered an independent risk factor for both, falls and hospital admissions[98-100]. The risk appears to be increased with SSRIs and SNRIs, especially in patients suffering from an impaired renal function and dementia. TCAs have virtually disappeared from clinical practice, due to their anticholinergic effects, orthostatic hypotension and ECG changes, which more likely occur in the elderly[101]. Low-dose doxepin, on the other hand, is considered to be well tolerated and therefore occasionally prescribed by general practitioners to improve sleep quality[102,103].

Sleep quality, as evidenced by polysomnography, was also improved by other antidepressants like mirtazapine and trazodone, which are recommended for elderly patients due to their good safety profile[57,53,55,104,105]. For the newer antidepressant vortioxetine, there are no studies to date that demonstrated an association with falls.

Anticonvulsants

Anticonvulsants are not only prescribed in the treatment of epilepsy but also in the psychiatric context for bipolar disorder, behavioral disorder, anxiety disorder and sleep disorder[58]. The therapeutic effects

through various mechanisms of action, including regulation of ion channels, blocking glutamate-mediated stimulating neurotransmitter interaction, and enhancing the inhibitory GABA transmission are very heterogenous[59-61]. Common side effects include sedation, nausea, and headache. However, more adverse effects, such as auditory and visual problems, hyponatremia, liver dysfunction and kidney disorders may also contribute to their fall risk. A clear association, especially in elderly patients, was demonstrated by Haasum et al. in their systematic review with two studies demonstrating a stastical significant association[62]. For instance Masud et al. found ORs of 2.8 for falls and 2.6, respectively, for recurrent falls, but with relatively wide confidence intervals[60].

Polypharmacy

In addition to the risk of falling posed by the individual drug, particular attention should be paid to polypharmacy[106-112]. Hand grip strength index is an important indicator of frailty in geriatric medicine and appeared significantly reduced under psychoactive polypharmacy, i.e., the simultaneous use of more than one psychoactive drug[113,114].

From a pharmacokinetic point of view, the risk of drug-drug interactions at the level of the hepatic cytochrome was increased up to 80% when five or more drugs were prescribed at the same time, especially in the elderly[63]. In particular, the inhibition of CYP2D6 enzyme, involved in the metabolism of several antidepressant drugs, may lead to elevated drug levels. It seems obvious that elderly patients, frequently affected by various comorbidities, are particularly exposed to this phenomenon. There are few population studies highlighting the real role of metabolic drug interactions in association with adverse events, like falls[64]. In line with these findings a recent meta-analysis attempted to prove that a reduction in medication also would lead to a reduction of falls. Unfortunately, with discouraging results[115,116].

Discussion

To date little is known about falls in psychiatric patients[51]. Literature on this subject, especially regarding younger patients, is lacking. A first case-control study on a general population sample aged between 25 and 60 years included 335 cases of patients who died or were hospitalized due to falls in the outpatient setting. The study revealed that falls also affected younger patients mainly subject to polypharmacy, thus bringing the fall event closer to a younger age group which is the host of psychiatric structures[117].

Given the high rates of falls in psychiatric wards in epidemiological studies, future research is needed to extent the scientific knowledge of falls also on psychiatric patients.

Our review instead shows that falls are of great clinical relevance, especially in the geriatric and psychogeriatric context. Most of the studies examining falls are based on results obtained in the outpatient setting. The situation in the inpatient setting – quite different due to the presence of acute pathologies – is represented by Leipzig et al. with only five studies reviewed. In fact, in the other reviews the composition of studies is similar[12-14,21,22].

Another limitation is the lack of randomized controlled trials in the selected study designs, which mainly consist of case-control and case-crossover studies, more prone to bias.

The research of risk factors for falls almost always leads to psychotropic drugs, on which we have focused in our research. Unfortunately, their use often occurs beyond approved psychiatric indications, such as the treatment of sleep disorders and psychomotor agitation. Therefore, the prescription of these drugs, developed mainly in the psychiatric field, can increase the risk of falls in elderly patients. In this case, it is often a “off-label” prescription, which may not be free of legal issues[39,85,118-120].

In fact, the elderly patient often presents various comorbidities, which interfere with the natural changes in pharmacokinetics and pharmacodynamics related to the ageing process, which can favour cognitive and motor alterations, and consequently lead to falls[71,107,121].

These changes lead to an increase in body-fat and a decrease in total body water. That is why water-soluble (hydrophilic) drugs have higher peak plasma levels in the elderly. Inversely, fat-soluble (lipophilic) drugs have a greater volume of distribution in the elderly[121]. Decreasing serum albumin concentration affect the protein binding potency of drugs. The age-related decrease in liver size lead to a reduced hepatic blood flow and cytochrome enzyme activity which compromise hepatic clearance of drugs. Decreased renal blood flow, decreased glomerular filtration (GFR) and tubular secretion have a considerable impact on the renal clearance of drugs[122]. In addition, the elderly suffer often of sarcopenia, which implies the loss of muscle strength with an increase in problems related to movement and therefore suggests a greater vulnerability to unwanted side effects[123-125].

A correlation of the physiological changes of ageing, in particular regarding pharmacokinetics, with polypharmacy and falls has been documented in several studies. An often reported example regards the interactions based on the CYP2D6 enzyme, where the drugs fluoxetine, paroxetine and metoprolol are metabolized. Fluoxetine and paroxetine are considered potent inhibitors of the CYP2D6 enzyme, with the consequent risk of increased plasma levels

of metoprolol when prescribed concurrently[126-129]. Therefore, as reported in a recent systematic review of the literature, in many studies, as expected, there is reported an increased risk of bradycardia and hypotension with the simultaneous prescription of metoprolol and paroxetine or fluoxetine[128].

Approximately 30% of hospital admissions of patients aged 75 or older are caused by adverse drug reactions[130]. The prevalence of drug interactions based on hepatic cytochrome enzymes was 80% when 5 drugs or more were prescribed[131]. Due to the numerous possible interactions, it remains a difficult task to attribute the fall to a specific drug.

Based on these considerations, it seems difficult to justify that prescribing these drugs often continues after discharge. To date evidence-based strategies for discontinuation of prescriptions after symptom relief are still missing[132,133].

In geriatric medicine, falls are considered as an independent syndrome which always requires a systematic approach to evaluate the specific variables involved[4,134].

The association between falls and sedative drugs such as benzodiazepines is well known and reported in various studies[12-14,22]. Antidepressants and antipsychotics have also been associated with falls in many studies, but it seems likely that the results are subject to bias. Leipzig et al. have already shown that the use of antipsychotics reduces the number of falls in psychiatric patients[21]. Their results demonstrate the importance of subgroup analysis and the inclusion of diagnoses in the study design to avoid bias and confounding. Confounding is a problem in most study designs examining fall risk[135]. Especially during hospitalization, clinicians often face symptoms which on the one hand require the use of psychiatric drugs, but on the other hand are considered risk factors for falls, for example in case of delirium. Although there are statistical methods that take the possible risk of confounding into account, it remains still a difficult task to include all the variables involved in the multifactorial genesis of falls in a model.

For example, "Time" as a variable, to document a direct association of the drug intake with the fall event, should be considered within the applied study designs, which is why the importance of prospective study designs must be emphasized.

Especially SSRIs, which are often recommended in the elderly, have unexpectedly shown an increased risk of falls in many studies. Despite, the neurobiological mechanism of action does not suggest a direct correlation with falls.

Depressive symptoms are very common in the elderly, which can lead to a significant impairment in quality of life[136]. In fact, social withdrawal, reduced physical activity with consequent loss of muscle mass and increased morbidity and mortality are factors which contribute to an increased risk of falls in patients with untreated depressive disorders. Therefore, it is important to consider these aspects when evaluating the introduction of antidepressant therapy[48,137]. At the time of antidepressant choice, there is a greater tendency to prescribe SSRIs in this category of frail patients (selective prescribing) due to their higher tolerability and acceptability profile compared to other classes of antidepressants, such as TCA drugs. This could be a potential confounder within the literature regarding the prescription of SSRI and falls in the elderly.

Limitations

Our review is not a complete summary of the literature on falls. We have restricted our research to psychopharmacological risk factors and discussed them with regards to their pharmacodynamic and pharmacokinetic properties. Other important risk factors, such as environmental factors and comorbidities, were not considered. Neither we considered the setting (in-patient and out-patient), which could also influence the risk of falls under certain medications due to the presence of acute illnesses.

Considerations

Clinicians should always consider pharmacological risk factors in their prescribing, especially in the elderly with greater comorbidities involved. Prescribing psychoactive medications is challenging and, especially in the context of falls, even more emphasis should be placed on developing individualized treatment algorithms. Since so far, there are hardly any evidence-based algorithms available, prescribing tools should be used whenever possible to facilitate the clinician to take pharmacodynamic and pharmacokinetic aspects into account, when prescribing risk medications. Simultaneous prescribing of several drugs with the same pharmacodynamic properties should be avoided.

Conclusions

Scientific research on the causes of falls in psychiatric medicine is lacking despite the risk factors appear very similar to those in elderly patients. Due to their effect on cognition and mobility research on risk factors for falls in the elderly predominantly is focused on psychotropic drugs. The identification of risk factors for falls remains subject to a high likelihood of bias and confounding, because quality study designs such as RCT or prospective studies are missing. The fall event can be a problem of clinical and sometimes legal relevance even in the psychiatric field. Therefore, considering pharmacokinetic

and pharmacodynamic properties when prescribing psychoactive medications seems crucial. Despite the tools and knowledge now available, the sensitivity to the fall syndrome in clinicians and psychiatric institutions is still low and little attention is paid to both the measurement and the reduction of risks.

Conflict of interests: the authors have no conflict of interests to declare.

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