Original Article

Significantly higher use of polypharmacy in elderly with hip fracture treated with psychotropics

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ABSTRACT

INTRODUCTION. The high prevalence of chronic medical conditions among older adults leads to an increased use of prescription medications and a heightened risk of polypharmacy, raising the risk of falls and fractures. Psychotropic medications influence balance, and therefore our aim was to describe the use of psychotropic medications and the association with polypharmacy in elderly patients with a hip fracture.

METHODS. A retrospective study of 200 patients aged 65 years or more admitted consecutively with a hip fracture.

RESULTS. In total, 98 of the 200 patients used psychotropic medications. These 98 patients used a higher number of drugs at the time of admission (an average of eight (6-11) versus six (3-10), p <0.001), had a higher risk of using five or more medications (odds ratio (OR) = 5.9; 95% confidence interval (CI): 2.75-12.7; p <0.001) and a higher risk of using ten or more medications (OR = 1.9; 95% CI: 1.05-3.5; p = 0.03). Furthermore, they were more likely to use analgesics (65.3% versus 48.0%; p = 0.01) and medications targeting the gastrointestinal tract (59.1% versus 40.2%; p = 0.01).

CONCLUSIONS. Psychotropic medication use was frequent in elderly patients with a hip fracture and strongly associated with polypharmacy. Psychotropic medications may potentially be a trigger to perform medication review in elderly patients to prevent re-occurrence hip fractures.

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It has been estimated that the elderly population will grow from 9% of the population in 2019 to approximately 16% in 2050 [1]. This growing rate comes with many challenges as the number of chronic medical conditions rises with age and requires more healthcare resources [2]. Furthermore, the rise in the number of elderly people is associated with an increase in medication prescriptions [3]. Such an increase in prescriptions may lead to polypharmacy (PP) or excessive polypharmacy (EPP) in elderly people [2, 3].

A remarkably high use of psychotropic medications has been described in the elderly population [4]. These prescription patterns are often identified as inappropriate and are strongly associated with adverse effects,

including anticholinergic side effects [4, 5]. Adverse effects may be misinterpreted as newly emerged symptoms or conditions that require treatment, which may lead to a phenomenon referred to as a "prescribing cascade". In addition, it has been demonstrated that the use of drugs with anticholinergic effects is associated with both short- and long-term mortality in older geriatric patients [6]. Thus, the frequent prescription of psychotropic medications, perhaps without proper indication, may potentially be a key to supporting medication review.

We previously collected data from 200 elderly patients aged more than 65 years who were admitted consecutively with a hip fracture, and we assessed the prevalence of medication-related falls leading to a hip fracture [7]. Approximately half of the patients used psychotropic medications, and these medications were often likely to have contributed to the fall episodes. Furthermore, PP was frequent in this population, which is in accordance with polypharmacy being a risk factor for falls [8]. However, the process leading to PP and EPP is not yet well described and the association between the use of psychotropic medications and PP/EPP, in particular, needs further evaluation as enhanced knowledge in this respect may possibly guide future medication reviews.

Thus, the aim of this study was to detail the use of psychotropic medications and the association with PP or EPP in a group of 200 elderly patients admitted consecutively with hip fractures.

METHODS

The study was a retrospective consecutive-admission study, for which Ethics Committee approval is not required. The Danish Patient Safety Authority approved the project, including transmission of the data from the medical records (case number: 3-3013-1950/1). Data were handled in accordance with the Danish Act on Personal Data Protection.

The study included 200 elderly patients over the age of 65 years, admitted consecutively to a Danish University Hospital with a hip fracture during a 24-week period in 2017. The study population was identified through a search in the hospital database using the International Classification of Diseases tenth version (ICD-10) codes for fracture of the femur (DS72-DS729). Additional data on the prevalence of medication-related falls leading to a hip fracture have been published previously [7].

Data regarding demographics, comorbidities and medication use at the time of admission were the focus of this study. More data regarding clinical and laboratory data, description of the fall episode and other diagnostic evaluations performed during admission were collected and the details have been published previously [7].

In this study, psychotropic medications were defined as anti-epileptics, dopaminergic agents, antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants and anti-dementia drugs and others like, e.g., antihistamines. An overview of the medications in each Anatomical Therapeutic Chemical (ATC) group used by patients in the study population can be found in (https://ugeskriftet.dk/files/a12210945_-_supplementary.pdf).The most frequently reported definition of PP is daily use of five or more medications, and EPP is commonly defined as daily use of ten or more medications [9]. These definitions were used in the study.

Data collection and statistical analysis

Data were collected and handled using Research Electronic Data Capture (REDCap) (Vanderbilt, USA). IBM SPSS statistics version 26 (IBM Corporation) was used to perform all statistical analyses. The Shapiro-Wilks test was used to check for normal distribution of the data. The population was divided into two groups: 1) patients using psychotropic medications and 2) patients not using psychotropic medications. Normal distribution was visualised as means ± standard deviations, and differences between groups were tested using an independent samples t-test. Not normally distributed data were visualised as medians (25th percentile-75th percentile), and a Mann-Whitney U test was used to test differences between groups. A χ^2 test was utilised in cases of dichotomous

data. Missing data were not imputed in the analysis as they were few, the number of patients with missing data is specified in the footnotes of the tables for each variable. A binary logistic regression test was utilised to generate odds ratios (ORs) of the dichotomous outcome variables. ORs are presented with 95% confidence interval (CI). All tests performed were considered statistically significant if $p < 0.05$.

Data sharing statement

The datasets generated and analysed in the present study are not publicly available because the Danish Patient Safety Authority must approve transmission of the data to other researchers on a case-by-case basis. Data are, however, available from the authors upon reasonable request and pending permission from the Danish Patient Safety Authority.

Trial registration: not relevant.

RESULTS

A total of 200 elderly patients aged more than 65 years with a hip fracture were included in the study. The 200 patients were divided into two groups: 1) patients using psychotropic medications (n = 98) and 2) patients not using psychotropic medications (n = 102). A summary of demographics, comorbidities and medication use of patients using and not using psychotropic medications is presented in **Table 1**. Those using psychotropic medications had a lower BMI and used a higher number of medications at the time of admission (Table 1). Furthermore, they were more likely to use analgesics and medications targeting the gastrointestinal tract than those not using psychotropic medications. The prevalence of diagnoses for diseases affecting the central nervous system was higher in those using psychotropic medications (67% versus 27%) (Table 1). Diagnoses affecting other organ systems were equally prevalent in both groups, except for a lower prevalence of diabetes type 2 in the group using psychotropic medications.

TABLE 1 Comparison of characteristics between patients using psychotropic medications and patients not using psychotropic medications.

	Using psychotropic medications (n = 98)	Not using psychotropic medications (n = 102)	p-value
Females[a], n (%)	61 (62.25)	67 (67.69)	0.61
Age[b], average (range), yrs	82 (74-88)	82 (76-88)	0.67
Height[c], mean ± SD, cm	167.4 ± 8.77	166.03 ± 10.00	0.31
Weight[d], average (range), kg	65 (54.5-75.5)	68 (58-79)	0.26
BMI[e], mean ± SD, kg/m²	23.41 ± 4.22	24.72 ± 4.27	0.04
Drugs at admission[f], average (range), n	8 (6-11)	6 (3-10)	< 0.001
Medications, n (%)			
Cardiovascular	80 (81.6)	83 (81.4)	0.96
Endocrine	57 (58.2)	56 (54.9)	0.64
Analgesics:			
Opioids	20 (20.4)	17 (16.7)	0.5
Weak analgesics	58 (59.1)	49 (48.0)	0.1
Analgesics, total	64 (65.3)	49 (48.0)	0.01
Gastrointestinal:			
Acid-lowering agents	29 (29.6)	21 (20.6)	0.1
Laxatives	41 (41.8)	25 (24.5)	0.01
Gastrointestinal, total	58 (59.1)	41 (40.2)	0.01
Respiratory	28 (28.6)	19 (18.6)	0.1
Comorbidities, n (%)			
CNS diagnoses:			
Previous ischaemic stroke	17 (17.3)	18 (17.6)	0.95
Dementia	25 (25.5)	5 (4.9)	< 0.001
Depression	22 (22.4)	< 5	-
Other CNS diagnoses[g]	22 (22.4)	5 (4.9)	< 0.001
CNS diagnoses, total	66 (67.3)	27 (26.5)	< 0.001
Hypertension	40 (40.8)	50 (49.0)	0.24
Osteoporosis	21 (21.4)	25 (24.5)	0.60
Atrial fibrillation	23 (23.5)	21 (20.6)	0.62
COPD	19 (19.4)	13 (12.7)	0.20
Ischaemic heart disease	17 (17.3)	10 (98)	0.12
Type 2 diabetes	6 (6.1)	21 (20.6)	< 0.05
Chronic renal failure	11 (11.2)	14 (13.7)	0.55
Oncologic diagnosis	10 (10.2)	8 (7.8)	0.56
Chronic heart failure	< 5	11 (10.8)	NA
Thyrotoxicosis	6 (6.1)	6 (5.9)	0.94
Aorta stenosis	< 5	8 (7.8)	-
Hypothyrosis	< 5	6 (5.9)	-
Benign prostate hypertrophy	5 (5.1)	5 (4.9)	0.95

CNS = central nervous system; COPD = chronic obstructive pulmonary disease; SD = standard deviation.
a) Missing patients: n = 0.
b) Missing patients: n = 0.
c) Missing patients: n = 10.
d) Missing patients: n = 17.
e) Missing patients: n = 24.
f) Missing patients: n = 0.
g) Comprises bipolar affective disorder, schizophrenia, Parkinson's disease, epilepsy, prior haemorrhagic stroke, chronic alcoholism, and other; each of these diagnoses occurred in < 5% of the patients.

Patients using psychotropic medications had an OR of 5.9 (95% CI: 2.75-12.7), p < 0.001, for using five or more medications; and an OR of 1.9 (95% CI: 1.05-3.5), p = 0.03, for using ten or more medications. The occurrence of polypharmacy is shown in (https://ugeskriftet.dk/files/a12210945_-_supplementary.pdf). **Figure 1** illustrates the number of patients in each group (using psychotropic drugs or not) treated with one, two, three, etc. different medications at the time of admission.

FIGURE 1 Distribution diagram of the number of prescribed medications at admission in patients treated and not treated with psychotropic medications. Groups with n < 3 are not shown.
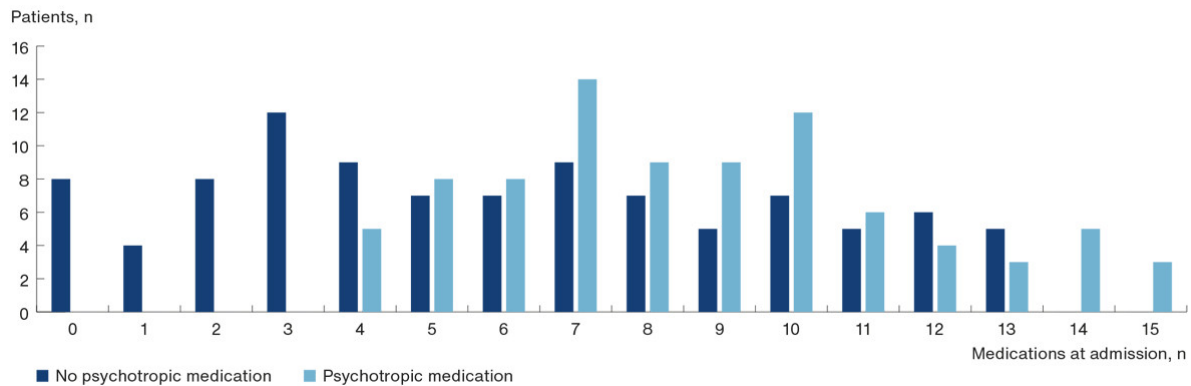
In **Table 2,** the number of used medications by category is compared between patients who did and did not use psychotropic medications. The medication classes presented are the six most frequently used medication classes in the total population.

TABLE 2 Number of non-psychotropic medications used by patients using psychotropic medications and patients not using psychotropic medications. The values are median (25th-75th percentile).

Medications	Using psychotropic medications	Not using psychotropic medications	p-value
Cardiovascular	3 (1-4)	2.5 (1-4)	0.72
Endocrine	3 (1-4)	2.5 (1-4)	0.72
Pain	1 (0-1)	0 (0-1)	0.04
Gastrointestinal	1 (0-1)	0 (0-1)	0.01
Respiratory	0 (0-1)	0 (0-1)	0.12

In total, 98 (54%) of the included patients used psychotropic medication at the time of admission. **Table 3** lists the number of patients treated with each type of psychotropic medication by ATC group.

TABLE 3 Psychotropic medication used at time of admission.

Pharmacological subgroup	ATC 3rd level	n (%)
Anti-epileptics	N03A	16 (8)
Dopaminergic agents	N04B	8 (4)
Antipsychotics	N05A	17 (8.5)
Anxiolytics	N05B	17 (8.5)
Hypnotics and sedatives	N05C	24 (12)
Antidepressants	N06A	53 (26.5)
Anti-dementia drugs	N06D	16 (8)
Other	R06A	3 (1.5)

ATC = Anatomical Therapeutic Chemical Classification.

DISCUSSION

The main finding of the present study was that elderly patients with hip fracture who used psychotropic medications at the time of their admission had significantly higher odds of being exposed to PP and EPP in addition to psychotropic medications. This was driven by a more frequent use of analgesics and laxatives in this group of patients. Moreover, we found a possible mismatch between using psychotropic medications and a proper indication justifying their use. The findings underline the importance of performing thorough medication reviews in patients at risk of falls and fractures, as recommended by the Danish Health Authority [10].

A study from 2016 describing the characteristics of elderly patients admitted to seven Spanish hospitals and treated with psychotropic medications found that psychotropic medication use was positively associated with PP and EPP [4]. Another study investigated factors associated with PP and EPP in elderly patients and found that psychotropic medications were used in 42% of patients with PP and 77% of patients with EPP [11]. This is consistent with our findings, indicating a positive association between psychotropic medication use PP and EPP.

The patients using psychotropic medications in the present study did not have a higher prevalence of common cardiovascular, respiratory or endocrine diseases than those not using psychotropic medications. This was an unexpected finding because previous reports have shown positive associations between use of psychotropic medications, weight gain [12], diabetes [12] and heart diseases such as chronic heart failure [13]. In contrast, we found a lower BMI and a lower prevalence of type 2 diabetes and chronic heart failure in those using psychotropic medications. Possible explanations for these apparent discrepancies between the present and other studies may be that the potential adverse effects of psychotropic medications may possibly make physicians less prone to prescribing them to elderly multimorbid patients, such as those with type 2 diabetes and chronic heart failure. Additionally, our findings may possibly have been affected by the study being restricted to patients with hip fracture because a low BMI is a risk factor for osteoporosis.

The higher prevalence of PP and EPP in patients using psychotropic medications was apparently driven by a higher prevalence of pain and obstipation. The whole study population had a high use of pain medications, which is rather common for elderly people [14]. However, significantly more patients using psychotropic medications used analgesics. In this regard, it is common for the elderly to be treated with more than one type of pain medication [14], and combination therapies adding antidepressant or antiepileptic medications to opioids have proven to be effective in pain management [15]. We therefore speculate if the significantly higher use of analgesics in the group of patients using psychotropic medications may, in some cases, have been linked to the use of antidepressant or antiepileptic medications as part of a combination pharmacotherapy. Furthermore, patients using psychotropic medications also used gastrointestinal medications to a higher degree.

The more frequent use of gastrointestinal medications, which was primarily driven by more patients using laxatives, may be connected to the use of pain medications as opioid analgesics are known to induce gastrointestinal adverse effects such as nausea, vomiting and constipation [16]. However, the prevalence of opioid use was not significantly higher in those using psychotropic medications than in those who did not; thus, the fact that several psychotropic medications have anticholinergic effects including constipation [5] may also have contributed to this finding. This suggests that use of psychotropic medications may elicit a prescription cascade in which laxatives are used to treat iatrogenic constipation [17], further contributing to PP and EPP.

A total of 98 (49%) of the patients were using psychotropic medications. However, only 67% of these patients were diagnosed with a condition related to the central nervous system in which psychiatric diseases were included. Thus, the prescription patterns of some psychotropic medications did not agree with the number of diagnoses. According to data from the Danish Health Data Authority, where all medications sold in the primary sector are documented, 31% of the population above the age of 65 years redeemed antidepressants from a Danish pharmacy, 12% redeemed antiepileptics and 8% redeemed antipsychotics in 2017 [18]. This agrees well with results in our population where 26.5%, 8.5% and 8% used antidepressants, antipsychotics and antiepileptics, respectively [7]. However, only 22.4% of those using a psychotropic medication were diagnosed with depression. Patients using antidepressants for other indications such as chronic pain or insomnia may have contributed to this inconsistency. Mirtazapine may be used off-label for insomnia owing to its sedative properties and was used by 8.5% [7]. Tricyclic antidepressants are also used to treat neuropathic pain [19] but were used by less than five patients [7]. Selective serotonin reuptake inhibitors were by far the most frequently used antidepressants in our population [7] and have no other indications apart from anxiety disorders [20]. However, very few cases of anxiety were identified within the population, meaning that this condition was unlikely to explain the remaining part of the antidepressant medication use.

The apparent incongruence between the listed diagnoses in the patient records and the use of antidepressants may reflect that depression is often handled in primary care and may not be the centre of attention during an acute admission due to hip fracture. However, it may also indicate treatment without a proper indication. In contrast to 8.5% using antipsychotics, we found that less than five patients among those using psychotropic medications were diagnosed with schizophrenia or bipolar affective disorder, which are two diseases primarily managed with antipsychotics due to psychotic episodes. In Europe, second-generation antipsychotic risperidone is the only antipsychotic approved to treat behavioural and psychological symptoms of dementia (BPSD). In our study, 22% of the patients who used psychotropic medications were diagnosed with dementia, and, therefore, it is possible that antipsychotics were used to treat BPSD. Altogether, the risk of polypharmacy, the possible risk of prescription cascades and possible absence of a clear indication in some cases underline the importance of scrutinizing the medication list in elderly patients with hip fracture using psychotropic medications.

Our study had limitations. The study was conducted on a selected group of elderly admitted to hospital due to hip fracture. A previous study on this group of patients found that the prevalence of suspected medication-related

falls was 41% [7], and thus it cannot be excluded that this group of patients used more medications than the general population of the same age. Moreover, the selected group may have a gender distribution, BMI and age that differs from that of the general population, which limits the extrapolation of our results to other groups of patients. Still, the findings in this selected group of patients suffering a hip fracture may support a clearer understanding of the mechanisms leading to PP and EPP, guide medicine review and hence guide future studies on interventions and research to prevent such serious outcomes.

CONCLUSIONS

Psychotropic medication use was common and positively associated with PP and EPP. An apparent incongruence was observed between the diagnoses listed in the patient records and the use of psychotropic medications. Furthermore, the associations with pain and gastrointestinal medications may indicate prescription cascades in patients using psychotropic medications. Conclusively, medication review should be prioritised in elderly patients using psychotropic medications to prevent reoccurrence of hip fractures, and it may be suggested to use psychotropic medications as a trigger to scrutinising medication review in the elderly.

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