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THE ASSOCIATION IN ELDERLY HOSPITALIZED PATIENTS, BETWEEN PSYCHOTROPIC DRUGS AND HIP FRACTURES RESULTING FROM FALLS

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Background/Study Context*: Psychotropic drug treatment has been associated with increased risk for falls and hip fractures in elderly patients. The authors examined the association between drug treatment and hip fractures resulting from falls in elderly hospitalized patients, focusing on the medications' anticholinergic properties.*

Methods*: This retrospective case-control study was conducted in an acute geriatric ward in a general medical center. Medical records, including demographic, clinical, biochemical, and pharmacological variables, of elderly patients with hip fractures from falls (*N = *185), admitted during a 2-year period, were reviewed and compared with a control group (*N = *187) of patients matched for age and gender and without hip fractures.*

Results*: The usage rates of antipsychotics, antidepressants, mood stabilizers, and various nonpsychiatric medications were similar in the two groups, except for hypnotics-anxiolytics (higher rates in hip-fracture patients). The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) and diastolic blood pressure constituted very modest predictors of falls (*R^2 *= .038,* p *= .004). There were no significant differences in the anticholinergic burden values, clinical dementia ratings, and comorbidity burden between the two groups.*

Conclusion*: The rate of psychotropic drug use in general and their anticholinergic burden are similar in acutely admitted elderly patients with or without hip fractures. However, higher usage rate of anxiolytics found in the patients with hip fractures may indicate that this is a risk factor for hip fractures related to falls in elderly patients living in the community.*

The elderly population is gradually increasing. Currently, it constitutes 10% of the general population in the Western world and is expected to reach 23% in the year 2050 (Tinetti, 2003). Falls are one of the major causes for nonfatal trauma and injuries that eventually lead to mortality. The incidence of falls among the elderly is increasing every year (Nurmi & Lüthje, 2002).

The etiology of falls is multifactorial and involves an array of risk factors. Medications, especially psychotropic drugs, have been implicated as a major contributor to falling among the elderly (French et al., 2006; Ray, Griffin, Schaffner, Baugh, & Melton, 1987; Svensson et al., 1991).

In this population hip fractures are associated with serious complications and often result in morbidity and mortality (Ray et al., 1987). The use of antidepressants, antipsychotics, and benzodiazepines is associated with a 2-fold increase in the risk for falling and hip fracture (Tinetti, 2003). The consumption of more than four medications, irrespective of their class, is also associated with increased risk for such occurrence (Tinetti, 2003).

Since anticholinergic side effects are associated with confusion, attention and cognitive deficits, and impairment in judgment and in spatial orientation, they have been proposed as contributors to falling (Ensrud et al., 2002; Flacker et al., 1998; Thapa, Gideon, Cost, Milam, & Ray, 1998). There is no consistency in the relationship between various classes of medications and the risk of falling (French et al., 2006). Benzodiazepines and antidepressants have also been implicated as contributors to falls (Cumming, 1998; Cummings et al., 1995; Ensrud et al., 2002; Herings, Stricker, de Boer, Bakker, & Sturmans, 1995; Leipzig, Cumming, & Tinetti, 1999; Thapa et al., 1998). Aizenberg et al. evaluated the relationship between the anticholinergic burden of psychotropic medications and falling among psychiatric geriatric inpatients (Aizenberg, Sigler, Weizman, & Barak, 2002). They found that high anticholinergic burden was significantly associated with higher risk for falling in a sample of geriatric patients not suffering from dementia and hospitalized in a psychiatric hospital.

The aim of the present study was to evaluate the association between falls and psychotropic drug treatment in elderly patients hospitalized in an acute geriatric department of a general hospital, with special attention given to the anticholinergic properties of these agents.

MATERIALS AND METHODS

This retrospective, case-control study reviewed the medical records of all elderly patients (age above 65) who were admitted to the acute geriatric department (Rabin Medical Center, Petah-Tikva, Israel) due to hip fractures resulting from falls, over a period of 2 years (2005–2006). The preceding or following elderly patients of the same age group and gender, with acute medical problems but without hip fractures, who were admitted to the same department, constituted the control group. Patients are admitted to the acute geriatric department directly from the emergency room and have a large array of acute pathologies (such as cardiovascular, infectious, gastrointestinal, respiratory, metabolic, neurological, and hematological) and also geriatric syndromes (such as delirium, dementia, nutritional, and functional decline).

As this is a retrospective, file-based study, a waiver of consent was obtained from the institutional review board (IRB).

The exclusion criteria were age under 65, abuse of alcohol and/or drugs, multitrauma patients such as survivors of vehicle accidents, and no past history of falling or hip fractures. Demographic data were collected as well as data concerning clinical, laboratory, and pharmacological parameters. Special attention was given to the use of psychotropic agents: antipsychotics, antidepressants, mood stabilizers, and hypnotics-anxiolytics.

The following parameters were evaluated for each participant, based on his or her record:

- Assessment of the level of dementia using the Clinical Dementia Rating (CDR) scale (Morris, 1993).
- Comorbidity using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Miller et al., 1992).
- The Anticholinergic Burden Score (ABS) (Aizenberg et al., 2002) was calculated according to the anticholinergic activity of the various agents as suggested by Shiloh, Nutt, and Weizman (1999) and Chew et al. (2008). As proposed by Chew et al. (2008), anticholinergic activity for each drug was rated in a range of 0–3. When there were several drugs with anticholinergic activity, the values were combined into a total ABS value in a manner similar to that described by Aizenberg et al. (2002).

Statistical Methods

The data were analyzed using unpaired Student's *t* test and Fisher's exact test, as appropriate. Bonferroni correction for multiple comparisons was employed as a post hoc test. Hierarchical regression was used to identify possible predictors of hip fractures in addition to anxiolytics as a primary factor. All results are expressed as mean ± *SD*.

RESULTS

Demographic and Clinical Variables

During the study period (2005–2006), data were collected from the records of 185 patients with hip fractures and 187 patients without hip fractures. No significant differences were found between the groups with regard to gender distribution (57 M:128 F vs. 62 M:125 F) and age (Table 1).

Table 1. Demographic, clinical, physiological, and biochemical characteristics of the study population

Characteristic	Group	*N*	Mean	*SD*	*t*	*p*
Age	No fracture	187	83.06	5.85	1.48	.14
	Fracture	185	84.01	6.48		
Cog CDR	No fracture	185	0.62	0.66	1.64	.10
	Fracture	184	0.51	0.63		
CIRS-G	No fracture	187	8.37	3.02	2.04	.042[a]
	Fracture	185	7.69	3.41		
Systolic BP (mm Hg)	No fracture	186	138.11	27.17	1.68	.09
	Fracture	185	142.77	26.08		
Diastolic BP (mm Hg)	No fracture	186	72.39	12.67	2.49	.013[a]
	Fracture	185	75.55	11.77		
Na (mmol/L)	No fracture	187	137.17	5.63	0.73	.47
	Fracture	184	137.55	4.35		
Creatinine (mg/dl)	No fracture	186	1.11	0.59	0.81	.42
	Fracture	185	1.05	0.82		
Urea (mg/dl)	No fracture	187	58.75	37.23	2.19	.03[a]
	Fracture	185	51.51	25.52		
Hb (g/dl)	No fracture	187	11.77	1.93	0.68	.50
	Fracture	185	11.89	1.44		
ABS	No fracture	187	1.19	1.44	1.03	.31
	Fracture	185	1.04	1.38		

Note. CDR = Clinical Dementia Rating; CIRS-G = Cumulative Illness Rating Scale for Geriatric; BP = blood pressure; Hb = hemoglobin; ABS = Anticholinergic Burden Score.

[a]Remains significant following Bonfferoni correction.

Neither were significant differences found in all the following variables: CDR (which evaluates the level of dementia as mentioned above), CIRS-G score, sodium, urea, creatinine, hemoglobin, and systolic and diastolic blood pressures. Even the three that seemed significant (CIRS-G, diastolic blood pressure, and urea) became nonsignificant following Bonferroni correction (Table 1).

In order to further analyze the interaction between the variables and the risk for falling, hierarchical regression analysis that used falls as a dependent variable and included the variables whose significance was lost following Bonferroni correction (CIRS-G, diastolic blood pressure, and urea) was conducted. This analysis indicated that CIRS-G and diastolic blood pressure, but not urea, modestly predicted hip fracture ($R^2 = .038$, $p = .004$; Table 2). No significant interaction between variables was detected.

Table 2. Hierarchical regression analysis with falls as a dependent variable

Variable	*B*	*SE*	OR [95% CI]	Significance
CIRS-G	.071	.033	1.073 [1.006–1.145]	.032
Diastolic BP (mm Hg)	−.022	.009	0.978 [0.961–0.995]	.011

Note. CIRS-G = Cumulative Illness Rating Scale for Geriatric; BP = blood pressure
OR = odds ratio.
Predictors: CIRS-G, diastolic BP, and urea; $R^2 = .038$, $p = .004$.
No significant interaction was found between variables.
CIRS-G, diastolic BP, and urea were entered into the model by a stepwise method. For the purpose of clarity, only the variables that were significant predictors are shown.

Table 3. Distribution of psychotropic drug use in the two groups

Group	No drugs	1 drug	2 or more drugs	Statistics
No hip fracture	67 (46.5%)	51 (27.3%)	49 (26.2%)	$\chi^2 = 1.81$, $df = 2$, $p = .40$ N.S.
Hip fracture	81 (43.8%)	62 (33.5%)	42 (22.7%)	

Pharmacological Variables

No significant differences were found in the distribution of the number of psychotropic medications used by both groups (number of medications: one medication and two or more medications; Table 3).

The rates of use of antipsychotics, antidepressants, mood stabilizers, and various nonpsychiatric medications were similar, with the exception of anxiolytics (higher in the patients with fractures), alpha blockers, and diuretics (Table 4). However, following Bonferroni correction only the difference in the rate of use of anxiolytics remained significant (20.5% vs. 9.1%; Fisher's exact test, $p = .002$; Table 4). It is of note that the antipsychotic medications were used mainly to attenuate agitation and to induce sleep. The pharmacological types of the hypnotic-anxiolytic agents used by the two groups were similar and included benzodiazepines (diazepam 5 mg, oxazepam 10 mg, lorazepam 1 mg, clonazepam 0.5 mg, nitrazepam 5 mg, and brotizolam 0.25 mg) and cyclopyrrolone (zopiclone 7.5 mg). The same was true for the antihypertension agents, namely, both groups used agents of a similar pharmacological type that included selective beta blockers (propanolol 15–30 mg, atenolol 12.5–50 mg, bisoprolol 5 mg) and alpha/beta blockers (carvedilol 6.25–12.5 mg). Although the mean blood pressure was higher in the hip-fracture group, the diastolic and systolic blood pressure ranges in the patients with hip fractures (50–108 and 102–209 mm Hg) and the ranges of the control group (39–114 and 87–224 mm Hg) were similar.

Table 4. The rate of use of the various drug classes in the two groups

Drug	No hip fracture	Hip fracture	Fisher's exact test significance
Psychotropic drugs			
Antipsychotics	25 (13.4%)	19 (10.3%)	0.42
Antidepressants	35 (18.7%)	35 (18.9%)	1.00
Mood stabilizers	0 (0%)	3 (1.6%)	0.12
Hypnotic-anxiolytics	17 (9.1%)	38 (20.5%)	0.002[a]
Other drugs			
Nitrates	31 (16.6%)	19 (10.3%)	.094
Beta blockers	71 (38.0%)	54 (29.2%)	.08
Alpha blockers	25 (13.4%)	12 (6.5%)	.037
Antiarrhythmics	11 (5.9%)	16 (8.6%)	.32
Diuretics	82 (43.9%)	58 (31.4%)	.014
Memantine	3 (1.6%)	1 (0.5%)	.62
Cholinesterase inhibitors	15 (8.0%)	16 (8.6%)	.85
Antiparkinsonians	20 (10.7%)	15 (8.1%)	.48
Anticonvulsants	7 (3.7%)	5 (2.7%)	.77
Digoxin	6 (3.2%)	9 (4.9%)	.44
Steroids	2.7 (5%)	4 (2.2%)	.75

[a]Remains significant following Bonferroni correction.

The agents considered anticholinergic were antipsychotics, antidepressants, and antiparkinsonians (Table 3). There was no significant difference in the ABS values between the two groups (Table 1).

DISCUSSION

The main finding of this study is that the rate of psychotropic drug use, the anticholinergic burden, and most of the laboratory parameters in elderly patients who sustained hip fractures as a result of falling, admitted to an acute geriatric ward, are similar to those of admitted elderly patients with no hip fractures. The only difference consisted of higher rates of hypnotic-anxiolytic drug use in the fracture group. CIRS-G and diastolic blood pressure constituted very modest predictors of falls ($R^2 = .038$, $p = .004$).

In a previous study in geriatric psychiatric inpatients (Aizenberg et al., 2002), higher ABS were found among patients who had experienced a fall compared with patients who had not fallen. However, in contrast to our expectations regarding the possible role of anticholinergic burden in falls and hip fractures of geriatric patients, no such association between ABS and hip fracture was found in nonpsychiatric geriatric patients. It seems that the use of psychotropic agents (antipsychotics, antidepressants, mood stabilizers), other than hypnotics-anxiolytics, was not associated with falls.

The same was true for all the nonpsychotropic agents, including the antihypertension drugs. It is possible that the ABS levels among psychiatric inpatients are higher than in geriatric populations where the main treatment consists of nonpsychotropic drugs with mild anticholinergic activity. In those cases in our nonpsychiatric population, the relatively low ABS levels were not sufficient to cause falls.

It could be argued that the population hospitalized as a result of falling and fracturing a hip was healthier to start with and would not have needed any hospitalization were it not for the hip fracture. Thus, it may have been more appropriate to compare our hip-fracture patients with a control group consisting of community, nonhospitalized, elderly subjects who, hypothetically, would demonstrate a lower rate of psychotropic drugs and lower anticholinergic burden. However, since the comorbidity burden, calculated by the CIRS-G and other clinical parameters, was similar in both patient groups, and since the study patients sustained falls, they cannot be considered to be healthier than the patients without fractures. As noted above, the etiology of falls is multifactorial, including age-related changes such as slow reaction time, impaired stability and protective responses, medications, and chronic diseases such as neuropathies and orthostatic hypotension that can lead to soft-tissue injuries and bone fractures (King, 2009). Therefore, in this sample of very old patients, with several chronic diseases, using many medications, the similar rates of psychotropic drugs and anticholinergic burden between groups is not completely surprising.

In contrast to other psychotropic agents, we did find higher rates of anxiolytic use among those who sustained falls. A similar association of anxiolytics and an increased risk for both falls and hip fractures has already been reported in other studies (French et al., 2006; Ray et al., 1987). The effects of hypnotics-anxiolytics on balance, gait, and equilibrium come as a consequence of their differential negative impact on vigilance and cognitive functions. Old age may alter and modify pharmacokinetic and pharmacodynamic parameters of these drugs, leading to a greater sensitivity to anxiolytics (Allain, Tue-Ferrer, Polard, Akwa, & Patat, 2005). It is possible that the fracture-causing effect of hypnotics-anxiolytics is related to high blood concentrations due to slow hepatic metabolism and lower renal function in the elderly.

This study has several limitations. Since it is a retrospective study, the data collected, particularly those that relate to the medications used by the patients, may be less accurate than it would be in a prospective study. Furthermore, it is possible that direct laboratory assessment of anticholinergic activity is more accurate than using global values of ABS elicited on the various drugs from the literature.

Despite these limitations, the strength of our study is its large and naturalistic sample that represents typical elderly patients with hip fractures, including patients of advanced age with several comorbidities and cognitive impairments.

CONCLUSIONS

The incidence of falls among the elderly increases every year and poses a major public health concern. Although the etiology is known to be multifactorial, one of the major risk factors may be the use of psychotropic medications.

In our sample study, the rate of psychotropic drug use and their anticholinergic burden were found to be similar in acutely admitted elderly patients whether they have or have not sustained hip fractures. Thus, the use of psychotropic drugs in general did not differentiate between the two groups and was not associated with increased risk for hip fractures. However, the higher usage rate of anxiolytics found in the patients with hip fractures may indicate that those are risk factors for hip fractures related to falls in elderly patients living in the community.

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