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Association between Acute Geriatric Syndromes and Medication-Related Hospital Admissions

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Abstract

Background—Elderly patients are at a four-fold higher risk of adverse drug events (ADEs) and drug related hospitalization. Hospitalization of an elderly patient is often preceded by geriatric syndromes, like falls or delirium.

Objectives—The primary aim of this study is to investigate whether geriatric syndromes were associated with ADEs in acutely admitted elderly patients.

Methods—Consecutive medical patients, aged 65 years or more, and were acutely admitted, were enrolled. An initial multidisciplinary evaluation was completed and baseline characteristics were collected. A fall before admission was retrieved from medical charts. Delirium was determined by the Confusion Assessment Method.

Results—A total of 641 patients were included. Over 25% had an ADE present at admission, 26% presented with delirium and 12% with a fall. Delirium was associated with the use of antidepressants, antipsychotics, and antiepileptics. In all ADEs (N=167), ADE was associated with a fall, with NSAIDs or diuretics, but not with pre-existing functioning, delirium or older age. For ADEs involving psychoactive medication (N=35), an association was found between delirium, fall, opioids and antipsychotics in bivariate analyses. A fall just before hospitalization (OR 3.69 [95% CI 1.41–9.67]), antipsychotics (OR 3.70 [95% CI 1.19–11.60]) and opioids (OR 14.57 [95% CI 2.02–105.30]) remained independently associated with an ADE involving psychoactive medication.

Conclusion—This prospective study demonstrated that in a cohort of elderly hospital patients a fall before admission and prevalent delirium are associated with several pharmacological groups and/or with ADE-related hospital admission.

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Keywords

Elderly patient; Atypical illness presentation; Fall; Acute admission; Delirium; Adverse drug event; Geriatric condition

Background

Pharmacotherapy is an important component of medical treatment but is often a cause of adverse drug events (ADEs). ADEs are the most frequent type of adverse events occurring in medical inpatients and a considerable part of hospital admissions are related to ADEs. ADEs have also been associated with unnecessary hospital admission.¹ Compared with younger patients, patients aged 65 years or older are at a four-fold higher risk for ADEs.² This can be ascribed to their comorbidities, complex care, presence of cognitive, social and functional limitations, use of multiple drugs, and altered pharmacokinetics and pharmacodynamics.^{3;4} A recent systematic review showed that the odds of being hospitalized by ADE-related problems is four times higher for elderly persons (16.6% vs. 4.1%).⁵ Approximately 50% of ADEs are preventable,^{4,5} and can be resolved if detected in time.

In the traditional model of medical diagnosis, there is a clear relationship between typical clinical signs and symptoms prior to or present at hospital admission. However, it is believed that this model does not accurately define illness presentations in older, vulnerable hospital patients.^{6;7} As observed commonly in geriatric medicine, many of these patients present atypically, such as pneumonia without fever, or with unintentional fall or delirium. The term 'geriatric syndrome' is used to capture these atypical presentations who do not fit into discrete illness categories. Geriatric syndromes are understood to have the following features: they occur in older, often vulnerable persons; although precipitated by one or more acute triggers, they are multifactorial in aetiology; they seldom follow a typically episodic course and they frequently lead to persistent functional impairment.^{8;9} An acute illness leading to hospitalization is often accompanied by one or more geriatric syndromes, especially falls and delirium (15–30% and 10%, respectively).^{10–13} These geriatric syndromes are associated with substantially poorer discharge outcomes such as functional decline, institutionalization, and mortality.¹⁴

Many ADEs present typically, for example with gastrointestinal bleeding, nausea, or rash. However, it is also common in elderly hospitalized patients that many ADEs present with atypical symptoms, and can be readily overlooked at admission. Since both geriatric syndromes (like delirium and falls) and ADEs are frequently found in acutely hospitalized elderly patients, a possible association or sequential time course may exist. For instance, adverse drug events may reveal themselves first as geriatric syndromes like delirium or falls before they lead to hospital admission. If this hypothesized association is recognized in a timely manner, early intervention aimed at the underlying cause of the ADE may prevent an unnecessary hospital admission and its attendant complications, such as functional decline.¹⁴

The overall aim of this study was to investigate whether a fall before admission and prevalent delirium are associated with specific pharmacological groups and ADE-related hospital admission in a cohort of acutely admitted medical patients aged 65 years and older.

Methods

Design and participants

This prospective cohort study was conducted between December 1st, 2002, and April 1st, 2006, at the Academic Medical Center, Amsterdam, a tertiary university teaching hospital. All consecutive patients aged 65 years or older who were acutely admitted to the Department of Internal Medicine were enrolled. Patients were excluded if they were unable to speak or understand Dutch or English, if they or their relatives did not give permission for the study, if they came under intensive care or cardiac monitoring, or if they were transferred to a ward other than Internal Medicine. The study was approved by the hospital's Medical Ethics Committee.

Measurements

The research team was composed of two attending physicians in geriatric medicine, a clinical nurse specialist, two research nurses, all trained in geriatrics and a clinical pharmacist. Patients, medical and nursing staff were interviewed by the nurses to determine study eligibility of patients within 48 hours of admission.

An initial, multidisciplinary evaluation was completed for all participants by members of the study team to identify prevalent delirium, present at the time of hospital admission. Delirium was scored within 24 hours after admission by research physicians using the Confusion Assessment Method (CAM).¹⁵ Information for diagnosing prevalent delirium was based on a psychiatric examination of the patient including cognitive testing (DSM IV criteria), medical and nursing records, including the Delirium Observation Screening Scale (DOS)¹⁶, and information given by relatives concerning the 24 hours prior to admission. The occurrence of one or more unintentional falls within one week before hospital admission was abstracted from the physician's notes in the medical record and/or from the discharge summary. The research physicians also completed a Charlson comorbidity index and the main diagnosis ICD 9 code, both based on information at discharge.¹⁷

The research nurses collected demographic and clinical data from all study participants. They also screened for global cognitive impairment using the Mini Mental State Examination (MMSE). Cognitive functioning before hospital admission was scored by medical history and the Informant Questionnaire on COgnitive Decline- short form (IQCODE-SF). The IQCODE-SF assesses global cognitive impairment based on the response of an informant who had known the patient for at least ten years.¹⁸ The informant was asked to recollect the patients' functioning two weeks prior to hospital admission and to compare it with his or her functioning ten years before. Patients with a mean score of 3.9 or more on the IQCODE-SF have serious cognitive impairment.^{19;20} To measure functionality, patients' relatives were asked to complete the modified 15-item Katz ADL-index score, also based on the patient's condition two weeks prior admission.²¹ This is a validated 15-item scale measure to rate (instrumental) activities of daily living ((I)ADL), modified from the original ADL index questionnaire developed by Katz et al. Performance is graded according to the number of disabilities (i.e., a higher score indicates a worse functional status).

Outcomes

The primary outcome was an ADE. An ADE was defined as an undesirable clinical manifestation consequent to and caused by the administration or omission of a particular drug or interacting drugs. To determine whether an ADE was associated with the cause leading to hospital admission, the discharge summary and medical record abstraction were separately reviewed by a clinical pharmacist and a geriatrician.

Our study was limited to drug-related incidents occurring prior to hospitalization and that led directly to a hospital admission. Drug-related incidents occurring during the course of a hospitalization were not considered in the context of this study. Drug-related incidents were detected using the following methods: (1) review of hospital discharge summaries; and (2) review of emergency department notes. All available discharge summaries relating to hospitalizations for the study population during the study were obtained for review. The information contained in these discharge summaries was reviewed for evidence of a drug related incident that led to an admission. Reviews of discharge summaries and medical record abstractions were performed by trained clinical pharmacist and geriatrician investigators, who also classified the involved drugs. Admissions were classified as drug-related if both reviewers judged the drug to have made a dominant or partial contribution to the admission. When raters disagreed, consensus was reached. Drugs that were present at admission and are often associated with ADEs were divided into pharmacological groups (Table 1).

Statistical analysis

Descriptive statistics were applied to describe baseline characteristics and results about ADEs and pharmacological groups. To identify potential associations between patients and/or ADEs and atypical illness presentations (fall or delirium) present on admission, a multivariate logistic regression analysis with backward selection was conducted, using variables with a p value ≤ 0.2 for selection. A p value < 0.05 was considered statistically significant. We hypothesized that there would be associations between falls and delirium, as between prior functional and cognitive status and delirium as well. Therefore these were tested separately before the multivariate logistic regression analysis took place. Associations were analyzed for all ADEs in general and also specifically for the ADEs involving psychoactive drugs as these drugs are known to contribute to delirium. All statistical analyses were performed using SPSS software (Statistics Package for Social Scientists, version 16.0).

Results

Study population

In total, 1092 consecutive patients were screened. A total number of 240 patients (22%) did not give informed consent or withdrew consent from the original study, 36 patients (3.3 %) were too ill, 44 patients (4 %) were not able to speak or understand Dutch and 131 patients (12%) could not be included within the predefined time frame.

A total of 641 patients were included in this study. Of these, 48 (10%) patients died in hospital. Table 2 shows the baseline characteristics of our study population. Mean age was 77.8 years (SD 7.9 years), 46.6 % were male, 67.6 % of the patients lived at home and 28.6 % had pre-existing cognitive impairment. The prevalence of delirium at admission and a fall prior to admission, was 25.9 % and 12 %, respectively, and 5.4 % of the patients had both a fall and delirium. Prevalent delirium and a prior fall were highly correlated ($p=0.046$). We previously demonstrated a strong independent association between prior cognitive and functional impairment with prevalent delirium in a population of acutely admitted medical patients.²⁸

ADEs

Table 1 contains the associations of fall and delirium with drug groups which are commonly associated with ADEs. The use of antidepressants, antipsychotics and antiepileptics were associated with delirium; none of these were related with a prior fall. Table 3 shows the distribution of ADEs over pharmacological groups and the percentage of ADEs due to a

drug group coinciding with a fall or delirium. A total of 167 ADEs contributed to an acute admission. Diuretics were most frequently associated with an ADE, followed by coumarins, immunosuppressants and NSAIDs. ADEs by antidiabetics, antidepressants, antihypertensives, and antipsychotics were related to more than half of the cases with a fall. ADEs by diuretics, theophylline, antipsychotics, antidepressants, antihypertensives and lithium occurred in many cases in combination with delirium.

Correlates of ADEs

Table 4 shows the analysis of variables associated with an ADE contributing to a hospital admission. According to the bivariate analysis, a confirmed ADE at admission was associated with a fall, and also with use of diuretics, NSAIDs and prednisolone. Delirium was not significantly associated with an ADE in this analysis. The multivariate logistic regression analysis showed that a fall just before acute hospitalization and diuretics were independently associated with an ADE-related hospital admission.

Table 5 shows the results of a similar analysis including only ADEs involving psychoactive medication (n=35). In this group, both delirium and falls were associated with ADEs, as were the use of antipsychotics and opioids. These associations remained similar after adjustment except the odds ratio for delirium (OR=1.93) did not remain significant. Post hoc power calculations revealed that our study did not have adequate power to detect a delirium effect.

Discussion

This study demonstrated that in a cohort of older hospitalized patients, a fall sustained one week before admission is associated with ADE-related hospital admissions and prevalent delirium is associated with specific pharmacological groupings. These findings have important clinical implications. From the perspectives of patient safety and health care costs, timely recognition of both geriatric conditions and their possible associations with an ADE might reduce unnecessary hospital admissions. Previous studies² have investigated incidence and types of preventable adverse events, but to our knowledge, our study is the first to study associations of geriatric syndromes and ADEs contributing to hospital admission. After adjustment for demographic and other variables, the association with falling as a geriatric syndrome contributing to hospital admission remained strong.

Over 25% of the elderly patients were hospitalized due to ADE-related admissions. Our results on the frequency of this number of ADEs are compatible with the literature.²² The prevalence rates of delirium in our study are consistent with those reported in literature.¹⁴ Although delirium had a high prevalence in another ADE study in older medical patients, the association between ADEs and delirium or other geriatric syndromes was not investigated.^{22,23} The prevalence of prior falls in our study is lower than that reported by other studies, although the difference is small. We attribute this to a relatively younger population (65 years and above) and to an underreported number of falls.^{12,13} The pharmacological groups most frequently causing an ADE in our study (diuretics, coumarins, NSAIDs and platelet aggregation inhibitors) correspond to findings in literature.^{24–26} Preventative measures should be focused on these high-risk groups. Our study showed that antidiabetics and antihypertensives were the most commonly prescribed drugs, and that antipsychotics and antidepressants coincided with a fall in more than half of the cases. Although a possible causative relationship was not studied, it can be hypothesized that uncontrolled blood glucose, low blood pressure and other failing physiological systems in older patients can facilitate falling and hospital admission.⁷

The strength of our research is that it is based on a large hospital study that provides prospectively collected data on geriatric syndromes and other characteristics in addition to the ADEs. This study investigates both community dwelling elders and residents of old peoples homes and nursing homes, giving a complete picture of the whole range of acutely hospitalized elderly persons. Because of the more detailed data on the patients' clinical presentation it was possible to incorporate relevant additional measures to study ADE-related hospital admissions. In particular, complete assessment of geriatric syndromes, by means of a Comprehensive Geriatric Assessment (CGA) has not been systematically accounted for in other ADE studies. The importance of these and perhaps also other geriatric conditions should not be underestimated because their presence reflects reduced physiological reserves and may throw a shadow on their functional trajectory after discharge.

Our study also has important limitations. Firstly, all ADEs were retrieved from discharge summaries, potentially resulting in a selection bias with only the most severe cases being detected. For instance there might be a possibility that sedative medications, that are associated with impaired physical function and falls, are under-reported, although our incidence and prevalence rates coincide with literature.^{22,23} Secondly, there might exist a potential diagnostic bias. As we might have been aware of the fact that the patient had a fall prior to admission – we might have been more likely to detect a hospital admission related to medication as well. Thirdly, we did not study the severity or preventability of ADEs because this was outside the scope of our study. Fourthly, we expected to confirm an association between a prior vulnerable state, reflected in functional and cognitive impairment or in the prevalence of delirium and ADE related admission, but in the bivariate analysis this could not be demonstrated for all three variables or for age per se. This obvious association could not be demonstrated in our population. Within a restricted population of acutely admitted older medical patients, higher age and other characteristics of frailty are the norm. This is consistent with other studies confined to the geriatric age group.²² Since the geriatric syndromes, delirium and falls, were only assessed after the ADEs had already occurred, temporal association and causality cannot be determined in our analyses, and may have influenced the associations seen, such as for delirium. Although delirium is often ascribed to medications and adverse drug events, in our present analysis, delirium did not retain significance in the final model, and was only associated with psychoactive medication. In the post hoc analysis our study did not have adequate power to examine a delirium effect. As we expected to find more evidence of also a relationship between delirium and ADEs, we carefully examined literature on this subject. In our review of the literature, we could not identify any previous studies examining the independent relationship between ADEs and geriatric syndromes (delirium and falls). In a large ambulatory cohort, only 2.4% of all ADEs presented with neuropsychiatric symptoms, including delirium.²³ Fourthly, some pharmacological groups show a strong association in the multivariate analysis. It is important to note that the geriatric syndromes and pharmacological groups might act as mediators of the effect between ADEs and hospitalization, thus, their independence and causal relationships cannot be established in these analyses, which must be considered associational only. Fifthly, some of the geriatric syndromes may be discounted in a manual review of these ADE lists because they were less clinically dramatic, less characteristic of drug effects in general or may have subtle pharmacological explanations. They may only become recognized when post hoc analyses are sought based on more refined pharmacological knowledge of illness presentations in vulnerable older patients. Additionally, geriatric syndromes presenting atypically often fall out of view because many preventative measures are single disease-oriented and not complex problem-oriented. Disease management is too often insufficiently equipped to address vulnerable patients whose health care utilisation is related to multiple interacting problems and

diseases. This study therefore has relevance to the shared care of elderly persons and promotes hospital care management of both diseases and disabilities in vulnerable patients.

Conclusions

In conclusion, to prevent elderly patients from unnecessary admissions, more proactive, preventative initiatives should be undertaken, especially in primary care. This could lead to a timely identification of ADEs revealing themselves as an atypical illness presentation, namely with a fall or delirium as a geriatric syndrome. Or even to prevention from an acute hospital admission. Additionally, geriatric syndromes presenting in hospital patients need a more systematic and holistic approach to recognize them in time as potential 'atypical' presentations of an ADE. Geriatric syndromes, especially falls, may indicate important warning signs and thus may require additional evaluations to understand potential underlying pathological processes like harmful medications.

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Table 1

Pharmacological Groups associated * with Delirium and Falls, n=647

Pharmacological group (n)	Falls (%)	p-value	Delirium (%)	p-value
Antidepressants, <i>n</i> = 38	6 (15.8)	0.77	15 (39.5)	0.05
Antipsychotics, <i>n</i> = 37	8 (21.6)	0.15	23 (62.2)	<0.001
Opioids, <i>n</i> = 15	1 (6.7)	0.38	5 (33.1)	0.52
Diuretics, <i>n</i> = 265	29 (10.9)	0.23	70 (26.4)	0.80
Antiepileptics, <i>n</i> = 9	0 (0)	0.21	7 (77.8)	<0.001
Prednisolone, <i>n</i> =69	6 (8.7)	0.33	12 (17.4)	0.09
NSAIDs, <i>n</i> =65	9 (13.8)	0.69	15 (23.1)	0.59

*
tested with Chi square

Table 2**Patient Characteristics at Admission**

Variable	Patients (n=641)
<u>Demographic</u>	
Age (mean, sd)	77.8 (7.9)
Male (%)	45.6
Years of education (mean, sd)	9.3 (3.5)
Ethnic background, n (%)	
Caucasian	88.5
<u>Social status, n (%)</u>	
Single / Widowed / Divorced	53.7
Married / Living with partner	46.3
<u>Living arrangement, n (%)</u>	
Independent	67.6
Senior residence	16.8
Old people home	10.7
Nursing home	3.9
Intermediate care	1.0
<u>Medical history</u>	
Charlson co-morbidity index, mean (sd)	3.4 (2.3)
Pre-existing functional impairment	
Katz score, mean (sd)	5.1(3.8)
Pre-existing cognitive impairment (%)	28.6
<u>Situation at admission</u>	
MMSE, mean (sd)	21.5 (6.9)
ADE associated hospital admission (%)	25.8
Delirium prevalence on admission (%)	25.9
Fall within one week before hospital admission (%)	12.0
<u>Diagnostic ICD category (%) *</u>	
Neurologic disease	0.8
Infectious disease	53.3
Endocrine disease	6.5
(Hematologic) malignancy	22.0
Pulmonary disease	8.2
Cardiovascular diseases	9.9
Gastrointestinal disease	33.5

sd = standard deviation; ADE=adverse drug events; MMSE= Mini Mental State Examination; ICD= International Classification of Diseases

* inclusion in multiple categories possible

Table 3

Pharmacological Groups Associated with All Identified Adverse Drug Events (n=167) and Prevalence of Delirium and Fall within that group

Pharmacological Group	ADEs n=167 (%)	Pharmacological group associated with ADE in those who sustained a fall (%) [#]	Pharmacological group associated with ADE in those with prevalent delirium (%) [#]
Diuretics	49 (29.3)	22.4	46.9
Coumarins	20 (12.0)	15.0	25.0
Immunosuppressants	20 (12.0)	10.0	5.0
NSAIDs	17 (10.2)	11.8	29.4
Antidiabetics	13 (7.8)	53.8	38.5
Platelet aggregation inhibitors (Acetylsalicylic acid / Carbasalate calcium)	11 (6.6)	9.1	9.1
Antibiotics	8 (4.8)	37.5	12.5
Opioids	8 (4.8)	12.5	28.6
Prednisolone	4 (2.4)	25.0	25.0
Antihypertensives	4 (2.4)	75.0	50.0
Antidepressants	3 (1.8)	50.0	100
Digoxin	2 (1.2)	0	0
Theophylline	2 (1.2)	0	100
Antipsychotics	2 (1.2)	50.0	100
Lithium	1 (0.6)	0	100
Calcium	1 (0.6)	0	0
Antihistamines	1 (0.6)	0	0
Diagnostics	1 (0.6)	0	0
Total	167	NA	NA

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; NA= Not Applicable; ADE=Adverse Drug Event;

[#] A patient could have both sustained a fall and have presented himself with delirium at admission in combination with an adverse drug event; percentages in columns two and three summated can therefore exceed 100%

Table 4

Factors associated with an ADE (n=167) Contributing to a Hospital Admission Identified by Bivariate and Multivariate Logistic Regression Analysis

Variable	Bivariate analysis		Multivariate analysis	
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
<u>Demographic</u>				
Age (continuous)	1.01	0.99–1.03		
Male (dichotomous)	1.25	0.86–1.81		
Yrs of education (continuous)	1.00	0.94–1.06		
Living independent (dichotomous)	0.82	0.46–1.46		
Social situation (dichotomous)	1.07	0.68–1.70		
<u>Medical history</u>				
Charlson co-morbidity index	0.97	0.89–1.05		
Pre-existing functional impairment				
Katz ADL index score	1.00	0.99–1.01		
Pre-existing cognitive impairment	1.00	0.99–1.01		
<u>Situation at admission</u>				
Prevalent delirium	1.21	0.81–1.80		
Fall within one week before admission	2.06	1.26 – 3.36	2.27	1.16 – 4.45
<u>Pharmacological group</u>				
Antidepressants	0.82	0.39–1.74		
Antipsychotics	1.18	0.57–2.44		
Opioids	1.53	0.54–4.38		
Diuretics	3.10	2.12 – 4.53	3.87	2.33 – 6.42
Antiepileptics	1.81	0.48–6.84		
Prednisolone	1.98	1.14 – 3.44	1.90	0.58–2.85
NSAIDs	2.82	1.60 – 4.97	5.87	2.70 – 13.01

ADE= Adverse Drug Event; in bold the significant results; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; ADL= Activities of Daily Living

Table 5

Factors associated with a Psychoactive Medication related ADE (n=35) Contributing to a Hospital Admission identified by bivariate and multivariate logistic regression analysis

Variable	Bivariate analysis		Multivariate analysis	
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
<u>Demographic</u>				
Age (continuous)	0.99	0.94–1.05		
Male (dichotomous)	1.78	0.72–4.41		
Living independent (dichotomous)	0.76	0.27–2.14		
Social situation (dichotomous)	0.99	0.43–2.28		
<u>Medical history</u>				
Charlson co-morbidity index	1.09	0.94–1.26		
Preexistent functional impairment				
Katz ADL index score	1.07	0.96–1.19		
Preexistent cognitive impairment	1.58	0.65–3.81		
<u>Situation at admission</u>				
Prevalent delirium	2.05	1.01 – 4.15	1.93	0.76–4.94
Fall within one week before admission	3.00	1.40 – 6.40	3.69	1.41 – 9.67
<u>Pharmalogical group</u>				
Antidepressants	1.83	0.61–5.48		
Antipsychotics	3.36	1.29 – 8.74	3.70	1.19 – 11.60
Opioids	5.71	1.72 – 18.90	14.57	2.02 – 105.30
Diuretics	0.78	0.38–1.58		
Antiepileptics	4.27	0.85–21.37		
Prednisolone	1.41	0.52–3.78		
NSAIDS	0.81	0.24–2.73		

ADE= Adverse Drug Event; in bold the significant results