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Antipsychotic prescription patterns in the management of delirium symptoms in hospitalized elderly patients

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Abstract

Objective: The objective of this study was to study the pharmacological management of delirium in elderly hospitalized patients in acute geriatric medical wards.

Method: We conducted a one-year retrospective cross-sectional study in patients 65 years of age or older who were admitted to an acute geriatric unit care at a teaching hospital with a delirium diagnosis.

Results: A total of 133 subjects were included in the study. Delirium was prevalent in 78% of patients. The average length of delirium was 13 days. Antipsychotics were prescribed to 74% of patients with delirium. Patients with hyperactive, mixed and hypoactive delirium received antipsychotics regularly in a proportion of 68%, 54%, and 34% respectively. The length of antipsychotic prescription was of 11 days. Risperidone was the most commonly prescribed agent given on a regular basis while haloperidol was chosen for the as required prescriptions. Fifty-five percent of demented patients received a daily prescription of antipsychotics compared to 46% in the non-demented population. A shorter length of delirium episodes in subjects with acetylcholinesterase inhibitors was also observed. A higher mortality rate was observed in the group of subjects receiving benzodiazepine during the delirium episode.

Conclusion: This study shows that antipsychotic treatment is widely, but not systematically prescribed in demented and non-demented patients in all types of delirium including hypoactive. Efforts should be made to increase appropriate antipsychotic prescription in this vulnerable population.

Keywords

Elderly patients, delirium, antipsychotic agents

Introduction

Delirium is an acute confusional disorder associated with impairment of cognitive and perceptual function, and an alteration in consciousness and attention. The onset of delirium occurs in a short time, often within a few hours or days, and the symptoms fluctuate throughout the day.[1]

The prevalence of delirium upon hospital admission is 25% while the incidence of in-hospital delirium ranges from 20 to 29%.[2] Delirium may decrease patient's functional capacity and increases healthcare costs. In a meta-analysis, mortality, institutionalization and dementia increased following a delirium.[3] The cost attributable to delirium ranges from $16,303 to $64,421 per year.[4]

This study aims to study the pharmacological management of delirium in elderly hospitalized patients in acute geriatric medical wards. The research hypothesis is that antipsychotic agents are widely used despite the lack of evidence.

Method

Study design

This study is a retrospective cross-sectional study in acute geriatric medical wards at the Centre Hospitalier de l'Université de Montréal (CHUM) from January 1 to December 31, 2012. To be included, subjects must be older

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than 65 years and have a diagnosis of delirium. Delirium diagnosis was confirmed when it was written in the patient chart or in the presence of validated keywords.[5] The diagnosis of delirium was made by experienced geriatricians according to the DSM-IV diagnostic criteria.[6] Subjects with a length of stay inferior to 24 hours, in palliative care, proceeding from or transferred to intensive care ward or in a post-operative period were excluded. Delirium tremens and delirium induced by alcohol and drug poisoning were not included. A patient could only be included once in the study.

The nursing protocol included a delirium assessment using the Confusion Assessment Method (CAM) for all patients in the geriatric ward upon admission and during their stay.[7] Medical management of delirium focuses on the rapid identification and treatment of the causes of delirium. At discharge, all medical diagnosis are reported in the medical summary chart and are coded by the medical archive service according to the International Classification of Diseases, 9th revision.[8] Patients were screened if their chart was tagged with the confusional state code (F05.0, F05.1, F05.8, and F05.9) during the study period. These medical charts were reviewed and selected according to the inclusion and exclusion criteria.

This study did not require the subject's consent as it is not an experimental study and the data was rendered anonymous at the beginning of the process. The study was approved by the CHUM research center ethics committee.

Outcome measures

The demographics, medical data, and the modified Cumulative Illness Rating Scale (mCIRS) were extracted from the medical records. The mCIRS measures the chronic medical illness burden. This tool was modified from the original CIRS and validated in the geriatric population. [9] Delirium was categorized according to the geriatrician's evaluation as hyperactive if the patient was hyperaroused, hyperalert, hallucinated, or agitated; hypoactive if the patient was hypoaroused or lethargic; mixed if the patient had alternating features of the hyper and hypoactive subtypes.[10] The delirium was considered to be prevalent if the diagnosis occurred within 48 h of hospital admission. All other deliriums were regarded to be incident. The onset of delirium was registered when a validated keyword was used by any professional caregiver in the patient chart. The resolution of delirium was registered when the patient was described as oriented, coherent, etc. for at least two consecutive days without any delirium symptoms reported by professional caregivers. Antipsychotic agents use, dose, dosage regimen, and duration were collected. The calculation of the length antipsychotic use in delirium excluded the patients whose antipsychotic before delirium since its use may not be restricted to delirium. Antipsychotic use before delirium wasn't used in the length calculation. Predetermined subgroup analysis was carried out for specific confounding variables: concomitant acetylcholinesterase inhibitor (AChEI) use, the presence of dementia, delirium categories, and benzodiazepine use.

Statistical analysis

SPSS software was used to assess the statistical analysis, and an alpha value of 0.05 was chosen. The continuous variables are described using means and standard deviation and categorical variable using proportions. In the subgroup analysis, differences between continuous variables are analyzed using Student t-test and categorical variable using chi-squared analysis. The difference between the duration of delirium and the antipsychotic prescription is analyzed using paired t-test. Missing data is inherent to retrospective chart based study. By default, all missing data for categorical variables were assigned the value 0 which meant not present and all missing data for continuous variables were collected as missing. A sensibility analysis will be carried out for all variables in which missing data accounted for more than 20% of the data.

Results

During the enrolment period, 432 patients were admitted in a geriatric care unit. There were 181 patients tagged with an ICD-9 code for delirium. A total of 48 patients (26.5%) were excluded for the following reasons: no delirium diagnosis (20), second episode of delirium (19), admitted in palliative care (4), in intensive care (1), not admitted in a geriatric ward (2), under 65 years old (1) and in post-operatory state (1). One hundred thirty-three subjects were included. The prevalence of delirium in medical geriatric wards was 30.8%. Prevalent delirium affected 104 (78%) patients. The demographic and medical characteristics of the study population are reported in Table 1. The patients' drugs before admission are reported in Table 2. Antipsychotics prescribed before admission was twice as frequent in demented patients (26%) compared to none demented patients (14%). Quetiapine (47%) was the most prescribed agent followed by risperidone (34%) and haloperidol (9%). Acetylcholinesterase inhibitors were present in 29 patients.

During hospitalization, 50 (38%) had hypoactive delirium, 44 (33%) a mixed form, and 39 (29%) a hyperactive form. Restraint use was necessary for 38% of patients. At discharge, 68 patients (51%) returned to their earlier residence, eight (6%) moved from their home to a senior residence, 12 (9%) from their home to a long-term care center (LTC), and 15 (11%) from a senior residence to LTC. Seventeen patients (13%) died and 10 patients (8%) were lost in follow-up due to a transfer to a non-geriatric unit.

Regarding medication, 98 (78%) patients were prescribed antipsychotics of which 73 (74%) patients were naïve to antipsychotics. Table 3 describes the antipsychotic medication during hospitalization. Among the 17 patients who received a regular antipsychotic in the hypoactive subpopulation, six had an antipsychotic prior to admission and 11 were started during the hospital stay.

The average length of delirium episodes was 13 days, where 10% of them lasted more than one month. After removing subjects who already had antipsychotics prior to admission, the mean duration of regular and pro re nata (PRN) antipsychotics were of 16.8 ($n = 46$) and 20.7 ($n = 66$) days respectively. There was no difference in duration between the delirium period and regular ($p = 0.072$) and PRN ($p = 0.104$) antipsychotic prescriptions. For the subgroup of patients receiving regular antipsychotics for a longer duration than delirium ($n = 9$), the mean difference was of seven days (mean duration 17 days; $p = 0.056$).

Table 1. Demographic and clinical characteristics of the study population.

Age, years – mean ± SD	86 ± 7
Female – no. (%)	83 (62)
Place of residence prior to admission – no (%)	
Own home	65 (49)
Senior residence	59 (44)
Long term care	9 (7)
Vision impairment – no. (%)	58 (44)
Hearing impairment – no. (%)	41 (31)
Smokers – no. (%)	15 (11)
Alcohol consumption – no. (%)	8 (6)
Cognitive status	
MMSE – mean ± SD	21 ± 6
Dementia – no. (%)	77 (58)
Dementia subtype – no. (%)	
Mixed	34 (26)
Alzheimer	25 (19)
Vascular	11 (8)
Lewy body	7 (5)
Dementia severity – no. (%)	
Mild	57 (74)
Moderate	15 (20)
Severe	5 (6)
Prior history of psychiatric disorder – no. (%)	8 (5)
CIRS score – mean ± SD	14,1 ± 4.9
CIRS elements – no. (%)	
Heart	69 (52)
Hypertension	109 (82)
Vascular	82 (62)
Respiratory	77 (58)
Eyes, Ears, Nose, Throat & Larynx	78 (59)
Upper GI	72 (54)
Lower GI	79 (59)
Hepatic	27 (20)
Renal	71 (53)
Genitourinary	95 (71)
Musculoskeletal	99 (74)
Neurological	77 (58)
Endocrine / metabolic & breast	89 (67)
Psychiatric	133 (100)

Table 2. Medication prior to admission.

Cardiovascular drugs – %	
Antiplatelet	53.4
Anticoagulant	15.8
Statin	30.1
Beta blocker	38.3
Digoxin	7.5
ACEI/ARB	48.1
CCB	30.1
Loop diuretic	16.5
Thiazide diuretic	12.0
Central nervous system drugs – %	
Antidepressant	31.6
Benzodiazepine	30.1
Antipsychotic	19.5
Antiepileptic	12.0
AChEI	21.8
Memantine	3.0
Other drugs – %	
PPI	45.9
Opiate	9.0
Vitamin D	49.6
Antimuscarinic	5.3
Insulin	4.5
Oral antihyperglycemic agents	4.5

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; AChEI: acetylcholinesterase inhibitors; PPI: proton pump inhibitor.

Table 3. Management of delirium symptoms according to the type of delirium.

	Hypoactive	Hyperactive	Mixed
Patients – no. (%)	50 (38)	44 (33)	39 (29)
Use of restraint – no. (%)	9 (18)	19 (44)	22 (57)
Antipsychotic use – no. (%)	25 (50)	36 (92)	38 (86)
Dosage regimen			
Regular basis only	5 (20)	4 (11)	1 (3)
As needed only	8 (32)	15 (42)	8 (21)
Regular and as needed	12 (48)	17 (47)	29 (76)
Timeline (antipsychotic on a regular basis)			
Antipsychotic prior to admission and kept at discharge	6 (35)	5 (24)	7 (23)
Antipsychotic started in hospital and kept at discharge	4 (24)	7 (33)	13 (44)
Antipsychotic only during hospital stay	7 (41)	4 (19)	7 (23)
Antipsychotic prior to admission and stopped at discharge	0	5 (24)	3 (10)

For patients who started an antipsychotic treatment, one-third continued after discharge (n = 24). For those who already had an antipsychotic at home, 69% kept the antipsychotics during hospitalization and after discharge. The description of the physician drugs selection, their dose and duration are described in Table 4.

Our first subgroup analysis compared subjects treated with and without AChEI prior and during delirium. The demographic characteristics were similar across both groups. The mean length of delirium was shorter (10 days) in the AChEI group compared to the other group (14 days) (p < 0.05). Delirium presentation and treatment were similar.

In the dementia subgroup analysis, the mean mini mental state examination (MMSE) score (19) was three points (confidence interval (CI): 1.0; 5.6) lower than in the non-demented population. The length of stay was 10 days shorter (CI: 1.7; 18.3) in the non-demented population (27 days). The mean duration of regular and PRN antipsychotic treatment was 22 and 24 days, respectively, in demented patients, which was 9 days (CI: 1; 17) longer than in patients without dementia. There were no significant differences in delirium lengths. Fifty-five percent of demented patients received a prescription of antipsychotics on a regular basis compared to 46% in the non-demented population. The rate of antipsychotics at discharge

Table 4. Description of antipsychotic agent selection in delirium.

Drug	Risperidone	Quetiapine	Olanzapine	Haloperidol
Regular prescription – no. (%)	96 (72)	44 (33)	8 (6)	8 (6)
Daily dose, mg – mean ± SD	0.5 ± 0.5	50 ± 62	3 ± 2.4	2.5 ± 2.2
Patients with PRN prescription – no. (%)	24 (18)	25 (19)	0	112 (84)
Proportion of PRN dose given	2%	7%	0	2%

was significantly higher for demented patients, reaching 39% compared to 21% of subjects without dementia.

There was no significant difference the demographic characteristics of the three delirium subtypes. As shown in Table 3, the mixed form had the highest proportion of patients with restraint, and with regular and PRN antipsychotic medication during their stay and at discharge. The average length of delirium was 19 days for the mixed form and 10 days for the hypoactive and hyperactive forms. PRN antipsychotic treatment lasted 12 days longer for the mixed type compared to the hypoactive form.

Among the 17 subjects who died during the study, 12 of them had benzodiazepine treatment during their delirium episodes. Among these 12 patients, eight didn't carry a benzodiazepine before admission. The rate of mortality of these subjects accounted for 21% compared to a 13% for the other subjects. ($p = 0.011$) Benzodiazepines were all used on a regular basis. They were mainly prescribed at bedtime indicating a use for insomnia rather than for agitation. The indication for benzodiazepine use was not clearly indicated in the chart.

Discussion

Delirium is often misdiagnosed especially in its hypoactive form. In the CHUM geriatric wards, the nursing staff is trained to recognize delirium and uses the CAM assessment tool. The observed prevalence of delirium in this study is similar to that in Inouye et al.'s literature review,[7] showing an average prevalence of 25%. It is possible that it might have been misdiagnosed in this study but the number is probably low because of the efforts in detection and prevalence similar to that of a comparable geriatric population. The sample is, therefore, representative of the delirium population of an acute geriatric ward.

Neuroleptic drugs remain widely used for delirium symptoms despite the FDA black box in elderly demented patients.[11] They are associated with an increased risk of stroke and mortality.[12] They were prescribed to 74.4% of our population. Hence, a larger proportion of prescription of regular antipsychotic was in the subjects suffering from dementia. We should state that the black box warning was for antipsychotics used to treat dementia-related behavioral disorders. It doesn't address the short term use of these drugs in delirium. Demented patients accounted for 75% of patients discharged with antipsychotics. This remains a particular concern since the possible adverse effects of antipsychotics will be monitored less closely in the community setting.

The Canadian guidelines state that psychotropic medications can be used for delirium,[13] but should be reserved for patients who are in significant distress due to agitation or psychotic symptoms. Surprisingly, neuroleptics were not only prescribed to the hyperactive and mixed delirium patients as a third of the hypoactive delirium population received antipsychotics regularly. The reason on this prescription is unclear. It could be explained by the prescription of chronic medication or the wrongful tagging of hypoactive delirium because of missing data in the patient chart. Regardless of the reasons, further efforts should be made in holding these drugs since they are generally inappropriate in hypoactive delirium.

The Canadian guidelines cannot recommend whether a regular or PRN dosage is preferable. Hence, there is no clinical trial on the efficacy and safety of PRN antipsychotic administration. The lack of data and clear recommendations can explain why regular and PRN and mostly both dosage regimen were used. The relevance of as required prescriptions may be questioned since less than 7% of possible doses are actually administered. We must point out that the study was carried out in a teaching hospital where medical residents prescribe and geriatricians can, later on, correct the prescription. This may explain the large range of prescription dosage. Clinical trials are needed to determine the most effective drug dosage regimen.

The length of antipsychotic use remains a controversial issue. The Canadian guideline recommends tapering antipsychotics as soon as possible. Studies on the efficacy of antipsychotics used an average of ten days treatment duration.[14–19] However, these studies are not specific to the geriatric population. Further clinical trials should investigate the efficacy and safety of a longer duration of antipsychotic treatment. Some patients were prescribed antipsychotics longer than the delirium period. This may be explained by prolonged antipsychotic tapering, a period of delirium unreported in the patient's chart or the development of behavioral and psychological symptoms of dementia.

The clinicians' choice regarding the antipsychotic agents was haloperidol for PRN treatment, risperidone and quetiapine for regular treatment. Since most subjects had dementia, the clinicians' choice of a regular treatment with atypical over typical antipsychotics follow the Canadian recommendations.[13]

Subjects treated with AChEI had on average four days less delirium than others, supporting the hypothesis that AChEI help to shorten delirium, in correlation with a possible disturbance in the cholinergic system initiating the delirium state. As all subjects with AChEI were subjects with dementia, the clinician could meet difficulties to clearly distinguish delirium episodes when the subject's medical history was not accessible. It could lead to a more vague perception of the distinction between the delirium and the underlying demented state. Some studies also suggested that delirium persists longer than believed, with symptoms lasting for months or years.[20] This idea of persistent delirium blurs a little more the boundaries between these two conditions. AChEI is mainly

used in Alzheimer and Lewy body dementia. It is possible that the type of dementia could also affect the outcome of delirium. Therefore, the efficacy of AChEI in delirium remains to be confirmed.

A higher mortality rate was observed in the group of subjects receiving benzodiazepine during the delirium episode. This raises a safety issue for the use of this drug in delirium patients even for insomnia. Abrupt discontinuation of benzodiazepine may cause delirium so it should be avoided or done with caution.[21] The initiation of benzodiazepine in delirium patient should be avoided until further studies assess the risk of benzodiazepine prescription in elderly patients with delirium.

As a retrospective study, the only information we could access is the one available in the medical charts; therefore missing data is a clear limit since information or patients can be missing if they weren't tagged with delirium in their chart summary. This study doesn't allow us to establish a causal link between the antipsychotic treatment and the evolution of delirium, but can provide an assessment of current clinical pharmacological management of delirium and guide future prospective studies.

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Declaration of Conflicting Interests

The authors declare that there are no conflicts of interest.

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