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Delirium Management in Patients with Cancer: Dosing of Antipsychotics in the Delirium Subtypes and Response to Psychopharmacological Management

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Abstract

Background: While delirium resolution and persistent delirium in hypoactive and hyperactive delirium have been studied to a certain extent, doses of antipsychotics administered remain unknown.
Methods: Patients treated for cancer were recruited at the Memorial Sloan Kettering Cancer Center (MSKCC). Sociodemographic, medical variables, the Memorial Delirium Assessment Scale (MDAS) subitems (1–10) as well as the Karnofsky scale of Performance Status (KPS) were recorded at baseline (T1), 2–3 days (T2) and 4–7 days (T3) and analyzed in respect to the subtypes of delirium and medication doses administered.
Results: Between haloperidol, risperidone, olanzapine and aripiprazole, differences existed in respect to the prevalence of dementia, stage of illness, baseline MDAS scores, delirium resolution, and functional status. When hyperactive delirium was present, doses reached fourfold those administered in hypoactive delirium. In particular, haloperidol and olanzapine were administered at higher doses in order to achieve symptom control. When aripiprazole was administered, dosing was similar between the subtypes. Generally, the response to management with antipsychotics was similar between the delirium subtypes, although a trend towards a greater response in hypoactive delirium was noted. However, factors known to cause persistent delirium influenced delirium resolution.
Conclusion: The interaction of factors contributing to resolved and persistent delirium in the hypoactive and hyperactive subtype remains complex. In general, the response was comparable between the subtypes. However, patients with hyperactive delirium required higher doses of antipsychotics in order to achieve symptom control (German J Psychiatry 2014; 17(1): 10-18).

Keywords: delirium, management, delirium resolution, delirium subtypes, dosing of antipsychotics

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Introduction

The management of delirium involves four steps: 1 – the identification of underlying etiologies, 2 – appropriate medical intervention to treat reversible etiologies, 3 – initiation of environmental interventions to provide safety and support management of delirium with antipsychotics, and 4 – relief of distressing symptoms with antipsychotics (Trzepacz et al., 1999). Although there is controversy on actively managing delirium with antipsychotics (Devlin & Skrobik, 2011; Girard et al., 2010), in particular in the elderly, the necessity of appropriate delirium management remains undebated (Cole et al., 2009; Cole, 2010; Fong et al., 2009; Gross et al., 2012; Kiely et al., 2009; Trzepacz et al., 1999).

Delirium resolution and persistent delirium have been an ongoing interest in research. However, results remain conflicting (Dasgupta & Hillier, 2010). Among sociodemographic variables, advanced age and dementia have been recognized as factors contributing to persistent delirium (Breitbart et al., 2002; Kiely et al., 2004; Levkoff et al., 1992; McCusker et al., 2003). In contrast, the absence of dementia has been associated with the complete reversal of delirium symptoms (Camus et al.,

2000; Inouye et al., 2007). Furthermore, the severity of illness or number of medical problems have also been identified as a factor contributing to persistent delirium (Inouye et al., 2007; Kelly et al., 2001). Among etiologies, hypoxic illness has been shown to cause persistent delirium (Lawlor et al., 2000). Further, the severity of delirium has been found to impact delirium resolution as well as the presence of hypoactive delirium (Breitbart et al., 2002; Kiely et al., 2004). Whether the baseline functional status causes prolonged delirium, has not yet been determined (Adamis et al., 2007; Breitbart et al., 2002; Kiely et al., 2004).

Few delirium management studies have examined the subtypes of delirium and have used different definitions for them. One review, basing the subtype on the level of alertness, has indicated that the hypervigilant subtype has had the most favorable outcome (Olofsson et al., 1996). Another study using the psychomotor subtype and managing delirium with Olanzapine has found lower response rates in patients with hypoactive delirium (Breitbart et al., 2002). In addition, advanced age, brain pathology, hypoxic illness, and severity of delirium have been identified as confounders to persistent delirium. In contrast, another study investigating management of delirium with risperidone has not been able to document differences in response between the hypoactive and hyperactive subtype (Liu et al., 2004).

To date, the dosing of antipsychotics in hypoactive and hyperactive delirium has not yet been studied. The etiopathological model of delirium describing a final pathway involving a dopamine-acetylcholine imbalance (Trzepacz, 2000) suggests a different management approach with higher levels of dopamine antagonism – i.e. higher doses of antipsychotics – in hyperactive delirium. Furthermore, the response to management with antipsychotics in the psychomotor subtypes of delirium remains understudied.

The purpose of this study was to explore dosing regimen of antipsychotics and their response in the management of the hypoactive and hyperactive subtype of delirium.

Methods

Patients

All patients were treated for cancer and recruited from referrals for delirium management to the Memorial Sloan Kettering Cancer Center (MSKCC) Psychiatry Service from July to November 2000 and from July 2004 to June 2006 (table 1). MSKCC is a 470 bed, private hospital specializing in the treatment of cancer, averaging more than 20,000 admissions every year. The Consultation-Liaison Psychiatry service performs on average more than 2,000 consultations yearly.

The inclusion criterion was meeting the DSM-IV-TR (American Psychiatric Association, 2000) criteria for delirium. Exclusion criteria included patient or family objections to pharmacologic intervention, inability to participate with delirium rating measures, and severe agitation interfering with the interview.

All patients and their families provided verbal consent to being evaluated and receiving antipsychotics for symptomatic relief of delirium. In patients with limited capacity to provide consent, the patient's primary caregiver provided verbal consent alongside with the patient's assent to intervention. All data was obtained from the routine care of patients diagnosed with delirium and entered into the Institutional Review Board (IRB)-approved database for subsequent analysis, and a waiver obtained for the data analysis.

Measurements

Delirium severity was measured with the MDAS, a 10-item, four-point, clinician-rated scale (Breitbart et al., 1997). The MDAS items reflect the diagnostic criteria for delirium in the DSM-IV-TR and assess disturbance in arousal and level of consciousness, cognitive functioning such as orientation, memory, attention, and perception, as well as psychomotor activity. MDAS scores higher than 10 identified the presence of delirium and MDAS scores of 10 or lower indicated the resolution of delirium in this analysis (Kazmierski et al., 2008; Lawlor et al., 2000). The categorization of delirium was based on the psychomotor subtype, hypoactive and hyperactive (Camus et al., 2000; Meagher & Trzepacz, 2000). Additional scales included the Karnofsky Scale of Performance Status (KPS) (Karnofsky & Burchenal, 1949) to provide a measure of physical performance ability. Scores of less than 50 indicate the inability to care for self, requiring hospital care, a score of 40 indicates a disability with the need for assistance, a score of 30 a severe disability requiring hospital admission, a score of 20 the need for hospital admission and active treatment in a very sick patient, and a score of 10 a moribund state.

Procedures

Sociodemographic and medical variables were collected at the initial assessment (T1). This information included age, gender, cancer diagnosis, stage of cancer (localized, advanced, metastatic, or terminal), current psychiatric diagnosis, history of dementia, presence of brain metastases, and contributing delirium etiologies. All etiologies deemed to be present were recorded. These etiologies included the administration of opioids and corticosteroids, hypoxia, infection, CNS disease, other CNS disease, and dehydration. MDAS and KPS scores were obtained, and side-effect rating was performed at initial diagnosis of delirium (T1) and repeated at 2-3 days (T2) and 4-7 days (T3).

Antipsychotic medication was initiated upon diagnosis of delirium and adjusted as determined by clinical response. Generally, haloperidol and risperidone were administered in more severe delirium. When sedation was required, olanzapine was administered. However, when patients were older or hypoactive delirium was present, olanzapine was not the medication of choice, since in a previous study, limitations have been shown in this population and type of delirium (Breitbart et al., 2002). Aripiprazole was chosen in an attempt to establish its efficacy and chosen usually in less severe delirium and the hy-

Table 1. Baseline and medical characteristics of patients (N=111)

	Hypoactive Delirium (N=49)	Hyperactive Delirium (N=62)	Statistics
Age (years)	64.9 (29-89, SD 12.6)	66.1 (23-85, SD 14.5)	-0.44 (109), p=0.658 [a]
Gender in %			1.09 (1), p=0.335 [b]
Male	53.9	62.9	
Female	46.1	37.1	
Preexisting dementia	14.3	24.2	1.69 (1), p=0.235 [b]
Cancer diagnosis in %			
Brain	6.1	14.5	1.81 (1), p=0.231 [b]
Endocrine	2	3.2	1.54 (1), p=0.504 [b]
Gastrointestinal	28.6	19.4	4.12 (1), p=0.107 [b]
Genitourinary	8.2	9.7	1.13 (1), p=0.386 [b]
Gynecological	10.2	8.1	0 (1), p=1 [b]
Head and neck	6.1	6.5	2.55 (1), p=0.230 [b]
Lung	20.4	22.6	1.77 (1), p=0.231 [b]
Sarcoma	8.2	6.5	0.55 (1), p=0.632 [b]
Lymphoma	2	-	0.04 (1), p=1 [b]
Skin	2	3.2	0.04 (1), p=1 [b]
Other	-	3.2	1.50 (1), p=0.213 [b]
Stage			
Localized	26.5	41.7	2.31 (1), p=0.160 [b]
Advanced	46.9	48.3	0 (1), p=1 [b]
Terminal	26.5	10	5.55 (1), p=0.024 [b]
Brain metastasis	12.2	6.5	1.12 (1), p=0.332 [b]
Etiologies			
Opioids	93.9	83.9	2.65 (1), p=0.140 [b]
Corticosteroids	49	45.2	0.16 (1), p=0.706 [b]
Hypoxia	42.9	32.3	1.32 (1), p=0.322 [b]
Infection	30.6	19.4	1.88 (1), p=0.188 [b]
CNS disease	14.3	11.3	0.22 (1), p=0.775 [b]
Other CNS disease	14.3	22.6	1.23 (1), p=0.333 [b]
Dehydration	8.2	3.2	1.31 (1), p=0.403 [b]
Total number of etiologies	5.2 (3-8, SD 1.0)	4.8(3-7, SD 1.0)	1235, p=0.078 [c]
MDAS scores at			
Baseline (T1)	16.1 (11-25, SD 3.7)	20.0 (12-30, SD 4.5)	2248, p<0.001 [c]
T2	9.9 (2-21, SD 3.8)	11.5 (1-25, SD 6.0)	1723, p=0.228 [c]
T3	7.3 (1-22. SD 4.0)	8.5 (1-23, SD 5.9)	1625, p=0.528 [c]
Resolved Delirium at			
T2	51	44	0.61, p=0.451 [b]
T3	86	70	4.08, p=0.070 [b]
KPS scores at			
Baseline (T1)	24 (10-40, SD 6)	24 (10-40, SD 6)	1637, p=0.420 [c]
T2	27 (10-60, SD 10)	30 (10-60, SD 11)	1775, p=0.106 [c]
T3	31 (10-60, SD 12)	35 (10-70. SD 14)	1807, p=0.078 [c]

[a] t-test, [b] Pearson's Chi-Square test, [c] Mann-Whitney U test

poactive subtype. In order to achieve symptom control in hyperactive delirium, usually higher doses of antipsychotics were prescribed.

In accordance with the guidelines for the treatment of delirium (Trzepacz et al., 1999), the standard approach was to manage delirium with antipsychotics and continue the necessary medical treatment, including risk factors for delirium such as opiates or corticosteroids, and to treat reversible underlying causes such as hypoxia, infection and dehydration. In order to recognize delirium in patients with comorbid dementia, the focus was set on the abrupt mental status change, the fluctuating course and disturbance of consciousness. In cases in which delirium could not be clearly separated from dementia, the patient was managed empirically in order to provide symptomatic relief to these patients and an improvement in mental status then confirmed the diagnosis of delirium.

Statistical analysis

Data analyses were performed with the Statistical Package for the Social Sciences (SPSS) 20 for Windows. Descriptive statistics were performed to characterize the sample sociodemographically and medically. Separate datasets describing individual medications were created for the comparison of dosing and response. The t-test for independent samples was used for data on the interval scale, such as the age of the patients, the Friedman test for multiple related measures, such as the course of change in MDAS scores of single medications, and the Kruskal-Wallis test for multiple independent measures, such as the comparison of MDAS scores at single times. The Mann-Whitney U test was computed when a comparison of two independent variables was required such as MDAS or

KPS scores and medication doses between hypoactive and hyperactive delirium. Categorical variables, such as the comparison of response to medications, were computed with Pearson's Chi-Square. For all implemented tests, post hoc, the alpha (α) was adjusted with the Bonferroni method. The significance level α was set at $p<0.05$.

Results

Baseline and management characteristics (Table 1)

Sociodemographic and medical variables were not much different between patients with hypoactive and hyperactive delirium. The age of the patients and the gender distribution were not different, nor was the prevalence of dementia or brain metastases. Altogether, patients had an advanced age and dementia existed between 14 and 24%. Among cancer diagnoses, no differences existed between the subtypes. Lung, gastrointestinal, gynecological cancer and sarcoma were the most common illnesses. However, the prevalence of terminal illness was higher in patients with hypoactive delirium. In these patients, one fourth had terminal illness and localized disease, almost half had localized disease, whereas in patients with hyperactive delirium, localized and metastatic disease was present between 42% and 48%, and terminal illness in only every tenth patient. Among etiologies, differences neither existed between the subtypes, nor in the total number of documented etiologies contributing to delirium. The administration of opioids and corticosteroids, hypoxia and infection were the most common identified etiologies contributing to delirium.

At baseline, delirium was more severe in patients with hyperactive delirium. The MDAS score reached 20, whereas in patients with hypoactive delirium, the MDAS mean score was 16. At T2 and T3, no differences existed between hypoactive and hyperactive delirium. Similarly, delirium resolved in approximately one half of patients at T2 and 70-86% of patients at T3, representing a trend towards greater response in hypoactive delirium. Altogether, MDAS scores improved over the course of management in both subtypes (Friedman χ^2 86.71-83.49(2), $p<0.001$).

The functional status as documented with the KPS score was low indicating very ill and functionally impaired patients and not different between patients with hypoactive and hyperactive delirium, although a trend towards more severe impairment at T3 was noted as well as improvement over the course of management in both subtypes (Friedman χ^2 36.36-57.65(2), $p<0.001$).

Baseline medical and management characteristics of haloperidol, risperidone, olanzapine, and aripiprazole (Tables 2a, b)

Between medications, differences were recorded in respect to the prevalence of dementia, stage of illness, medication doses, baseline MDAS scores, delirium resolution, and functional status. The age of patients and gender distribution were not different.

Dementia was more prevalent in patients managed with aripiprazole with hyperactive delirium. In patients managed with haloperidol, terminal illness was present in one third of patients compared to every twentieth in those with hypoactive delirium.

With respect to the dosing of medication, haloperidol was administered at nearly fourfold the dose in hyperactive delirium compared to hypoactive delirium. Similarly, olanzapine was administered at double the dose in hyperactive delirium to achieve symptom control. Furthermore, at baseline, risperidone was administered at 50% higher doses in hyperactive delirium, whereas at T2 and T3 the difference did not yield significance. Only in patients managed with aripiprazole, dosing was similar between the subtypes of delirium.

At baseline, delirium was more severe in patients with hyperactive delirium managed with risperidone and aripiprazole, whereas no differences between medications existed at T2 and T3. With respect to hyperactive delirium, differences between medications were documented in baseline MDAS scores; in olanzapine-managed patients delirium was less severe (Kruskal-Wallis χ^2 11.86(3), $p=0.008$).

Only in patients managed with aripiprazole, delirium resolved more often when hypoactive delirium was present. Generally, delirium resolved at rates between 29% and 80% at T2 and 58% to 100% at T3. At T2 and T3, in patients with hypoactive delirium, a trend toward superior delirium resolution existed between medications (χ^2 7.40-7.54(3), $p=0.052$-0.060)

In respect to severity of illness and functional status, patients managed with haloperidol for hypoactive delirium were more severely ill and functionally impaired, whereas patients managed with aripiprazole for hypoactive delirium were less ill and impaired (Kruskal-Wallis χ^2 8.33-13.76(3), $p=0.003$-0.040). In patients managed for hyperactive delirium, no difference existed between medications.

Table 2a. Baseline, medical and management characteristics (haloperidol and risperidone)

	Hypoactive delirium and haloperidol	Hyperactive delirium and haloperidol	Statistics	Hypoactive delirium and risperidone	Hyperactive delirium and risperidone	Statistics
Age	65.2 (42-86, SD 13.2)	61.3 (23-84, SD 18.6)	-0.67(33), p=0.505 [a]	66.0 (29-90, SD 14.3)	69.0 (53-84, SD 9.2)	-0.70 (30), p=0.487 [a]
Gender in %			2.56(1), p=0.153 [b]			0.53 (1), p=0.716 [b]
Male	50	76		69	56	
Female	50	24		31	44	
Preexisting dementia	21.4	14.3	0.30(1), p=0.664 [b]	19	25	0.18 (1), p=1 [b]
Stage						
Localized	21	57	4.38(1), p=0.080 [b]	25	31	0.16 (1), p=1 [b]
Advanced	43	29	0.76(1), p=0.477 [b]	63	57	0.13 (1), p=1 [b]
Terminal	36	5	5.67(1), p=0.028 [b]	13	13	0 (1), p=1 [b]
Medication dose at						
Baseline (T1)	1.5 (1-6, SD 1.5)	5.6 (1-16, SD 2.7)	230, p=0.004 [c]	0.8 (0.25-2, SD 0.5)	1.2 (0.5-2, SD 0.5)	181, p=0.049 [c]
T2	1.7 (1-6, SD 1.7)	5.9 (1-16, SD 3.6)	218, p=0.016 [c]	1.0 (0.25-2, SD 0.6)	1.3 (0.5-3, SD 0.7)	158, p=0.270 [c]
T3	1.8 (1-6, SD 1.8)	5.9 (1-16, SD 3.6)	225, p=0.008 [c]	1.1 (0.25-2, SD 0.7)	1.5 (0.5-3, SD 0.8)	164, p=0.184 [c]
MDAS scores at						
Baseline (T1)	18.8 (12-25, SD 4.7)	22 (13-30, SD 4.7)	199, p=0.083 [c]	15.3 (11-20, SD 2.5)	20.1 (12-26, SD 3.8)	218, p=0.001 [c]
T2	11.3 (2-21. SD 5.0)	10.6 (3-25. SD 5.9)	131, p=0.583 [c]	10.2 (5-15. SD 3.3)	12.7 (1-24. SD 6.1)	165, p=0.171 [c]
T3	9.4 (2-22, SD 5.2)	6.9 (1-21, SD 5.5)	104, p=0.145 [c]	6.6 (2-14, SD 3.2)	8.4 (1-22, SD (5.5)	153, p=0.361 [c]
Delirium resolution at						
T2	29	48	1.27(1), p=0.311 [b]	44	31	0.53 (1), p=0.716 [b]
T3	64	71	0.20(1), p=0.721 [b]	94	75	2.13 (1), p=0.333 [b]
KPS scores at						
Baseline (T1)	19 (10-30, SD 8)	24 (10-30, SD 6)	209, p=0.037 [c]	24 (20-30, SD 5)	24 (20-30, SD 5)	120, p=0.780 [c]
T2	21(10-30, SD 15)	30 (10-50, SD 10)	226, p=0.007 [c]	27 (20-30, SD 9)	28 (20-40, SD 8)	145, p=0.539 [c]
T3	24 (10-40, SD 19)	37 (10-60, SD 14)	230, p=0.004 [c]	31 (20-50, SD 9)	33 (20-50, SD 10)	138, p=0.724 [c]

[a] t-test, [b] Pearson's Chi-Square test, [c] Mann-Whitney U test

Table 2b. Baseline, medical and management characteristics (olanzapine and aripiprazole)

	Hypoactive delirium and olanzapine	Hyperactive delirium and olanzapine	Statistics	Hypoactive delirium and aripiprazole	Hyperactive delirium and aripiprazole	Statistics
Age	62.0 (32-80, SD 12.9)	64.2 (37-78, SD 11.3)	-044(21), p=0.664 [a]	65.7 (46-76, SD 8.7)	72.5 (36-85, SD 13.4)	-1.31 (19), p=0.207 [a]
Gender in %			0.03(1), p=1 [b]			2.29 (1), p=0.153 [b]
Male	50	46		33	67	
Female	50	54		67	33	
Previous dementia	10	23	0.67(1), p=0.604 [b]	0	42	4.92 (1), p=0.045 [b]
Stage						
Localized	30	23	0.14(1), p=1 [b]	33	47	0.15 (1), p=1 [b]
Advanced	30	62	2.25(1), p=0.214 [b]	44	50	0.06 (1), p=1 [b]
Terminal	40	15	1.78(1), p=0.341 [b]	22	8	0.81 (1), p=0.553 [b]
Medication dose at						
Baseline (T1)	2.8 (2.5-5, SD 0.8)	6.2 (2.5-15, SD 0.8)	111, p=0.003 [c]	14.4 (10-20, SD 5.3)	15.8 (5-30, SD 7.0)	59, p=0.754 [c]
T2	3.5 (2.5-5, SD 1.3)	7.3 (2.5-15, SD 1.3)	108, p=0.008 [c]	15.6 (10-20. SD5.3)	16.3 (10-30. SD 6.4)	56, p=0.917 [c]
T3	3.8 (2.5-5, SD 1.3)	7.7 (5-15, SD 1.3)	100, p=0.007 [c]	18.9 (10-30, SD 6.0)	17.9 (10-30, SD 7.2)	48, p=0.702 [c]
MDAS scores at						
Baseline (T1)	14.4 (11-19, SD 3.0)	16.5 (12-26, SD 3.5)	86, p=0.208 [c]	15.6 (11-20, SD 2.8)	19.9 (12-25, SD 4.3)	86, p=0.023 [c]
T2	8.5 (4-12. SD 2.7)	10.8 (4-20. SD 5.2)	79, p=0.410 [c]	8.3 (2-13. SD 3.2)	12.6 (4-23. SD 7.1)	70, p=0.277 [c]
T3	6.8 (2-12, SD 3.2)	9.6 (2-20, SD 6.1)	80, p=0.376 [c]	5.7 (1-9, SD 2.7)	10.3 (3-23, SD 7.0)	75, p=0.148 [c]
Delirium resolution at						
T2	80	54	1.70(1), p=0.379 [b]	67	42	1.29 (1), p=0.387 [b]
T3	90	69	1.43(1), p=0.339 [b]	100	58	4.92 (1), p=0.045 [b]
KPS scores at						
Baseline (T1)	24 (20-30, SD 5)	23 (20-30, SD 5)	59, p=0.738 [c]	29 (20-40, SD 8)	28 (20-40, SD 6)	49, p=0.754 [c]
T2	29 (20-40, SD 7)	26 (10-40, SD 9)	53, p=0.483 [c]	34 (20-60, SD 15)	36 (20-60, SD 16)	57, p=0.862 [c]
T3	31 (20-40, SD 9)	28 (10-40, SD 11)	57, p=0.605 [c]	40 (10-60, SD 19)	42 (20-70, SD 17)	57, p=0.862 [c]

[a] t-test, [b] Pearson's Chi-Square test, [c] Mann-Whitney U test

Discussion

These findings indicated that delirium resolved at similar rates in hypoactive and hyperactive delirium. The course of delirium was affected by severity of delirium and medical illness, pre-existing dementia and level of functioning, factors known to cause persistent delirium. However, higher doses of antipsychotics were required to achieve symptom control in patients with hyperactive delirium.

In particular, in patients with hypoactive delirium, illness was more severe as documented by increased rates of terminal illness and decreased levels of functioning. In addition, a trend towards more etiologies contributing to delirium in this sample was noted. In contrast, delirium was more severe in hyperactive delirium, which has been shown to recover faster than the hypoactive subtype (Olofsson et al., 1996). All these factors have been known to influence the course of delirium.

In general, the doses of medication administered and the rates to which delirium resolved were in line with the existing literature (Seitz et al., 2007). In haloperidol-managed patients, delirium was more severe in the hyperactive subtype, however, resolved further as evidenced by the difference in MDAS scores at baseline and T3. In contrast, terminal illness was more commonly present, illness was more severe and the level of functioning was impaired in patients with hypoactive delirium. The doses of haloperidol for hyperactive delirium were fourfold the dose administered in hypoactive delirium.

In risperidone-managed patients, delirium was more severe when the hyperactive subtype was present. The severity of illness and level of functioning were similar. At baseline, patients with hyperactive delirium required 50% higher doses than those with hypoactive delirium. At T2 and T3, the difference did not reach significance; however, given that the doses of risperidone were the lowest and the sample size was limited, differences would most likely show in larger sample sizes throughout the management course of delirium.

Generally, delirium in the olanzapine-managed patients was less severe in this sample of patients. Still, the medication doses required to achieve symptom control in the hyperactively delirious patients was twice the dose administered to the hypoactively delirious.

In the aripiprazole-managed patients, pre-existing dementia was documented in close to half of the patients with hyperactive delirium, whereas none were found in hypoactive delirium. Also, delirium was more severe in hyperactive delirium. Thus, considering that delirium severity and pre-existing dementia can cause persistent delirium, it is not surprising that the response was less in patients with hyperactive delirium. In addition, no difference in medication administration was noted between the subtypes. For one, this could be explained by the aripiprazole dosing recommendations after introduction, which were generally higher than later recommendations. Also, the pharmacodynamic characteristic of aripiprazole reaching comparable dopamine (D2) antagonism across increasing doses (DeLeon et al., 2004) could have contributed, in contrast to haloperidol, risperidone and olanzapine, which feature a dose-dependent dopamine antagonism.

Overall, hypoactive and hyperactive delirium achieved similar response rates in this delirium sample. However, delirium was more severe in hyperactive delirium, which is a known cause for persistent delirium. At T2, there was a trend towards superior response and the illness was more severe and the level of functioning more impaired in hypoactive delirium. In addition to the differences in pre-existing dementia, stage of illness, MDAS scores, delirium resolution, and functional status, the complexity of factors contributing to persistent delirium became apparent and could have influenced the results.

The response to hypoactive delirium was previously documented as equal (Liu et al., 2004) and inferior (Olofsson et al., 1996). However, the subtyping of delirium was based on the impairment in alertness, which represented a different approach. In the study using olanzapine in the management of delirium, a number of factors causing persistent delirium - such as advanced age, presence of dementia, more severe delirium, hypoxic illness and brain pathology - were present in the patients with hypoactive delirium. These factors could have confounded the less favorable results in these patients (Breitbart et al., 2002). The literature describing the response in the psychomotor subtypes of delirium remains limited.

The choice of antipsychotic in the management of delirium is usually based on their pharmacodynamic profile. Haloperidol remains the gold standard although atypical antipsychotics were shown to have comparable efficacy (Seitz et al., 2007). Extra-pyramidal symptoms are common at higher doses, whereas risperidone provides a certain level of protection by its serotonin-2a antagonism increasing dopamine in the nigrostriatal pathways (Lieberman et al., 1998). If sedation is desired, olanzapine represents a good choice. However, limitations may exist in elderly patients and the hypoactive subtype (Breitbart et al., 2002). Aripiprazole offers a novel mechanism of action with its partial dopamine agonism (DeLeon et al., 2004). However, evidence about its utility in the management of delirium still remains scarce. It was not possible to devise management strategies between haloperidol, risperidone, olanzapine and aripiprazole from this study since these antipsychotics were not compared against each other. Instead, the focus was set on their efficacy in the delirium subtypes, hypoactive and hyperactive delirium. Generally, the efficacy in hypoactive and hyperactive delirium proved to be comparable.

Although the data collection has strengths, including the systematic evaluation and documentation of etiologies contributing to delirium, nonetheless, several important limitations have to be noted: This study was based on a retrospective analysis of prospectively collected data. The etiologies contributing to delirium were categorized and recorded when present. The recording of etiologies was not complete and further etiologies – including not recognized ones – were not recorded. The selection of antipsychotic intervention was not random and was based on the treating physicians' preferences.

Furthermore, all patients had cancer diagnoses and the generalizability of these results to the non-cancer population may be limited. The use of antipsychotics in the management of delirium has not been approved by the regulatory agencies, and the use of antipsychotics in elderly patients with dementia carries a black-box warning of increased risk of death (Jeste et al., 2008; Schneider et al., 2005). Furthermore, the use of typical and atypical antipsychotics increases the risk for cerebrovascular accidents, the risks and benefits have to be weighed and the indication clearly set (Sacchetti et al., 2010). Thus, further research is required to confirm these findings.

In summary, the response to antipsychotics in the management of the delirium subtypes was similar. Although a trend towards greater response in hypoactive delirium existed, factors contributing to persistent delirium were also present. When hyperactive delirium was present, higher doses of antipsychotics were required to achieve symptom control.

Conflicts of interest: None.

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