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Haloperidol, risperidone, olanzapine and aripiprazole in the management of delirium: A comparison of efficacy, safety, and side effects

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ABSTRACT

Objective: The aim of this study was to compare the efficacy and side-effect profile of the typical antipsychotic haloperidol with that of the atypical antipsychotics risperidone, olanzapine, and aripiprazole in the management of delirium.

Method: The Memorial Delirium Assessment Scale (MDAS), the Karnofsky Performance Status (KPS) scale, and a side-effect rating were recorded at baseline (T1), after 2–3 days (T2), and after 4–7 days (T3). Some 21 cases were case-matched by age, preexisting dementia, and baseline MDAS scores, and subsequently analyzed.

Results: The baseline characteristics of the medication groups were not different: The mean age of the patients ranged from 64.0 to 69.6 years, dementia was present in between 23.8 and 28.6%, and baseline MDAS scores were 19.9 (haloperidol), 18.6 (risperidone), 19.4 (olanzapine), and 18.0 (aripiprazole). The doses of medication at T3 were 5.5 mg haloperidol, 1.3 mg risperidone, 7.1 mg olanzapine, and 18.3 mg aripiprazole. Over one week, the decline in MDAS scores between medications was equal, and no differences between individual MDAS scores existed at T2 or T3. After one week, the MDAS scores were 6.8 (haloperidol), 7.1 (risperidone), 11.7 (olanzapine), and 8.3 (aripiprazole). At T2, delirium resolution occurred in 42.9–52.4% of cases and at T3 in 61.9–85.7%; no differences in assessments between medications existed. Recorded side effects were extrapyramidal symptoms (EPSs) in haloperidol- and risperidone-managed patients (19 and 4.8%, respectively) and sedation with olanzapine (28.6%).

Significance of Results: Haloperidol, risperidone, aripiprazole, and olanzapine were equally effective in the management of delirium; however, they differed in terms of their side-effect profile. Extrapyramidal symptoms were most frequently recorded with haloperidol, and sedation occurred most frequently with olanzapine.

KEYWORDS: Delirium, Aripiprazole, Haloperidol, Olanzapine, Risperidone, Antipsychotics.

INTRODUCTION

Delirium is common in the course of hospitalization, and its incidence varies with the age of the patient and illness severity (Elie et al., 1998). In the general hospital setting, the occurrence of delirium may reach an average of 30% in medically ill patients and 40% in the hospitalized elderly (Bucht et al., 1999; Lipowski, 1989). In addition to interventions such as providing a safe and supportive environment, the guidelines for the management of delirium published by the American Psychiatric Association (Trzepacz et al., 1999) recommend the use of typical antipsychotics, in particular haloperidol. However, with increasing frequency, atypical antipsychotics are selected as the initial somatic intervention for amelioration of the symptoms

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of delirium due to their favorable side-effect profile (Lonergan et al., 2007; Rea et al., 2007).

The current literature highlights the efficacy and tolerability of atypical antipsychotics in providing relief from the distressing symptoms of delirium (Lonergan et al., 2007; Rea et al., 2007). Studies have not been able to show differences in efficacy between haloperidol and aripiprazole (Boettger et al., 2011*a*), risperidone (Han & Kim, 2004; Kim et al., 2005; Liu et al., 2004), or olanzapine (Hu et al., 2004; Skrobik et al., 2004), and between risperidone and olanzapine (Kim et al., 2010). However, differences in the side-effect profile have been documented. Haloperidol and aripiprazole have been shown to be equally effective in the management of hypoactive and hyperactive delirium, but extrapyramidal symptoms were more common in haloperidol-treated patients (Boettger et al., 2011*a*). No differences in efficacy have been shown between haloperidol and olanzapine, and both medications caused a substantial rate of side effects. EPSs were more commonly encountered with haloperidol in both studies (Hu et al., 2004; Skrobik et al., 2004). In particular, dystonia was measured in up to 31.9% of patients managed with haloperidol and in up to 2.9% of olanzapine-managed patients, whereas sedation/drowsiness was found in 22.2% of haloperidol-managed patients and 18.9% of olanzapine-managed patients (Hu et al., 2004). Studies comparing haloperidol and risperidone (Han & Kim, 2004; Kim et al., 2005; Liu et al., 2004) have suggested similar efficacy for both medications, with response rates ranging from 58.3 to 75% (haloperidol) and 42 to 77.8% (risperidone). Another study assessing risperidone and olanzapine in the management of delirium found similar response and side-effect rates but concluded that risperidone may result in poorer response rates in older age populations (Kim et al., 2010). More recent studies could not find differences among haloperidol, risperidone, and olanzapine (Grover et al., 2011; Yoon et al., 2013).

To date, the literature comparing the typical and atypical antipsychotics with respect to efficacy and side effects remains limited and warrants further expansion. So we performed an analysis of patients receiving haloperidol, risperidone, olanzapine, and aripiprazole in the management of delirium in order to further explore the comparative efficacy and side-effect profile of these medications.

METHODS

Patients

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

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

All patients and their families provided verbal consent to be evaluated and receive antipsychotics for symptomatic relief of delirium. In patients with a limited capacity to provide consent, the patient's primary caregiver provided verbal consent alongside the patient's assent to intervention. All data were obtained from the routine care of patients diagnosed with delirium and entered into the institutional review board-approved database for subsequent analysis, and a waiver was obtained for the data analysis.

Measurements

Delirium severity was measured with the MDAS, a 10-item, 4-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 greater than 10 identify the presence of delirium, and MDAS scores of 10 indicate resolution of delirium in our analysis (Kazmierski et al., 2008; Lawlor et al., 2000). Categorization of delirium was based on the motoric subtype: hypoactive or hyperactive (Camus et al., 2000; Meagher et al., 2000). Additional instruments included the Karnofsky Performance Status (KPS) scale (Karnofsky & Burchenal, 1949) to provide a measure of physical performance ability and an abbreviated version of the Udvalg for Kliniske Undersogelser Side-Effect Rating Scale (UKU) to record the side effects of the antipsychotics (Lingjaerde et al., 1987).

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, preexistent dementia, presence of brain metastases, and contributing delirium etiologies. MDAS and KPS scores were obtained and side-effect rating performed at initial diagnosis of delirium (T1) and repeated at 2–3 days (T2) and 4–7 days (T3).

The psychiatrist providing the initial diagnosis of delirium decided which antipsychotic to prescribe. Patients received haloperidol, risperidone, olanzapine, or aripiprazole. If the patient's delirium worsened as evidenced by clinical observation or MDAS scores, the current antipsychotic was discontinued and an alternate antipsychotic substituted.

Statistical Analysis

Data analyses were performed with the Statistical Package for the Social Sciences (SPSS, v. 20) for Windows. Descriptive statistics were performed on the dataset to characterize the sample sociodemographically and medically. The primary interest was MDAS score, and the side-effect profile was secondary. Separate datasets describing individual medications were created for comparison of efficacy and side-effect profile. The t test for independent samples was employed for data on the interval scale including age. A MANOVA was computed for the course of haloperidol, risperidone, aripiprazole, and olanzapine over time, and the between factor was the medication administered; MDAS scores at baseline, T1, and T2 were set as dependent measures. For multiple related measures, such as the course of change in MDAS scores for single medications, the Friedman test was utilized, and for multiple independent measures, such as comparison of MDAS scores at single times, the Kruskal–Wallis test. Categorical variables, such as the comparison of delirium resolution rates among medications, were computed with Pearson's chi-square test. For all implemented tests, post hoc, alpha (α) was adjusted with the Bonferroni method. The significance level for α was set at $p < 0.05$.

Composition of Sample

The sample size for each medication was determined by the medication with the lowest number of patients, which was aripiprazole. The data for haloperidol, risperidone, and olanzapine were matched to the aripiprazole sample based on age, preexisting dementia, initial MDAS scores, and delirium subtype.

RESULTS

Baseline Characteristics of Patients

The age of the patients did not differ between groups and ranged from 64.0 (haloperidol) to 69.6 years (aripiprazole). Gender was evenly distributed, with 38.1% male (haloperidol and olanzapine) and 47.6% female patients (risperidone and aripiprazole). The prevalence of preexistent dementia was not different, and was documented in 23.8% of haloperidol- and risperidone-managed patients and in 28.6% of aripiprazole- and olanzapine-managed patients.

Cancer diagnoses and stages were diverse (Table 1). There were no significant differences between types of cancer or stages of illness and medication regimens. The etiologies contributing to delirium were multifactorial and similar between medication groups. The most frequent etiologies were the administration of opioids [81% (risperidone) to 95.2% (haloperidol)], the administration of corticosteroids [33.3% (haloperidol) to 61.9% (risperidone)], the presence of hypoxia [28.6% (olanzapine) to 52.4% (risperidone)], current infection [9.5% (aripiprazole) to 47.6% (risperidone)]. and the presence of central nervous system (CNS) disease (from 9.5% for haloperidol to 33.3% for aripiprazole).

The severity of delirium did not differ at baseline and ranged from 18 to 30 on the MDAS. In the haloperidol-managed patients, the mean MDAS score was 19.9, in risperidone-managed 18.6, in aripiprazole-managed 18.0, and in olanzapine-managed patients 19.5. Hypoactive delirium and hyperactive delirium were present in 42.9 and 57.1%, respectively.

Management of Delirium with Haloperidol, Risperidone, Olanzapine, and Aripiprazole

The mean medication doses at T3 were 5.5 mg haloperidol, 1.3 mg risperidone, 18.3 mg aripiprazole, and 7.1 mg olanzapine. MDAS scores decreased in all medication groups. In haloperidol-managed patients, MDAS scores were 19.9 at baseline and decreased to 9.9 at T2 and 6.8 at T3 (Friedman $\chi^2 = 38.30(2)$, $p < 0.001$). In risperidone-managed patients, MDAS scores declined from 18.6 at baseline to 11.2 at T2 and to 7.1 at T3 (Friedman $\chi^2 = 29.95(2)$, $p < 0.001$). Aripiprazole-managed patients had a baseline MDAS score of 18.0, declining to 10.8 and 8.3 at T2 and T3, respectively (Friedman $\chi^2 = 31.87(2)$, $p < 0.001$). In olanzapine-managed patients, MDAS scores were 19.4 at baseline and 13.8 and 11.7 at T2 and T3 (Friedman: $\chi^2 = 13.23(2)$, $p < 0.01$). The decline of MDAS scores between medications over time was equal (MANOVA: Wilks's lambda 0.04, $F(634.4)$, $p < 0.001$). As a result, there were no differences between medications at any single observation point during the observation period (T2, T3) (Kruskal–Wallis, ns). The delirium resolution rates ranged from 42.9% (olanzapine and risperidone) to 52.4% (aripiprazole) at T2 and from 61.9% (olanzapine) to 85.7% (risperidone) at T3 and did not differ between medications (Table 2).

Side Effects

Side effects or lack of response were encountered in all medication groups and ranged from 4.8 (risperidone)

Table 1. *Baseline and medical characteristics of patients*

	Haloperidol ($n = 21$)	Risperidone ($n = 21$)	Aripiprazole ($n = 21$)	Olanzapine ($n = 21$)	Statistics
Age	64.0 (36–79, $SD = 11.7$)	67.2 (29–84, $SD = 12.7$)	69.6 (36–85, $SD = 11.9$)	65.6 (51–84, SD 13.4)	$t(40) = 1.024$, $p = 0.312$[a]
Gender (M/F in %)	38.1/61.9	47.6/52.4	47.6/52.4	38.1/61.9	0.778(3), $p = 0.886$[b]
Preexistent dementia (in %)	23.8	23.8	28.6	28.6	0.246(3), $p = 0.486$[b]
Cancer diagnosis (in %)					
Brain	4.8	4.8	19	*	6.462(3), $p = 0.154$[b]
Endocrine	–	4.8	4.8	*	2.049(3), $p = 1.0$[b]
Gastrointestinal	28.6	23.8	23.8	9.5	2.545(3), $p = 0.154$[b]
Genitourinary	4.8	–	19	*	9.144(3), $p = 0.051$[b]
Gynecological	19	4.8	9.5	*	5.455(3), $p = 0.199$[b]
Head and neck	14.3	4.8	14.3	14.3	4.208(3), $p = 0.154$[b]
Lung	19	38.1	–	28.6	3.746(3), $p = 0.338$[b]
Sarcoma	9.5	–	9.5	*	4.20(3), $p = 0.323$[b]
Lymphoma	–	4.8	–	14.3	6.30(3), $p = 0.186$[b]
Skin	–	9.5	–	*	6.146(3), $p = 0.154$[b]
Breast	–	–	–	9.5	6.146(3), $p = 0.241$[b]
Other	–	4.8	–	23.8	12.205(3), $p = 0.013$[b]
Stage (in %)					
Localized	38.1	28.6	38.1	23.8	1.474, $p = 0.754$[b]
Advanced	52.4	57.1	47.6	71.4	2.722, $p = 0.515$[b]
Terminal	9.5	14.3	14.3	4.8	1.369, $p = 0886$[b]
Brain metastases (in %)	4.8	9.5	14.3	23.8	3.661(3), $p = 0.381$[b]
Etiologies (in %)					
Opioids	95.2	81	90.5	81	2.824(3), $p = 0.523$[b]
Corticosteroids	33.3	61.9	52.4	33.3	5.190(3), $p = 0.187$[b]
Hypoxia	33.3	52.4	38.1	28.6	2.827(3), $p = 0.499$[b]
Infection	23.8	47.6	9.5	28.6	7.843(3), $p = 0.061$[b]
CNS disease	9.5	14.3	33.3	23.8	7.386(3), $p = 0.070$[b]
Dehydration	–	4.8	4.8	4.8	21.367(3), $p = 0.047$[b]

*Recorded as "other cancer."[a] t test. [b]Pearson's chi-square test.

Table 2. *Management characteristics of haloperidol, risperidone, aripiprazole and olanzapine*

	Haloperidol ($n = 21$)	Risperidone ($n = 21$)	Aripiprazole ($n = 21$)	Olanzapine ($n = 21$)	Statistics
Medication dose (in mg)					
Baseline (T1)	4.9 (1.5–16, $SD = 2.4$)	0.9 (0.5–2, $SD = 0.4$)	15.2 (5–30, $SD = 6.22$)	3.5 (2.5–10, $SD = 1.9$)	–
T2	5.5 (1.5–16, $SD = 3.5$)	1.1 (0.5–3, $SD = 0.7$)	16.0 (10–30, $SD = 5.84$)	5.2 (2.5–15, $SD = 3.1$)	–
T3	5.5 (1.5–16, $SD = 3.5$)	1.3 (0.5–3, $SD = 0.7$)	18.3 (10–30, $SD = 6.58$)	7.1 (2.5–20, $SD = 4.7$)	–
MDAS scores					
Baseline (T1)	19.9 (12–25, $SD = 3.4$)	18.6 (11–026, $SD = 4.5$)	18.0 (11–25, $SD = 4.3$)	19.4 (14–26, $SD = 3.8$)	2.396(3), $p = 0.497$[a]
T2	9.9 (2–21, $SD = 5.34$)	11.2 (1–24, $SD = 5.6$)	10.8 (2–23, $SD = 10.8$)	13.8 (1–26, $SD = 7.5$)	3.573(3), $p = 0.311$[a]
T3	6.8 (1–17, $SD = 4.8$)	7.1 (1–22, $SD = 5.1$)	8.3 (1–23, $SD = 8.3$)	11.7 (1–26), $SD = 8.8$)	4.140(3), $p = 0.249$[a]
Delirium resolution (in %)					
T2	47.6	42.9	52.4	42.9	0.526(3), $p = 0.964$[b]
T3	76.2	85.7	76.2	61.9	3.238(3), $p = 0.418$[b]
Side effects (in %)					
Any side effect	19	4.8	9.5	42.9	11.735(3), $p = 0.009$[b]
EPS—dystonia	9.5	–	–	–	3.036(3), $p = 0.1.0$[b]
EPS—parkinsonism	19	4.8	–	–	12.60(3), $p = 0.012$[b]
Sedation	–	–	–	28.6	19.385(3), $p = 0.001$[b]
Worsening	–	–	9.5	14.3	3.802(3), $p = 0.661$[b]
Multiple side effects	9.5	–	–	14.3	6.30(3), $p = 0.186$ [b]

MDAS = Memorial Delirium Assessment Scale; EPS = extrapyramidal symptom.
[a]Kruskal–Wallis test. [b]Pearson's chi-square test.

to 9.5 (aripiprazole), 19 (haloperidol), and 42.9% (olanzapine). The administration of olanzapine most frequently caused side effects, followed by haloperidol, aripiprazole, and risperidone. In particular, haloperidol and also risperidone caused extrapyramidal symptoms (19 and 4.8%, respectively). The most commonly recorded side effect was sedation (28.6% with olanzapine). Sedation may have clinical utility in patients with hyperactive delirium.

DISCUSSION

These findings indicate that the atypical antipsychotics risperidone, aripiprazole, and olanzapine and the typical antipsychotic haloperidol were equally effective in the management of the symptoms of delirium. The side-effect profile, however, was very different. In particular, haloperidol caused increased rates of EPSs and olanzapine substantial sedation, while the administration of risperidone and in particular aripiprazole caused less adverse to no side effects.

A number of studies have compared the safety and efficacy of haloperidol and risperidone, aripiprazole, and olanzapine and found similar efficacy in the management of delirium. Compared to previous findings, the dosing of medication was similar: haloperidol (5.5 mg), risperidone (1.3 mg), aripiprazole (18.3 mg), and olanzapine (7.1 mg). In previous investigations, the dosing of risperidone ranged from 0.75 to 1.7 mg (Han & Kim, 2004; Kim et al., 2005; 2010; Liu et al., 2004), aripiprazole was administered at 8.9–18.3 mg (Boettger et al., 2011*a*), olanzapine at 2.4– 8.2 mg (Hu et al., 2004; Kim et al., 2010; Skrobik et al., 2004), and haloperidol doses ranged from 1.7 to 6.5 mg (Boettger et al., 2011*a*; Han & Kim, 2004; Hu et al., 2004; Kim et al., 2005; Liu et al., 2004). The efficacy rates of medications were similar to previous findings. In our analysis, 76.2% of haloperidol-managed patients (58.3–87.5%), 85.2% of risperidone-managed (42–84.4%), 76.2% of the aripiprazole-managed, and 61.9% (64.7–82.4%) of the olanzapine-managed patients achieved delirium resolution.

Side effects were encountered with most medications, most commonly EPSs and sedation in haloperidol- and olanzapine-managed patients (19 and 28.6%, respectively). More extrapyramidal symptoms with haloperidol-managed patients have been known (Boettger et al., 2011*a*; Hu et al., 2004), and sedation is a common side effect of management with olanzapine and has previously been described in 18.9% of patients. Side effects in patients managed with aripiprazole and risperidone were less frequent.

The sample in our analysis was evenly distributed. The patient population did not differ in age, gender, preexistent dementia, type and stage of cancer, and etiology. A different recording approach within the olanzapine cases, categorizing multiple diagnoses (marked with an asterisk in Table 1) in the category "other," increased the number of "other" cancers artificially.

Patients in this sample were of advanced age, ranging from 64.0 to 69.6 years, exceeding the age range documented in other studies. This is not particularly surprising, as advanced age and comorbid dementia are among the main risk factors for developing delirium (Elie et al., 1998). Both advanced age and comorbid dementia may be associated with a prolonged and refractory course of delirium (Boettger et al., 2011*b*), thus potentially reducing the response rates in the observation period.

These findings provide further evidence indicating that haloperidol, risperidone, aripiprazole, and olanzapine were similarly efficacious in the management of delirium, but had different side-effect profile. As a consequence, the choice of antipsychotic for the management of delirium may be less determined by efficacy than by side-effect profile, including potentially desirable side effects such as sedation.

Although the data collection had strengths—including the systematic evaluation and documentation of etiologies contributing to delirium, the case matching reducing differences between groups, as well as the observation and recording of side effects—several important limitations have to be noted. Our analysis was based on a retrospective analysis of prospectively collected data. The selection of antipsychotic intervention was not random or based on the treating physicians' preferences. Furthermore, all patients had cancer diagnoses, and the generalizability of these results to the noncancer population may perhaps 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). All patients were case-matched to the lowest number of cases in each group, and the total number of patients included in the analysis was limited to 21 for each medication group. As a consequence, further investigations, particularly double-blind, randomly assigned, controlled designs of atypical and typical antipsychotics, are required to confirm these results.

In summary, our analysis provided further results indicating that the typical antipsychotic haloperidol and the atypical antipsychotics risperidone, aripiprazole, and olanzapine are similarly efficacious in the management of delirium; however, their side-effect profiles are different. As a consequence, the choice of an antipsychotic was less determined by its efficacy than its side-effect profile, including the use of atypical instead of typical antipsychotics, and

reducing extrapyramidal symptoms, as well as the potentially desirable side effect of sedation.

CONFLICTS OF INTEREST

The authors state that they have no conflicts of interest to declare.

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