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Antipsychotic-induced akathisia in cancer settings

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1 INTRODUCTION

Akathisia is a neuropsychiatric syndrome characterized by a subjective inner feeling of restlessness and a compulsion to move accompanied by repetitive movement of the legs that can also affect the trunk and arms.¹

In clinical settings akathisia occurs as an adverse effect of medications. The *Diagnostic and Statistical Manual for Mental Disorders* fifth edition defines medication-induced akathisia as a subjective complaint of restlessness, often accompanied by excessive movements, developed within a few weeks of starting or raising the dosage of a medication or after reducing the dosage of a medication used to treat extrapyramidal symptoms.² While several drugs can cause akathisia, antipsychotics are most commonly associated with this adverse effect.¹ These drugs are thought to block D2/D3 receptors at the ventral striatum in the central nervous system causing akathisia.³ High-potency, first-generation antipsychotics have a higher prevalence of akathisia, compared with low-to intermediate-potency first- and second-generation atypical antipsychotics. Second-generation antipsychotics differ in terms of their propensity for akathisia as well, with higher rates reported for aripiprazole and lurasidone compared with iloperidone, quetiapine, and clozapine.

The prevalence, phenomenology, and management of antipsychotic-induced akathisia in delirium and palliative care settings have not been vigorously studied. In a recent systematic review, a total of 10 studies that reported incidence of antipsychotic-induced akathisia in delirium settings were found. Neither of these studies used objective scales for the assessment of akathisia. Among those studies, the prevalence of akathisia varied from 0% to 28.5%, depending on the antipsychotic used and the dose of antipsychotic. A higher incidence was found in patients taking haloperidol and ziprasidone.⁴ In a study published in 2013, Crawford and colleagues found an incidence of akathisia of 11% in hospice and palliative care settings at a dose of 2.1 mg of haloperidol daily. The authors concluded that patients with terminal illnesses may be at higher risk for development of this extrapyramidal adverse effect.⁵ A Japanese study found a prevalence of akathisia of 4.8% in 483 patients with cancer who met criteria for different psychiatric diagnoses.⁶

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Assessing for akathisia in patients with cancer can be challenging. For instance, in these settings, patients can often develop delirium because of dehydration, malnutrition, metabolic abnormalities, and opioid use among other causes. Delirium often presents with cognitive impairment, anxiety, and agitation. These symptoms overlap with akathisia symptoms.⁷ Moreover, patients with a history of anemia and restless legs syndrome, Parkinson's disease, or other neurodegenerative diseases affecting the basal ganglia may be more sensitive to development of antipsychotic-induced akathisia.

The aim of this study is firstly to determine the prevalence of anti-psychotic-induced akathisia in patients with cancer and comorbid psychiatric conditions by using an objective scale and secondly to explore whether there are differences in rates of akathisia depending on the antipsychotic used, the dose of the antipsychotic, and the indication for which the antipsychotic was used.

2 METHODS

Between October 2014 and March 2015, patients with cancer taking antipsychotic medications were evaluated for akathisia by using clinical evaluation and the Barnes Akathisia Rating Scale (BARS) after initiation of an antipsychotic medication as part of routine clinical practice. The BARS was developed by Thomas Barnes in 1985 for the measurement of antipsychotic-induced akathisia and is the most widely used scale clinically for assessment of this condition.⁸ An institutional review board exemption was obtained for retrospective collection of the data to determine the point prevalence of akathisia.

A total of 39 patients were assessed for akathisia. Age, gender, cancer diagnosis, psychiatric diagnosis—as determined by 2 board-certified psychiatrists—and list of medications were collected. The doses of all antipsychotics and other drugs known to cause akathisia as an adverse effect were collected. Finally, we reviewed the scores of the BARS subscales, namely, subjective (awareness and distress), objective, and global akathisia scores.

The details of the management and outcome of patients who met criteria for antipsychotic-induced akathisia according to the clinical evaluation and the BARS were included in the data collection.

3 RESULTS

While 6 out of 39 (15.3%) patients reported subjective inner feelings of restlessness, only 2 out of 39 (5.1%) patients with cancer met criteria for antipsychotic-induced akathisia as per clinical evaluation and BARS. Twenty-two out of the 39 patients were prescribed antipsychotic medications for treatment of symptoms of delirium. So, among cancer patients with delirium who were on antipsychotics ($n = 22$), only 2 (9.0%) of them developed antipsychotic-induced akathisia. Both patients who developed akathisia were taking haloperidol (Table 1).

Of the subgroup of patients who had delirium ($n = 22$), 8 (36.3%) had hyperactive, 9 (40.9%) had hypoactive, 4 (18.1%) had mixed, and 1 (4.5%) had unspecified subtype of delirium. Olanzapine was the most common antipsychotic used. Twenty-three out of 39

(58.9%) patients were treated with this drug, followed by haloperidol (n = 9, 23.0%), quetiapine (n = 4, 10.2%), aripiprazole (n = 2, 5.1%), and chlorpromazine (n = 1, 2.5%). Thirty-three out of 39 (84.7%) patients were on standing dose of antipsychotics; 6 out of 39 (15.3%) were taking antipsychotics as needed only. For those who were on standing doses, the mean dose of antipsychotic medication in chlorpromazine equivalents was 84.24 mg daily. The median and mode chlorpromazine equivalent doses were 50 mg daily.

All medications, in addition to antipsychotics, that could cause akathisia were reviewed. Fifteen out of 39 patients (38.4%) were additionally taking akathisia-inducing medications that were not antipsychotics such as lithium, venlafaxine, duloxetine, fluoxetine, citalopram, sertraline, mirtazapine, bupropion, linezolid, metoclopramide, or prochlorperazine.

The small number of patients who met criteria for antipsychotic-induced akathisia (n = 2) did not allow for any group comparisons. As a result the 2 cases are discussed below in a case series format (Table 2).

3.1 Case 1

A 71-year-old man, with a history of metastatic prostate cancer to the cervical and lumbar spine with no psychiatric history and with history of smoking 1 pack per day for 25 years, was admitted to intensive care unit for treatment of bacteremia. The psychiatry team was consulted for evaluation of delirium as the patient had cognitive changes and a fluctuating level of alertness. A C) scan of the brain showed nonspecific white matter changes. On evaluation patient was calm and reported no pain. On cognitive evaluation he had difficulty spelling backwards, could not repeat a sentence, could not copy a pentagon, and could not accurately draw a clock. He was diagnosed with delirium hypoactive subtype and started on intravenous haloperidol 0.5 mg every 4 hours as needed and 0.5 mg twice daily standing.

Patient was evaluated weekly for akathisia as part of routine clinical care. For the first 2 weeks his BARS scores were "0" in the subjective, objective, and global scales. He showed no symptoms of akathisia on clinical evaluation. On week 3, the patient scored 2 in subjective awareness, 1 in subjective distress, 3 in objective akathisia subscales of the BARS, and 3 in global clinical assessment of the BARS, which are consistent with akathisia of moderate severity. The patient showed constant mild movement of the legs while sitting and reported moderate feeling of restlessness and mild distress. The dose of haloperidol was decreased to intravenous 0.5 mg once daily, and his symptoms improved within 24 hours, reporting only mild restlessness that did not lead to any distress. On objective assessment he only had mild movement of the limbs. A week later, he was switched from haloperidol 0.5 mg daily to olanzapine 2.5 mg every night by mouth and akathisia symptoms remitted.

3.2 Case 2

A 55-year-old man with a history of acute myeloid leukemia, 60 days following bone marrow transplant, was admitted for treatment of graft-versus-host disease affecting his liver and gastrointestinal system. He had no past psychiatric history. He developed acute kidney failure after treatment with tacrolimus. Patient became confused, became disoriented, and reported hallucinations of "circles" and "things."

On evaluation by the psychiatry team, he showed impairments in attention, registration, working memory, and executive functioning. He was treated with intravenous haloperidol 0.5 mg twice daily for delirium of mixed subtype. A day after initiation of haloperidol, he developed akathisia symptoms. His BARS scores were 2 for subjective awareness, 3 for subjective distress, 3 for objective akathisia, and 5 for global subscales, which is consistent with severe akathisia. Haloperidol was switched to 0.5 mg twice daily as needed only. Two days later, he continued to report subjective inner feelings of restlessness and distress but showed no objective signs of akathisia. The patient was not given any haloperidol for the following week. A week later, he was started on quetiapine 25 mg every night by mouth for treatment of symptoms of delirium. The day after, his BARS scores were 2 for subjective awareness, 2 for subjective distress, 0 for objective akathisia, and 0 for global assessment, which are not consistent with akathisia. Clinical evaluation was also not consistent with akathisia.

4 DISCUSSION

In our sample of 39 patients, only 2 patients (5.1%) developed akathisia, both of whom were on intravenous haloperidol at relatively low doses (ie, 1 mg daily). During the course of their hospitalization, they were not any other akathisia-inducing agent. None of the patients in our sample were taking oral haloperidol, so we could not compare risk of akathisia between oral and intravenous haloperidol uses. Clinicians must carefully monitor for akathisia symptoms on both oral and parenteral forms of haloperidol and other antipsychotics. None of our patients taking other antipsychotic medications (olanzapine, quetiapine, chlorpromazine, and aripiprazole) developed akathisia. Although our sample is small, our study shows that use of antipsychotics at low doses, namely, a median and mode dose of 50 mg chlorpromazine equivalents daily, is associated with low risk for akathisia. Congruent with prior studies, haloperidol remains to be the antipsychotic with the highest risk for akathisia as an adverse effect.^{4,5} While 1 patient developed akathisia 2 weeks after the start of the antipsychotic, the other presented with akathisia 1 day after initiation of halo-peridol. The onset of symptoms may vary. Nonetheless, when choosing an antipsychotic in patients with cancer, the clinician must keep in mind side effects from other neuroleptics. For instance, chlorpromazine may have a lower risk profile of akathisia but a higher risk of anticholinergic adverse effects and hypotension. These adverse effects can potentially worsen delirium and morbidity in debilitated patients. Atypical antipsychotics such as olanzapine have been related to somnolence, altered gait, hyper-glycemia, transient elevation of liver enzymes, worsening of edema, and higher risk for urinary tract infection, something problematic in physiologically compromised population in the intensive care unit or transplant units. Knowledge of these adverse effects will help clinicians judge the best choice when a neuroleptic is indicated.

In our group of patients, none of those who were taking more than one akathisia-inducing medication developed akathisia. Those who developed akathisia were naïve to antipsychotics, antidepressants, mood stabilizers, and other psychotropics. Therefore, akathisia risk could be higher in patients who are antipsychotic or psychotropic naïve.

Decrease and discontinuation of the offending agent were helpful for both patients with akathisia. In cases where an anti-psychotic medication is still needed for treatment

symptoms of delirium, anxiety, or agitation, clinicians must consider an antipsychotic less likely to induce akathisia such as quetiapine or olanzapine.

The diagnosis of akathisia in the medically ill remains challenging. Clinician's bedside assessment and different akathisia assessment scales are the only tools. In our sample 6 out of 39 (15.3%) patients reported subjective inner feelings of restlessness and distress. "Inner feelings of restlessness" can be a symptom of delirium, anxiety, and mood disorders in the medically ill. Cognitive impairment in the context of delirium may complicate the assessment of subjective inner feelings of restlessness, leading to false- negative assessments for akathisia. Nevertheless, for the diagnosis of akathisia, objective symptoms are required. In our study, the use of BARS for the evaluation of objective findings of akathisia was the key to differentiating patients with akathisia from those who had symptoms associated with other neuropsychiatric conditions.

Total prevalence in our sample was low, 5.1%, when compared with other studies, with up to 28.5% akathisia prevalence.⁹ This difference could be due to the facts that we used low doses of antipsychotic medications and that we increased the specificity of akathisia diagnosis by using an objective measurement, namely, BARS. The fact that akathisia symptoms started after the commencement of the offending agent (ie, haloperidol) and attenuated with the decrease or discontinuation of it supports the diagnosis of antipsychotic-induced akathisia in our sample.

5 CONCLUSION

The assessment and management of antipsychotic-induced akathisia in patients with cancer remain challenging. Subjective anxiety and mood symptoms are difficult to differentiate from subjective akathisia symptoms. Moreover, the assessment of akathisia in patients with cognitive impairment and in patients with hyperactive subtype of delirium is challenging. Amelioration of akathisia symptoms after decrease or discontinuation of the offending agent can help support the diagnosis. Cancer patients taking antipsychotic medications even at low doses and especially those taking haloperidol must be carefully examined and evaluated for akathisia.

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Key Points

1. The incidence of antipsychotic-induced akathisia in cancer and palliative care settings has not been vigorously studied.
2. Haloperidol poses a higher risk for antipsychotic-induced akathisia in patients with cancer.
3. In cases of patients with akathisia in which antipsychotics are still needed for the treatment, olanzapine, quetiapine, and chlorpromazine at low doses may be a safer choice.
4. The assessment and management of antipsychotic-induced akathisia in patients with cancer remain challenging, especially in patients with delirium, in which cognitive impairment complicates the evaluation of the side effect.
5. A thorough clinical history and evaluation together with the use of objective scales remain the gold standard assessment. Amelioration of akathisia symptoms after decrease or discontinuation of the offending agent can help support the diagnosis.

TABLE 1

Prevalence of antipsychotic-induced akathisia in patients with cancer

	Total Sample (n = 39)	Patients With Delirium (n = 22)	Patients on Haloperidol (n = 9)	Patients Not on Haloperidol (n = 30)
Akathisia prevalence	5.1%	9.0%	22.2%	0%

TABLE 2

Characteristics of patients with akathisia

Akathisia	Age, y	Gender	Cancer Diagnosis	Psychiatric Diagnosis	Antipsychotic	Daily Dose,mg	BAS S	BAS D	BAS O	BAS G	Management
Case 1	71	Male	Prostate	Delirium, hypoaactive	Haloperidol	1	2	1	3	3	Decrease dose to 0.5 mg and switch to olanzapine 2.5 mg
Case 2	55	Male	Acute myeloid leukemia	Delirium, mixed	Haloperidol	1	2	3	3	5	Discontinuation of haloperidol and switch to quetiapine 25 mg

Abbreviations: BAS S, Barnes Akathisia Scale subjective awareness subscale; BAS D, Barnes Akathisia Scale subjective distress subscale; BAS G, Barnes Akathisia Scale global assessment subscale; BAS O, Barnes Akathisia Scale objective akathisia subscale.