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*OBM Geriatrics*

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Case Report

# Olanzapine-Induced Hypothermia: A Case Report in an Elderly Black Male Patient Diagnosed with Bipolar 1 Type Disorder

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**Academic Editor:** Pietro Gareri

*OBM Geriatrics*
2024, volume 8, issue 3
doi:10.21926/obm.geriatr.2403288

**Received:** March 18, 2024
**Accepted:** August 26, 2024
**Published:** September 14, 2024

**Abstract**

There are few reports that describe incidence of hypothermia in patients treated with olanzapine. We report a case of an elderly 83-year-old black male, readmitted to the state psychiatric hospital December 2023 due to psychiatric exacerbation after 6 months of successful discharge to community, who experienced a fall and profound hypothermia with bradycardia that resulted in a 10-day acute hospitalization in January 2024. Medical workup was unrevealing except for multivessel disease found on CT stroke study of the brain. When patient returned to inpatient psychiatric hospital, his psychiatric medications, including both quetiapine and olanzapine, were restarted at half the dose. The next morning, the patient was again hypotensive, bradycardic and hypothermic. For this patient, only the olanzapine was new upon the most recent admission, and thus this case report supports the other few reports already published, implicating olanzapine in the pharmacologic adverse effect of drug induced hypothermia.

**Keywords**
Drug-induced hypothermia; adverse drug reaction; olanzapine; elderly; falls; falls risk

## 1. Introduction

Hypothermia is diagnosed based on a body temperature of less than 35 degrees Celsius (°C) [1]. The general risk factors for hypothermia include extrinsic environmental conditions as well as intrinsic individual conditions that alter an individual's ability to insulate their body, and the capacity to compensate for heat loss [2, 3]. Hypothermia can be divided into different categories based on the severity [4]. Mild hypothermia can be defined as a body temperature between 33 to 35°C and notable for shivering, cold diuresis, and pale skin. Moderate hypothermia occurs at a body temperature between 28 and 33°C and has reduced shivering, bradycardia, and hyporeflexia. Lastly, severe hypothermia can be defined as a body temperature less than 28°C, with more intense bradycardia, hypotension, hypoventilation, oliguria, and eventually coma before death [4].

Drug-induced hypothermia associated with the use of antipsychotic medication presents as a rare, but potentially dangerous adverse effect [3, 4]. Impaired thermoregulatory control has been observed across the entire spectrum of antipsychotic classes and is reported in the package insert for multiple antipsychotic mediations such as aripiprazole, risperidone, olanzapine, and several other second generation antipsychotics; temperature dysregulation is reported as a possible adverse effect [5-7]. Although this mechanism is still not fully understood, Ferreira and colleagues suggest that the modulation of hypothalamic AMPK phosphorylation by olanzapine controlling energy balance could alter body temperature [8]. A systemic review of antipsychotic-induced hypothermia revealed that certain patient specific predisposing factors may put an individual more at risk of developing this adverse effect. These predisposing risks of developing hypothermia include, but may not be limited to, being elderly, diagnosis of hypothyroidism, diabetes, kidney or liver failure, sepsis, alcohol intoxication, benzodiazepine use, or history of cerebrovascular accident [4]. In addition, a low muscle mass results in a decreased production of body heat, which can also be due to reduced movement, making both the very young and very old more at risk for developing hypothermia [1, 2]. In our case, the patient is elderly, diabetic, and uses lorazepam giving him multiple concurrent risk factors for developing antipsychotic induced hypothermia.

Again, this is not the first known case strongly implicating olanzapine-induced hypothermia. However, we present a case of an elderly black male with only one change to his medication regimen. After both initiation, and re-challenge of olanzapine, our patient suffered two separate hypothermic, bradycardic, and hypotensive episodes. There is a considerable polypharmacy component to our case as well which makes it unique and perhaps even more compelling than previously published cases found in the literature.

## 2. Case Report

The study was conducted following the Declaration of Helsinki, and approved by the Research Monitoring Committee for Institutional Review Board Protocols of the Buffalo Psychiatric Center on

April 24th, 2024. Informed consent to publication was not applicable, as the patient is now deceased and has no consent for notification of next of kin.

An 83-year-old adult black male was hospitalized at an inpatient psychiatric facility for bipolar type 1 disorder (current most recent episode manic, with psychotic features), on December 8th, 2023, after a 6-month successful discharge to community, who then subsequently experienced psychiatric exacerbation requiring readmission to the same inpatient psychiatric hospital in Upstate New York. During the most recent admission, he was treated with hydroxyzine 50 mg twice daily (anxiety), lorazepam 2 mg twice daily (anxiety), oxcarbazepine 300 mg twice daily (mood stabilization) and quetiapine 100 mg daily and fluphenazine 5 mg twice daily along with fluphenazine decanoate 50 mg every other week for psychosis, which were the same antipsychotics he received during the previous admission. The patient was prescribed an additional 10 mg of olanzapine intramuscularly (IM) for any dose of quetiapine refused, but no doses were refused. Thus none of the IM olanzapine was administered during this time. Newly added to the regimen for the most recent admission was olanzapine 10 mg twice daily on January 12th, 2024. His medical diagnoses included essential hypertension (treated with carvedilol, bumetanide, and nifedipine), type 2 diabetes (treated with sitagliptin, insulin glargine), insomnia (treated with melatonin) and chronic kidney disease (CKD) stage III. The patient did not have a history of hypothermia or bradycardia during his previous admission. There is no family history of similar reaction or diagnosis, and the patient had not previously received olanzapine.

The sequence of events establishing this case report began with a fall the patient experienced on January 14th, at which time the patient was medically evaluated at the scene of the fall. The patient sustained a small hematoma to the right side of his head, prompting the initiation of a neuro-check protocol, and on January 15th was observed to be obtunded with altered mental status and sent by ambulance to an affiliated acute care hospital for a 10-day admission. Upon admission, the patient was hypothermic with temperature of 32°C (89.6°F), and bradycardic with a pulse of 50, but the medical work up was otherwise unrevealing with the exception of observed multivessel disease found on CT stroke study. The psychiatric medications were withheld, with the exception of oxcarbazepine (which was continued), and the patient's mental status and vitals improved. Upon return to the inpatient psychiatric facility, the prescriber restarted all the previous psychiatric medications at half the dose. The following morning the patient was observed to be again hypothermic and bradycardic (63/46 mmHg, HR 47, RR 18, SPO2 98% T: 32.5°C (90.5°F axillary), 32.9°C (91.22°F rectal) and was sent again to the acute care hospital where the same psychiatric medications were discontinued, and the patient's vitals returned to normal baseline (Table 1).

**Table 1** Timeline of the event.

| Date | Additional details |
|---|---|
| December 8th, 2023 | After 6-month successful discharge to community, patient presented with a psychiatric exacerbation |
| December 18th, 2023 | T: 95.9°F, HR: 62, BP 140/76 |
| December 28th, 2023 | refused |
| December 31st, 2023 | T: 96.8°F, HR 73, BP 153/83 |
| January 12th, 2024 | Olanzapine **10 mg twice daily** added to medication regimen |
| January 14th, 2024 | Patient had a fall, and when evaluated found to be bradycardic with vitals upon exam: BP 128/80 HR: 68, RR: 18 |
| January 15th, 2024 | 0830: reported to be flat and minimally conversive. Per on call psychiatrist no seizure like movements or neurologic deficits noted upon exam.<br>Decision to transfer to acute care hospital |
| January 16th, 2024<br>Hospitalization #1 | T: 32°C (89.6°F) upon arrival<br>Vitals: T: 36.6°C (97.9°F), BP 117/71, HR: 50, SpO2 98%. IV sodium chloride 0.9% bolus and then 1 L continuous infusion administered.<br>Impression that patient presents with acute encephalopathy of unclear etiology, but possibly due to polypharmacy.<br>Continued to be followed by neurology.<br>No further hypothermic readings (all reported to be within normal limits) |
| January 25th, 2024 | Discharged to return back to inpatient psychiatric hospital.<br>Note that patient was restarted on all psychiatric medications, including olanzapine, at half dose. |
| January 26th, 2024 | 0835: Report of altered mental status, lethargy request to re-evaluate. |
| January 26th, 2024<br>Hospitalization #2 | Transfer summary: patients vitals 63/46 mmHg, HR 47, RR 18, SPO2 98%<br>T: 32.5°C (90.5°F axillary), 32.9°C (91.22°F rectal) |
| January 27th, 2024 | T: 31.2°C (88.16°F rectal) |
| | No further hypothermic readings, all within normal limits<br>Discharged to return back to inpatient psychiatric hospital |
| January 30th, 2024 | 2000: HR: 63, RR: 18 BP 170/80 |
| January 31st, 2024 | 0000: Temp: 97°F, HR: 74, RR: 16, BP: 150/73<br>0400 and 8AM: refused vitals<br>1200: HR: 85, RR:16, BP 135/79<br>2000: refused vitals |

No further hypothermic readings or out of range vitals at the writing of this case, all returned within normal limits.

## 3. Discussion

As previously described, the exact mechanism of how olanzapine and other antipsychotic medications induce hypothermia is not completely understood. One possible mechanism that explains why hypothermia occurs with these medications may involve the hypothalamus [9]. Temperature regulation occurs with the involvement of neurotransmitters, which include

dopamine, serotonin, and norepinephrine. The drug receptor activity of different antipsychotic medications may play a role as well. Serotonin is involved in thermoregulation, and olanzapine specifically has a strong affinity for the 5HT-2A receptor. In addition, antipsychotics have some alpha 2 adrenergic blocking effects which could potentially increase hypothermic effects due to the inhibited response of the periphery to cooling, which would normally lead to vasoconstriction and shivering in an attempt to increase body temperature [9].

There are several causes of hypothermia that extend beyond environmental factors such as cold exposure. However, since the patient had no history of hypothermia or olanzapine use, the possibility of olanzapine-induced hypothermia cannot be ignored. Our patient presented as bradycardic and hypothermic after two trials of olanzapine. He also had an altered mental status. A case report published in 2013 by Ankit Kansagra et al., described a case of a patient with hypothermia secondary to olanzapine in the setting of renal failure [10]. This case described an 80-year-old male patient with insulin dependent diabetes, stage 3 kidney disease, and bipolar disorder. Similar to our case, this patient was also an elderly male, with diabetes and insulin regimen, as well as bipolar disorder. The case described the patient as having an altered mental status prompting his admission into the hospital. He previously had gastroenteritis and subsequent dehydration; however, his wife indicated that there were no environemental exposusres, and their home was at an adequate temperature. Kansagra et al. reported their patient's medication list as follows: olanzapine 5 mg twice a day, aspirin, insulin, amlodipine and donepezil. His temperature upon hospital admission was 88.2°F, heart rate of 30 bpm, and systolic blood pressure of 60 mmHg. The patient was treated for suspected sepsis but eventually this was ruled out due to negative cultures. Other possible factors of hypothermia include environmental exposure, severely advanced hypothyroidism, neurologic malignancy, and adrenal insufficency, which were evenutally ruled out as well during the 15 day hospital stay. Overall, the authors described the cause of this admission as prolonged hypothermia from olanzapine in a patient with chronic kidney disease. Our findings are in agreement with those from this case including the altered mental status, hypotension, bradycardia, and hypothermia. However, in contrast to this case, our patient was just started on olanzapine while Kanasagra's patient had been controlled on olanzapine [10]. Based on the pharmacokinetics of olanzapine, no dosage adjustment is necessary for any degree of kidney impairment. However, the half life increases by 1.5 times in the elderly population [5].

Polypharmacy is always a concern in elderly patients. In our case, the patient was on several CNS depressants including lorazepam, quetiapine, and hydroxyzine that could have contributed to his altered mental status which returned to baseline once all of the agents were discontinued in the acute care hospital. However, the question remains as to whether drug interactions or concominant pharmacodynamic effects of the combination used could lead to such a severe hypotensive and bradycardic event. If the patient became bradycardic first, it is still notable that only the olanzapine was new to the regimen. He had previously been receiving treatment for hypertension that he tolerated well (see Table 1). The addition of anticholinergic medications such as quetiapine and hydroxyzine may have contributed to his altered mental status and fall if they had been newly prescribed, but since these were medications in his preexisting regimen, they were likely not the cause of the severe bradycardia and hypotension [11].

Another case report available in the literature arguably resembles the characteristics of our case relative to the polypharmacy component. While the 76-year-old woman in this case was not on hydroxyzine, she was taking olanzapine, quetiapine, valproic acid and oxcarbazepine [12]. In

contrast to this case, our patient was not on valproic acid, but was on a benzodiazepine. The elderly female patient presented by author Oluwadamilare O Ajayi et al., had multiple episodes of hypothermia after tolerating her antipsychotic regimen for years [12]. She did not have diabetes like our patient, but she was obese and had hypertension, hypothyroidism, atrial fibrillation, and coronary artery disease. This patient's case became quite complicated with multiple urinary tract infections and other symptoms that made it difficult to determine the exact cause of the recurrent hypothermia. However, the authors concluded that the patient's advanced age may have contributed since as stated earlier, patients with a low muscle mass and lack of movement have a lower ability to thermoregulate. Unlike our patient without thyroid dysfunction, the authors considered their patient's hypothyroidism as an exacerbating factor of the hypothermic event, which has been established as another cause and reported in the aforementioned systemic review [4].

As our case and several others describe, it may appear that elderly patients are at a higher risk of developing hypothermia from antipsychotic medications. However, a literature review of case reports completed by Kansagara et al. found that there are reports of this adverse effect occurring in psychiatric patients as young as 17 years old [10]. Another literature review completed by Rob J. van Marum et al. found that reports in the WHO database showed that risperidone had the highest number of reports of drug-induced hypothermia with clozapine second, followed by olanzapine [9]. Based on the 480 reports reviewed, 55% of these reports had to do with antipsychotic drugs, with 27% of those reports involving risperidone [9]. This multiple case report review additionally found that most of the time, the hypothermia adverse event was notable after the initation of the drug or an increased dose, which is comparable to our own patient case.

When comparing our case to the Naranjo Algorithm, which is an adverse drug reaction probability scale as shown in Table 2, it can be interpreted that this adverse event was definitely due to olanzapine [11]. The fact that our patient improved after the removal of olanzapine and relapsed once reinitiated after the first hospital stay helps to solidy this idea. To reiterate, our case also had a unique aspect compared to other cases found in the literature due to the stable preexisting polypharmacy component of our patient's medication regimen. Since the patient had previously been discharged to the community on this regimen (except the olanzapine) and was in remission for 6 months before having a psychiatric exacerbation, it is unlikely that any of the other existing medications in his regimen induced hypothermia. Although it could be argued that the anitcholinergic properties and central nervous system depressing effects of quietiapine, lorazepam and hydroxyzine could have contributed to the patient's altered mental status, it is unlikely that they contributed to the hypothermia based on the existing case reports that have found antispychotics, and notably olanzapine as being the primary suspect in this rare and potentially lethal adverse effect.

**Table 2** Naranjo: Adverse Drug Reaction Probability Scale [11].

| | |
|---|---|
| Are there previous reports of this reaction? | **YES (+1 point)** |
| Did the adverse event appear after the suspected drug was administered? | **YES (+2 points)** |
| Did the adverse event improve when the drug was discontinued or a specific antagonist was administered? | **YES (+1 point)** |
| Did the adverse event reappear when the drug was re-administered? | **YES (+2 points)** |
| Are there alternative causes that could on their own have caused the reaction?<br>**Hypothermia of unknown origin** | **YES (-1 point)** |
| Did the reaction reappear when a placebo was given? | **N/A** |
| Was the drug detected in blood or other fluids in concentrations known to be toxic? | **N/A** |
| Was the reaction more severe when the dose was increased or less severe when the dose was decreased?<br>**No, it was the same magnitude** | **NO (+1)** |
| Did the patient have a similar reaction to the same or similar drugs in any previous exposure?<br>**Drug re-challenged after first hospital admission** | **YES (+1 point)** |
| Was the adverse event confirmed by any objective evidence?<br>- **bradycardia**<br>- **temperature**<br>- **blood pressure**<br>- **Altered mental status** | **YES (+1 point)** |
| Score 5-8 indicates that this reaction was probable.<br>Only a score of 9 is definite.<br>The reaction followed a reasonable sequence of events after exposure and showed a recognized response. The reaction was confirmed by withdrawal of the medication and reappeared with subsequent re-exposure [11]. | **Total Score: 7** |

In conclusion, although antipsychotic-induced hypothermia is considered a rare side effect, prescribers should not ignore it. Healthcare professionals also should not dismiss low body temperatures as equipment error. Protocols established to recheck whenever an abnormal temperature reading is observed and to record all observations is imperative to recognizing potential antipsychotic-induced hypothermia. Individuals diagnosed with serious mental illness may lack insight and be unable to describe or recognize significant changes to body temperature, so healthcare providers should be vigilant in monitoring for physiologic changes, such as shivering or sweating to prompt further temperature checks. The use of higher doses of any psychiatric medication, including olanzapine, in an elderly patient with multiple medical conditions, including CKD, may contribute to increased risk of numerous adverse effects, therefore lower doses and slower titrations are always advised when clinically appropriate.

**Author Contributions**

We declare an equal contribution of the authors to the writing of this case report. All listed authors concur in the submission and are responsible for its content; they have agreed to its

publication and have given the corresponding author the authority to act on their behalf in all matters pertaining to publication.

**Competing Interests**

The authors have no conflict of interests to disclose.

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