

Confused, cold, and lethargic

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Ms. K, age 48, presents with new-onset altered mental status, hypotension, bradycardia, and severe hypothermia. How would you manage her?



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CASE Confused and cold

Ms. K, age 48, is brought to the emergency department (ED) by her husband because she has become increasingly lethargic over the past 2 weeks and cannot attend to activities of daily living. She is incontinent of stool and poorly responsive.

Ms. K's husband reports that lethargy culminated in his wife sleeping 30 continuous hours. She has a history of a ruptured cerebral arteriovenous malformation (AVM) complicated by a secondary infarct 7 years ago, with residual symptoms of frontal lobe syndrome. Until 2 weeks ago, however, she was in her usual state of health.

Symptoms have included depression, mood lability, impulsivity, disinhibition, poor focus, and apathy. An outpatient psychiatrist has managed these symptoms with antidepressants and atypical antipsychotics.

When Ms. K arrives in the ED, she is taking citalopram, 30 mg/d, and paliperidone, 6 mg/d. Her psychiatrist started paliperidone 2 months ago, increasing the dosage to 6 mg/d 6 weeks before presentation because of worsening mood lability, disinhibition, and paranoia regarding her caregivers. Her husband denies any other medication changes or exposure to environmental toxins.

In the ED, Ms. K is confused and oriented only to person. Vital signs are: pulse 46 bpm; blood pressure, 66/51 mm Hg; respirations,

12/min; and temperature, 29.9°C (85.8°F) via bladder probe.

What is your differential diagnosis?

- major depressive disorder, severe, with catatonic features
- exposure to cold
- hypothyroidism
- drug-induced hypothermia
- stroke
- sepsis
- delirium

The authors' observations

Hypothermia is core body temperature <35°C (95°F).¹ It often is caused by exposure to low ambient temperature (*Table 1, page 72*),¹ but Ms. K's husband denied that she had been exposed to cold. Because of Ms. K's neurologic history, stroke was high on the differential diagnosis, but physical examination did not reveal evidence of focal dysfunction and was significant only for altered mental status.

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Disclosure

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continued

Table 1

Causes of hypothermia

Diabetic ketoacidosis
Drugs
Low ambient temperature
Multisystem trauma
Prolonged cardiac arrest
Sepsis
Severe hypothyroidism
Source: Reference 1

Clinical Point

Medications for frontal lobe syndrome include typical and atypical antipsychotics, dopamine agonists, and mood stabilizers

Ms. K had no posturing, rigidity, negativism, or excessive motor activity that would suggest catatonia. Before she became lethargic, her husband had not noted any deterioration of mood, although she did exhibit other behavioral changes that prompted her outpatient psychiatrist to increase the dosage of paliperidone. Although Ms. K began experiencing persecutory delusions—she believed that her caregivers were trying to harm her—she and her family denied perceptual disturbances. On examination, she did not appear responsive to auditory or visual hallucinations.

Frontal lobe syndrome is defined as a set of changes in the cognitive, behavioral, or emotional domains, often leading to disturbed affect, alteration of attention, aphasia, perseveration, disinhibition, and personality changes.² These symptoms are not specific to lesions in the frontal lobes but can arise from lesions anywhere in the frontal-striatal-thalamic circuit.³ Causes include traumatic brain injury, neurodegenerative disorders, cerebrovascular disease, tumors, and aging.² Recommended treatment incorporates psychosocial interventions with drug treatment to target specific symptoms. Medications reported to be effective include typical and atypical antipsychotics to target aggression and agitation; benzodiazepines to reduce arousal; antidepressants for mood symptoms, dopamine agonists (eg, bromocriptine) to

decrease apathy, and mood stabilizers to target mood lability.⁴

Before her AVM rupture, review of Ms. K's psychiatric history revealed no psychiatric symptoms or impaired functioning. When hospitalized for the AVM repair, she was started on sertraline. She began seeing a psychiatrist 2 years later because of increased agitation and behavioral disturbances, and aripiprazole was added. Persistent agitation prompted a trial of divalproex sodium, which was discontinued because of slurred speech and increased distractibility. Aripiprazole was tapered and replaced with paliperidone because of poor response. Citalopram was initiated 1 year before she presented to the ED.

Which tests would you order?

- brain MRI
- infectious evaluation (lumbar puncture with analysis of cerebrospinal fluid, complete blood count, blood cultures, chest radiographs)
- endocrine panel
- urine toxicology screen

EVALUATION Hypothermia

Laboratory tests reveal multiple abnormalities, including thrombocytopenia (platelet level, $53 \times 10^3/\mu\text{L}$), altered coagulation (partial thromboplastin time, 55.6 s), elevated levels of hepatic transaminases (aspartate aminotransferase, 168 U/L; alanine aminotransferase, 357 U/L), and increased alkaline phosphatase (206 U/L). Other mild metabolic disturbances include: sodium, 149 mEq/L; CO_2 , 33 mEq/L; and blood urea nitrogen, 24 mg/dL.

These laboratory values are consistent with complications of hypothermia.¹

ECG reveals sinus bradycardia (40 bpm) and Osborn waves (additional deflection at the end of the QRS complex), which are seen often in hypothermia.¹ Head CT and brain MRI show chronic changes after Ms. K's right temporoparietal AVM rupture, but no acute abnormality. Urinalysis, blood cultures, and



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Table 2

Naranjo Causality Scale: Connecting adverse events to a drug

Question	Yes	No	Do not know/ Not done
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected drug was given?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0
Did the adverse reaction appear when the drug was readministered?	+2	-1	0
Are there alternative causes that could have caused the reaction?	-1	+2	0
Did the reaction reappear when a placebo was given?	-1	+1	0
Was the drug detected in any body fluid in toxic concentrations?	+1	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Scoring: <ul style="list-style-type: none"> • >9 = definitive adverse drug reaction • 5 to 8 = probable adverse drug reaction • 1 to 4 = possible adverse drug reaction • 0 = doubtful adverse drug reaction 			
Source: Reference 6			

Clinical Point

The Naranjo Causality Scale often is used to evaluate whether an adverse clinical event has been caused by a drug

chest radiographs are negative for infection. Urine toxicology screen is negative. Results of thyroid function tests and pituitary hormones studies are significant only for hyperprolactinemia of 155.7 ng/mL, a known adverse effect of antipsychotics.⁵

Ms. K is admitted and rewarmed passively and with warm IV fluids; by day 10 of hospitalization, temperature is stable (>35.1°C [95.2°F]). Thrombocytopenia, transaminitis, and altered mental status resolve.

Ms. K's oral medications, including citalopram and paliperidone, have been held since admission because of her altered mental status. The psychiatry service is consulted to evaluate whether her presentation could be related to her change of medication.

A literature search reveals no report of paliperidone-induced hypothermia, but we consider it a possible explanation for Ms. K's presentation. Lamotrigine (titrated to 50 mg/d), a benzodiazepine (oral lorazepam

as needed), and discontinuing antipsychotics are recommended. After she returns to her baseline functioning, Ms. K is discharged to a skilled nursing facility.

Ms. K presents to the ED 2 days after discharge with altered mental status. Vital signs are: blood pressure, 90/55 mm Hg; pulse, 59 bpm; respiratory rate, 14/min; and temperature, 34.4°C (93.9°F) via bladder probe (**Figure, page 75**). Laboratory tests were significant for hepatic transaminitis (aspartate aminotransferase, 75 U/L; alanine aminotransferase, 122 U/L) and elevated alkaline phosphatase (226 U/L). A review of records from the nursing facility revealed that Ms. K was receiving paliperidone because of an error in the discharge summary, which recommended restarting all prior medications.

The authors' observations

The Naranjo Causality Scale,⁶ which categorizes the probability that an adverse event is related to a drug (based on several

Table 3

Risk factors for hypothermia

Drug	<ul style="list-style-type: none"> • 5-HT_{2A} receptor antagonism > dopamine receptor antagonism (eg, atypical antipsychotics) • Peripheral α₂-adrenergic blockage (eg, chlorpromazine, risperidone, clozapine, thioridazine)
Patient	<ul style="list-style-type: none"> • Schizophrenia diagnosis • Preexisting brain damage
Environment	<ul style="list-style-type: none"> • Low ambient temperature

Source: References 7-12,15

Clinical Point

Patients with preexisting brain damage—such as Ms. K—might be at increased risk of antipsychotic-induced hypothermia

variables, including timing of the drug administration with the onset of event, drug dosage and levels, response relationships to a drug, including re-challenge when possible, and previous patient experience with the medication), often is used to evaluate whether an adverse clinical event has been caused by a drug (Table 2). We applied the Scale to Ms. K's case, which revealed a score of 7—indicating a *probable* adverse drug reaction. The sequence of events in Ms. K's case that led to a paliperidone challenge-dechallenge-rechallenge, and the resulting hypothermia, are, we concluded, evidence of an adverse drug reaction.

Using the World Health Organization database for adverse drug reactions, van Marum et al⁷ found 480 reports hypothermia with antipsychotics as of 2007 (compared with 524 reports of hyperthermia in the same period); 55% involved atypical antipsychotics, mainly risperidone. There are no case reports of paliperidone-induced hypothermia; however, several reports of hypothermia have been attributed to risperidone, and paliperidone is the primary active metabolite of risperidone.⁵

To identify risk factors for hypothermia with antipsychotic use, van Marum et al⁷ performed a literature search for case reports of antipsychotic-induced hypothermia, which revealed no association with age or sex. The most common diagnosis in cases of antipsychotic-induced hypothermia was schizophrenia (51%). In 73% of the cases, hypothermia followed the start

or dosage increase of the antipsychotic. These observations have been noted in case reports and case series of hypothermia associated with antipsychotic use.⁸⁻¹²

Mechanism of action

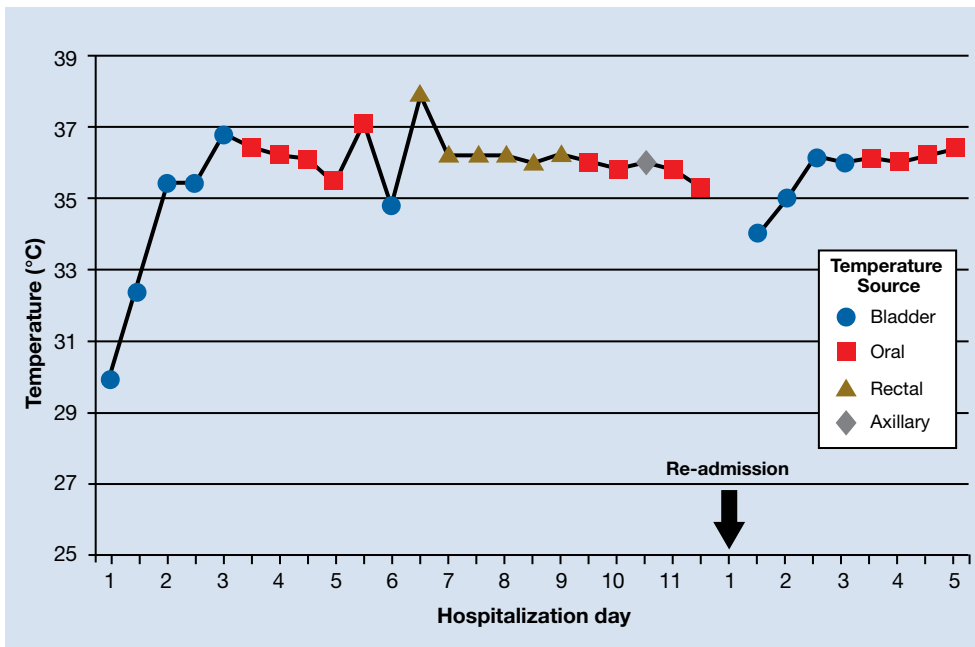
One proposed mechanism for antipsychotic-induced hypothermia includes preferential 5-HT_{2A} receptor antagonism over D₂ receptor antagonism.^{7,12} It has been believed that, under normal conditions, the action of dopamine to reduce body temperature and the action of serotonin to elevate it are in balance.⁹

Another possible mechanism is peripheral α ₂-adrenergic blockade, which might increase the hypothermic effect by inhibiting peripheral responses to cooling, such as vasoconstriction and shivering.^{7,8} Boschi et al¹³ found that antipsychotics cause hypothermia in rats when the drug is administered intraperitoneally but not when given intratheally. Perhaps for these reasons, in the early 1950s, before its psychotropic properties were known, chlorpromazine was used during surgery to induce artificial hibernation and suppress the body's response to cooling.⁷ The therapeutic activity of paliperidone is mediated through a D₂, 5-HT_{2A}, and α ₂-receptor antagonism⁵; these mechanisms could, therefore, be contributing to Ms. K's hypothermia.

Patients with preexisting brain damage—such as Ms. K—might be at increased risk of antipsychotic-induced hypothermia.^{7,8}

Figure

Ms. K's temperature during hospitalization



Clinical Point

Persons with schizophrenia might be at increased risk of developing hypothermia when exposed to low temperatures

This includes focal damage to central thermoregulatory centers, such as the pre-optic anterior hypothalamic region,¹⁴ and more diffuse damage seen in patients with cognitive impairment or a seizure disorder.⁸

Studies of people with schizophrenia show a decrease in core temperature after administration of an antipsychotic,¹⁵ raising the possibility of an impairment of baseline thermoregulatory control. Such thermal dysregulation in patients with schizophrenia might be explained by changes in neurotensin levels.⁷

The neuropeptide neurotensin has been implicated in the regulation of prolactin release and interacts to a significant degree with the dopaminergic system.¹⁶ When administered to animals, neurotensin suppresses heat production and increases heat loss.¹⁷ The neurotensin level in CSF was found to be lower in non-medicated patients with schizophrenia than in healthy controls, with an inverse correlation between the severity of symptoms and the neurotensin level.¹⁸

Additionally, persons with schizophre-

nia might be at increased risk of developing hypothermia when exposed to a low environmental temperature.^{7,8} Kudoh et al¹⁹ investigated temperature regulation during anesthesia in patients with chronic (≥ 7 years) schizophrenia receiving antipsychotics, and compared findings against what was seen in controls. The team reported that patients with schizophrenia had significantly lower intraoperative temperatures.

A published analysis of cases and studies of antipsychotic-induced hypothermia describes the combination of drug variables, patient variables, and environmental variables that contribute to thermal dysregulation (*Table 3*).^{7-12,15} The recommendation for practitioners is that, when considering an antipsychotic for a patient at high risk of thermal dysregulation, your choice of an agent should take that risk into account, especially when that drug is one that has comparatively stronger serotonergic and peripheral α -adrenergic effects. You should monitor patients closely for hypothermia after starting and when increasing the dos-

Clinical Point

Monitor patients at risk of thermal dysregulation for hypothermia after starting and when increasing the dosage of an antipsychotic

Related Resource

- Espay AJ, et al. Frontal lobe syndromes. <http://emedicine.medscape.com/article/1135866-overview>. Updated September 17, 2012. Accessed November 3, 2012.

Drug Brand Names

Aripiprazole • Abilify	Lamotrigine • Lamictal
Bromocriptine • Parlodel	Lorazepam • Ativan
Chlorpromazine • Thorazine	Paliperidone • Invega
Citalopram • Celexa	Risperidone • Risperdal
Clozapine • Clozaril	Sertraline • Zoloft
Divalproex sodium • Depakote	Thioridazine • Mellaril

age of the drug. In patients with schizophrenia who might have a problem with baseline thermoregulation, advise them to take measures to counteract their increased susceptibility to low ambient temperatures.

OUTCOME Readmission

Ms. K was readmitted, rewarmed, and discharged to a skilled nursing facility 4 days later, after baseline function returned to normal and temperature stabilized. Paliperidone is now listed in her electronic medical record as “drug intolerance.”

This case also highlights the importance of adequate medication reconciliation at admission and discharge, especially when using an electronic medical record system, because what might otherwise be considered a minor mistake can have devastating consequences.

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Bottom Line

Thermal dysregulation—hyperthermia and hypothermia—can occur secondary to an antipsychotic. Determining whether a patient is at increased risk of either of these adverse effects is important when deciding to use antipsychotics. Recognizing agents that can cause hypothermia is essential, because management requires prompt discontinuation of the offending drug.