

# A chilling complication

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Mr. S experiences recurrent hypothermia during treatment for multiple medical problems and psychotic symptoms. Could antipsychotics be the cause?



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## **CASE** Hypothermic and confused

Mr. S, age 38, is brought to the emergency room after being found unresponsive. He has a history of poorly controlled type I diabetes. On admission his core body temperature is 35.5°C (95.9°F), blood pressure is 98/70 mm Hg, respiration is 12 breaths per minute, and pulse is 88 beats per minute. The emergency room physician believes Mr. S has syndrome of inappropriate antidiuretic hormone of unknown cause and a urinary tract infection. As emergency room clinicians address these problems, Mr. S becomes increasingly confused and his responses to questioning do not make sense. His Mini-Mental State Examination score is 7/30, indicating severe cognitive impairment.

Further workup includes a brain MRI, which shows mild cerebral atrophy; HIV testing, which is negative; cosyntropin stimulation test, which indicates normal adrenal function; and a lumbar puncture, which indicates non-polio enterovirus. The hospital's infectious disease service is consulted, but because Mr. S is not exhibiting encephalitis no intervention is recommended.

Several days after admission, Mr. S becomes agitated and has visual hallucinations. The medical team requests a psychiatric consultation. Although Mr. S initially reported he had no psychiatric history, he later reveals he had visual hallucinations and stopped eating an undetermined time prior to being

admitted because he believed his food was poisoned. The patient's father reports that for the past 3 to 4 months, Mr. S has had poor sleep, poor concentration, and pain in his back, stomach, and feet.

The psychiatrist decides the patient's symptoms are the result of a long course of delirium secondary to his medical condition. He starts oral risperidone, 1 mg bid. Mr. S' temperature at this time is 36.8°C. Mr. S fails to improve, so the psychiatrist initiates quetiapine, 100 mg qhs. Two days after starting the combination of risperidone and quetiapine, Mr. S' temperature is 35.2°C.

## **The authors' observations**

Body temperature dysregulation as a result of antipsychotic use can manifest as hyperthermia in the case of neuroleptic malignant syndrome or, less commonly, hypothermia.<sup>1</sup> Symptoms of hypothermia—defined as a core body temperature of <35°C (<95°F)—include delirium, slurred speech, and ataxia (*Table 1, page 58*).<sup>2</sup> However, a hypothermic patient can be asymptomatic.

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Table 1

**Hypothermia symptoms**

Delirium
Slurred speech
Ataxia
Fatigue
Incoordination
Subjective coldness
Shivering
Bradycardia
Source: Reference 2

A recent literature review<sup>3</sup> evaluated hypothermia cases following antipsychotic use reported in the PubMed and Embase databases (43 case reports) and the World Health Organization's database of adverse drug reactions (480 reports). In this sample:

- More than one-half of patients had schizophrenia, 41% were male, and the mean age was 49.
- The reported mean body temperature was 32.6°C, with a range of 20°C to 36.1°C.
- 80% of hypothermia episodes occurred during an antipsychotic start, change, or dosage increase.
- 57% occurred within 2 days of a start, change, or dosage increase, and 16% occurred between days 2 to 7.

**TREATMENT Antipsychotic changes**

Mr. S' disorganized behavior continues, but a workup for delirium is negative. Because the patient experiences cogwheel rigidity, the psychiatrist decreases risperidone and titrates quetiapine to 150 mg bid. Mr. S' temperature rises to 36.8°C, and risperidone is stopped. Because of Mr. S' continued disorganized behavior and low blood pressure, the psychiatrist changes the antipsychotic to ziprasidone, 40 mg bid. Within 5 days of this switch, Mr. S' temperature drops from 36.4°C to 35.4°C, and then slowly returns to normal.

Mr. S' mental status continues to wax and wane. He is not eating and is losing weight. Because the psychiatrist feels that ziprasidone is causing sedation, he switches to aripiprazole, 10 mg/d, approximately 1 week later. On aripiprazole Mr. S exhibits low temperatures (35.7°C), hypotension, and a pulse of 106. Although his medical condition is stabilized, Mr. S reports hearing male voices mumbling to him and is paranoid, stating he believes people are out to get him.

The psychiatrist increases aripiprazole to 15 mg/d. Within 2 days Mr. S' temperature drops to 34.7°C, then gradually normalizes over the next 7 days. Aripiprazole is increased to 20 mg. Mr. S' mental status improves and he is fully oriented, but his temperature drops to 34.1°C. His blood glucose continues to fluctuate despite normal dietary intake.

**Which receptors or neurotransmitters are implicated in antipsychotic-induced hypothermia?**

- a) serotonin (5-HT) receptors
- b) alpha-2 adrenergic receptors
- c) gamma-aminobutyric acid (GABA) receptors
- d) dopamine
- e) norepinephrine

**The authors' observations**

Antipsychotics can influence thermoregulation by effects on the anterior preoptic hypothalamus. One possible mechanism is related to effects on the serotonin system. Atypical antipsychotics—which have a strong affinity for 5-HT<sub>2A</sub>—seem to be implicated in this reaction.

Another possible mechanism is action on alpha-2 adrenergic receptors, which may increase the hypothermic effects by inhibiting peripheral responses to cooling such as vasoconstriction and shivering. In addition, mixing atypical antipsychotics with mood stabilizers and benzodiazepines contributes to this reaction.<sup>4</sup>

GABA may have a role in hypothermia. Experiments with rats have shown that L-methionine-DL-sulfoximine infusions into the dorsal raphe nucleus of rats slows sero-

**Clinical Point**

**Effects on the serotonin system may explain atypical antipsychotics' influence on thermoregulation**

Table 2

## Mr. S' temperature during hospitalization

Hospitalized day	Core body temperature (°C)*	Antipsychotic
Admission	35.5	None
8	36.8	Started risperidone, 1 mg bid
11	35.2	Added quetiapine, 100 mg po qhs
14	36.8	Stopped risperidone, increased quetiapine to 150 mg bid
18	35.4	Switched to ziprasidone, 40 mg bid
23	35.7	Switched to aripiprazole, 10 mg/d
30	34.7	Increased aripiprazole to 15 mg/d
38	34.1	Increased aripiprazole to 20 mg/d
76	33.1	Switched to risperidone, 0.5 mg am and noon and 1 mg qhs
107	37.0	None

\*Normal core body temperature is 37°C (98.6°F)

tonin turnover, which decreases the release of GABA synthesis, and both induce hypothermia.<sup>5</sup>

Other neurotransmitter systems involved include dopamine and norepinephrine and their increased metabolism. One study compared clozapine with risperidone, quetiapine, and olanzapine with regard to dopamine receptor affinity in rats.<sup>5</sup> Clozapine had a greater affinity for D1 compared with D2 receptors. Researchers used antipsychotic-induced hypothermia to measure this. Clozapine, olanzapine, and risperidone produced dose-dependent hypothermia, which researchers were able to prevent by blocking the D1 receptor.

Other factors can contribute to hypothermia in patients taking antipsychotics, including:

- pre-existing brain damage
- lesions of the preoptic anterior hypothalamic region
- neurotensin, a thermoregulatory neuropeptide
  - ambient temperature
  - apathy and indifference resulting from antipsychotic use, which may dampen behavior aimed toward thermoregulation, such as using blankets when sleeping.

Some cases have suggested coexisting infections may play a role in temperature dysregulation.<sup>1</sup> Other compounding factors may include elevated thyroid-stimulating hormone and hypothyroidism at the time of temperature drop.<sup>1</sup>

**OUTCOME** Multiple infections

Mr. S remains hospitalized because of complications related to his diabetes, which contribute to fluctuations in mental status consistent with delirium. Two months into Mr. S' hospital stay, the psychiatrist decides to address these symptoms by restarting risperidone, 0.5 mg in the morning and 1 mg in the evening. Within several days of restarting risperidone, Mr. S' temperature drops from 37°C to 35.1°C. One day after another dose of risperidone, 0.5 mg, is added at noon, the patient's temperature drops to 33.1°C. Mr. S continues to be lethargic and confused and is hypoglycemic.

Earlier that month, a blood culture from Mr. S was found to be positive for *Clostridium difficile* and *Staphylococcus aureus*. Both infections were treated and resolved, seemingly independent from the times Mr. S' temperature dropped with addition of antipsychotics.

**Clinical Point**

Pre-existing brain damage or coexisting infection can contribute to hypothermia in patients taking antipsychotics

continued

## Clinical Point

Be vigilant for hypothermia when starting or changing an antipsychotic or increasing a dosage

Mr. S eventually decompensates and is admitted to the ICU, where he is intubated. There, the patient has positive cultures for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *enterococci*. While in the ICU Mr. S continues to receive risperidone, and his temperature drops to 30.5°C.

Mr. S improves and he is subsequently sent to the medical floor, then he is discharged to a long-term acute care facility. His temperature continues to range between 33°C and 34°C for 2 weeks, then returns to normal after all antipsychotics are discontinued.

### The authors' observations

This case report documents periods of hypothermia in a male patient who received various antipsychotics during treatment. It appears that his hypothermia occurred in conjunction with starting and changing antipsychotics and increasing dosages (Table 2, page 59).

Mr. S' case is unique in that it involves hypothermia apparently in response to multiple atypical antipsychotics in 1 patient over a prolonged time; to our knowledge, no other such cases exist. This was a complicated case of a patient with multiple serious comorbidities. We feel, however, that antipsychotics were the major contributor to Mr. S' hypothermia because the drops in temperature occurred as discrete periods tied to times of antipsychotic use.

Close monitoring of drug serum levels—particularly when starting, changing, or

## Related Resource

• Gibbons GM, Wein DA, Paula R. Profound hypothermia secondary to normal ziprasidone use. *Am J Emerg Med.* 2008;26(6):737.

### Drug Brand Names

Aripiprazole • Abilify	Risperidone • Risperdal
Clozapine • Clozaril	Vancomycin • Vancocin
Olanzapine • Zyprexa	Ziprasidone • Geodon
Quetiapine • Seroquel	

### Disclosure

The authors report no financial relationship with an company whose products are mentioned in this article or with manufacturers of competing products.

increasing a dosage—may help prevent antipsychotic-induced hypothermia. Be vigilant for behavioral changes and problems that could contribute to hypothermia, such as social isolation and inappropriate dress, as well as comorbidities such as infection. It is unclear at what core body temperature to consider stopping an antipsychotic or decreasing the dosage.

### References

1. Blass DM, Chuen M. Olanzapine-associated hypothermia. *Psychosomatics.* 2004;45(2):135-139.
2. Mayo Foundation for Medical Education and Research. Hypothermia: first aid. Available at: <http://www.mayoclinic.com/health/first-aid-hypothermia/FA00017>. Accessed March 31, 2008.
3. van Marum RJ, Wegewijs MA, Loonene AJ, et al. Hypothermia following antipsychotic drug use. *Eur J Clin Pharmacol.* 2007;63(6):627-631.
4. Chen KC, Yang YK, Chen PS, et al. Two case studies of hypothermia induced by an increased dosage of zotepine in a combination therapy. *Psychiatry Clin Neurosci.* 2003;57(4):369-371.
5. Oerther S, Ahlenius S. Atypical antipsychotics and dopamine D1 receptor agonism: an in vivo experimental study using core temperature measurements in the rat. *J Pharmacol Exp Ther.* 2000;292(2):731-736.

## Bottom Line

Antipsychotic-induced hypothermia may be triggered by starting, changing, or increasing dosages. Pre-existing brain damage, coexisting infections, and thyroid dysfunction can contribute to hypothermia in patients taking antipsychotics. Close monitoring of medication serum levels may help prevent the condition.