

# Paliperidone-Induced Hypothermia

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## Background

**Thermoregulation**, the process of maintaining stable core temperature, is a major homeostatic function necessary for survival.<sup>1,2,3</sup>

- Accomplished through afferent sensing, central control and efferent responses
- Under normal conditions, temperature-raising effects of serotonin and lowering effects of dopamine are in balance

**Stable Temperature:**  
Serotonin (5-HT) ↑ = Dopamine (D2) ↓

**Hypothermia** is defined as core body temperature less than 95°F (35°C).<sup>2,3</sup>

- Associated with poor neurological outcomes
- Potentially fatal if left undetected and untreated

### Classification and Symptoms<sup>2,3</sup>

- Mild** (35 – 32.1°C): shivering, tachycardia, lethargy, impaired fine motor skills, pallor
- Moderate** (32 – 28°C): absence of shivering, bradycardia, bradypnea, atrial dysrhythmias, loss of consciousness
- Severe** (< 28°C): apnea, ventricular dysrhythmias, delirium, pulmonary edema, coma

### Factors Inducing Hypothermia<sup>2</sup>

|                        |   |
|------------------------|---|
| <b>Environmental</b>   | Exposure to low temperature   |
| <b>Neurological</b>    | Head trauma, stroke, tumor, schizophrenia                             |
| <b>Metabolic</b>       | Hyperglycemia, hypothyroidism, hypoadrenalism, hypopituitarism        |
| <b>Pharmacological</b> | Alcohol, sedatives, atypical antipsychotics (AP), general anesthetics |
| <b>Iatrogenic</b>      | Aggressive fluid resuscitation  |
| <b>Dermal</b>          | Burn disease, severe psoriasis, dermatitis                            |

## Initial Presentation

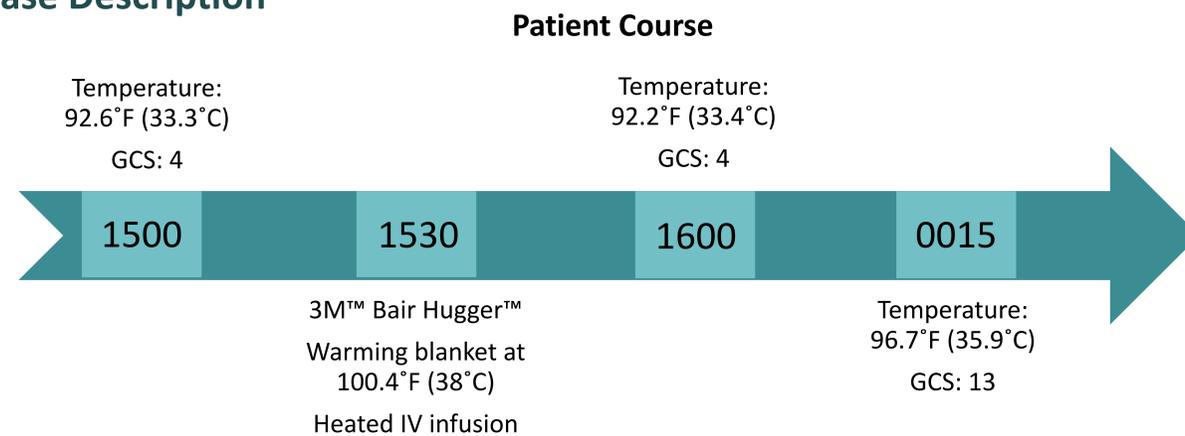
A **29-year-old male** presents with altered mental status, agitation and combativeness. Glasgow Coma Scale (GCS) at presentation was 4. Patient was found to be hypothermic with a rectal temperature of 92.6°F (33.7°C)

**Past medical history** is pertinent for neurocognitive disorder secondary to traumatic brain injury (TBI) and cerebrovascular accidents (CVAs) in the brainstem and basal ganglia.

**One week prior to presentation**, AP regimen was changed

- Initiated on paliperidone extended-release (ER) 6 mg daily for 7 days
- Then, planned to transition to Invega Sustenna® (paliperidone) long-acting injection

## Case Description



### Differential Diagnosis

|  |  |  |   |
|--|--|--|---|
| <b>Infectious Etiology</b> <ul style="list-style-type: none"> <li>White blood cells: 5.0 x 10<sup>3</sup>/uL</li> <li>Lactate: 0.7 mmol/L</li> <li>Normal chest X-ray</li> </ul> | <b>Neurologic Abnormality</b> <ul style="list-style-type: none"> <li>Head computed tomography (CT) scan unchanged</li> </ul> | <b>Adrenal Insufficiency</b> <ul style="list-style-type: none"> <li>Cortisol: 9 UG/dL</li> </ul> | <b>Hypothyroidism</b> <ul style="list-style-type: none"> <li>Thyroid Stimulating Hormone: 4.855 IU/mL</li> <li>Free thyroxine (T4): 0.58 ng/dL</li> </ul> |
|--|--|--|---|

### Patient Course (continued)

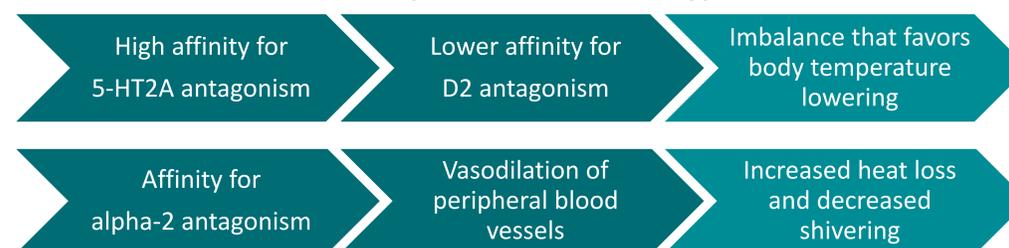
Risperidone therapy was introduced on Day 13 of hospital admission. Patient was ultimately discharged on risperidone 1 mg in the morning and 2 mg at bedtime. There were no subsequent episodes of hypothermia.

## Pharmacology Review

| Receptors | Receptor Binding Affinity <sup>4,5</sup> |               |
|-----------|--|---------------|
|           | Risperidone*                             | Paliperidone* |
| D2        | 4  | 1.6           |
| 5-HT2A    | 0.5                                      | 1.1           |
| Alpha-1   | 3  | 3.9           |

\*Represented as nanomolar concentrations required to block 50% of receptors in vitro

### Mechanism of Risperidone-Induced Hypothermia<sup>5,6</sup>



### Equipotent Dosing<sup>4,5</sup>

Risperidone 4 – 6 mg/day

Paliperidone ER 6 – 12 mg/day

## Discussion

Published case reports regarding hypothermia secondary to oral paliperidone are scarce.

**Paliperidone**, an active metabolite of risperidone, is an atypical antipsychotic that demonstrates antagonism of serotonin, dopamine and peripheral alpha-2 receptors.<sup>7,8,9</sup>

- Through serotonergic antagonism, paliperidone can cause hypothermia as serotonin's temperature-raising potential is blunted.

In contrast, **risperidone** has higher affinity for serotonin and lower affinity for dopamine receptors.<sup>9,10</sup>

- As a result, risperidone has greater potential for causing hypothermia when compared to paliperidone.

According to retrospective studies, patients are most at risk for AP-induced hypothermia upon AP therapy initiation and/or AP dose increase.<sup>5,6,9</sup>

- Predisposing factors** should also be considered, including advanced age, neurological disabilities and adrenal insufficiencies

### Naranjo Adverse Drug Reaction (ADR) Probability Scale<sup>11</sup>

| Question   | Answer | Points                                |
|--|--------|---------------------------------------|
| Previous conclusive reports on this ADR?             | Yes    | +1                                    |
| ADR appear after the drug was administered?          | Yes    | +2                                    |
| ADR improvement upon drug discontinuation?           | Yes    | +1                                    |
| Alternative cause(s) that could have caused the ADR? | No     | +2                                    |
| ADR confirmed by any objective evidence?             | Yes    | +1                                    |
| <b>Total Score = 7</b>                               |        | <i>Probable adverse drug reaction</i> |

## Hypothesis

We theorize that differences in drug dosing contributed. Patient was transitioned to a risperidone dose equivalent to half of his original paliperidone dose, which would influence degree of receptor activity leading to less potential for risperidone-induced hypothermia.<sup>8</sup>

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## Disclosures

Authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter of this presentation: Mary Bailey Jones, Desiree Kosmisky