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## CASE REPORT

# Severe recurrent hypothermia in an elderly patient with refractory mania associated with atypical antipsychotic, valproic acid and oxcarbazepine therapy

Oluwadamilare O Ajayi, Suzanne Holroyd

Department of Psychiatry & Behavioral Medicine, Joan C. Edwards School of Medicine at Marshall University, Huntington, West Virginia, USA

**Correspondence to**

Dr Suzanne Holroyd, holroyds@marshall.edu

Accepted 30 October 2017

**SUMMARY**

Hypothermia is a rare but serious condition that has been associated with various psychiatric medications. We present a 76-year-old woman with refractory mania who developed multiple episodes of severe hypothermia associated with several psychiatric medications including olanzapine, quetiapine, valproic acid and oxcarbazepine. These episodes resolved following discontinuation of the agents. The patient had never experienced hypothermia before, despite having been on these or similar agents for many years. With traditional treatments for mania not feasible, other medications were used to treat her including lithium, clonazepam, gabapentin and the novel protein kinase c inhibitor tamoxifen. The regimen resulted in some success and importantly, without triggering hypothermia. This case alerts clinicians to the rare side effect of hypothermia in response to various psychiatric medications, the fact that patients can suddenly develop this intolerance and suggests possible medications that may be used safely without triggering hypothermia.

**BACKGROUND**

Hypothermia, a body temperature less than 35°C/95°F, may be caused by exposure, infection, adrenal insufficiency, hypothyroidism, drug effects and lesions of the pituitary or hypothalamus, the primary brain regions of thermoregulation. Antipsychotics, both typical and atypical, and valproic acid (VPA) have been associated with hypothermia. Hypothermia from such agents is rare but is thought to involve mechanisms of 5-hydroxytryptamine<sub>2</sub> (5-HT<sub>2</sub>) receptors and  $\gamma$ -aminobutyric acid/gaba-aminobutyric acid (GABA).<sup>1-5</sup>

We present a 76-year-old woman with severe mania who had multiple episodes of severe hypothermia in the setting of atypical antipsychotic, VPA and oxcarbazepine therapy, after years tolerating such medication. The authors would like to emphasise the importance of this rare potentially life-threatening adverse effect of neuroleptic-induced hypothermia to all physicians, which occurs regardless of the duration of drug intake, to help them identify the condition early and treat it effectively.

**CASE PRESENTATION**

Our patient is a 76-year-old obese (body mass index 36.6 kg/m<sup>2</sup>) woman treated on a chronic geriatric psychiatry unit for 3 years for severe refractory mania. Medical history includes hypothyroidism, coronary artery disease, atrial fibrillation and hypertension. Her mania is characterised by grandiose and paranoid delusions, aggressive and hypersexual behaviours. She had been treated with lithium 300 mg/day, VPA 750 mg/day, olanzapine 5 mg/day, quetiapine 600 mg/day and lorazepam 1 mg pro re nata (PRN). Her non-psychiatric medications included amlodipine 2.5 mg/day, aspirin 325 mg/day, levothyroxine 88  $\mu$ g/day, loratadine 10 mg/day, metoprolol 25 mg/day, furosemide 20 mg/day and omeprazole 20 mg/day.

Five days prior to her first hypothermia, VPA was increased to 1000 mg/day for 1 day and then decreased back to 750 mg/day due to sedation. The day before the first hypothermia, the patient was started on trimethoprim/sulfamethoxazole (TMP/SMX) for a urinary tract infection (UTI). The next day, the patient appeared confused. She was transferred to the local emergency room (ER), where her rectal temperature was found to be 33.7°C/92.7°F. She was admitted to the medical intensive care unit (MICU) for possible sepsis, started on cefepime and placed on a Bair Hugger to resolve the hypothermia. Chest X-ray, thyroid-stimulating hormone (TSH), free thyroxine (free T<sub>4</sub>), complete blood count (CBC) and comprehensive metabolic profile (CMP) were normal; lithium level was 0.4 mmol/L (0.0–1.5 mmol/L) and total valproate levels were 42.6  $\mu$ g/mL (normal 50.0–150.0  $\mu$ g/mL). Blood cultures were negative and there were no other signs indicating sepsis. By day 3, she was back at baseline and the medical team discontinued quetiapine and VPA, uncertain if the hypothermia may have been precipitated by those medications. She returned to the psychiatric unit.

Two days following discontinuation of VPA and quetiapine, her mania worsened leading to an increase in olanzapine from 5 to 10 mg/day and finally 20 mg/day. Additionally, quetiapine and VPA were reintroduced at 300 mg/day and 250 mg/day, respectively. Improvements were noted for a period of 1 week, before mania worsened further, prompting the increase of quetiapine and VPA



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**To cite:** Ajayi OO, Holroyd S. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-222462

to 600 mg/day and 500 mg/day, respectively. Oxcarbazepine was initiated as a mood stabiliser and titrated to 600 mg/day. Following these changes, her temperature trended downwards from 36.7°C to 35.9°C and then 35.1°C (98°F–96.7°F and then 95.2°F). Psychoactive agents were held as a standing order to hold psychiatric medications for temperature less than 35°C/95°F was in place. Olanzapine and VPA, suspected as inciting agents, were discontinued while other psychiatric medications were resumed. Urine analysis (UA) conducted at this time revealed a UTI which was treated with ciprofloxacin. The patient subsequently developed hyponatraemia requiring the discontinuation of oxcarbazepine.

A month following this borderline event, her mania worsened. Quetiapine was increased to 800 mg/day. Gabapentin 600 mg/day was added to help control mania. Within several days of these medication changes, hypothermia returned with a rectal temperature of 32.8°C/91°F. Psychoactive medications were held and she was transferred to the ER, where rectal temperature was 32.2°C/90°F. ECG, chest X-ray, cardiac enzymes, CMP, lactic acid, CBC with differential, TSH, free T4, UA and cultures obtained revealed no abnormalities. Lithium level was 0.7 mmol/L. Patient was warmed with Bair Huggers, becoming normothermic within 5 hours, and returned to the psychiatric unit. This was considered her second true hypothermia.

On return, she was restarted on 300 mg/day quetiapine every night and titrated over 20 days to 500 mg/day. She then experienced her third hypothermia with a rectal temperature of 34.4°C/94°F. Due to this, quetiapine suspected as the inciting agent was subsequently discontinued.

One month following this third hypothermia, her manic symptoms became extreme including no sleep, aggression and worsening psychosis. Gabapentin was titrated to 2800 mg/day with some improvement in sleep but not other manic symptoms. VPA was now reintroduced at 250 mg/day every night with further titration to 500 mg/day every night. A UA at that time confirmed a recurrent UTI and TMP/SMX was started. As a precaution, discontinuing VPA was considered; however, her manic symptoms were so extreme that VPA was increased to 1000 mg/day. On the night of the increase in VPA dose, she became hypothermic with a rectal temperature of 34.7°C/94.5°F. She was transferred to the ER and treated for hypothermia with warming blankets. UA demonstrated the UTI had cleared (day 5 of 7-day course of TMP/SMX). VPA level was within therapeutic range at 60.1 µg/mL (50.0–150.0 µg/mL). She was discharged to the psychiatry unit. VPA was discontinued as it was thought to be contributory to the hypothermia.

At this point, the team decided to exclude all agents suspected to induce hypothermia in the patient, explicitly VPA and all antipsychotics. Oxcarbazepine was excluded due to hyponatraemia. Gabapentin dose was adjusted to a dose of 3000 mg/day and lorazepam was replaced with clonazepam with 3 mg/day.

Two weeks following the fourth hypothermia, she experienced two further hypothermic events within a 48-hour period. She was on day 2 of a course of TMP/SMX for a known UTI. Rectal temperature was 33.5°C/92.3°F and she was transferred to the ER. She was placed on Bair Huggers and discharged back to the psychiatric unit after a confirmed rectal temperature of 36.8°C/98.3°F. Within 24 hours of being discharged, a rectal temperature of 35°C/95°F was noted, prompting transfer back to the ER. A UA conducted at this point was normal. She was admitted, and after return to normothermia and endocrine consultation discharged.

## INVESTIGATIONS

All the above-mentioned UTIs were diagnosed based on positive urinalysis results reflecting elevated leucocyte esterase and abnormally elevated white cell counts with confirmatory cultures revealing *Morganella morganii* and *Escherichia coli*.

Endocrinology consult was obtained to explore other aetiologies for her hypothermia. An MRI revealed no evidence of lesions in the pituitary or hypothalamus, regions known to be involved in thermoregulation. Cortisol levels and cosyntropin stimulation tests conducted yielded benign results, ruling out adrenal insufficiency as an aetiology.

## TREATMENT

The treatment team explored options for psychiatric medication given the severity of the mania and the inability to tolerate antipsychotics, VPA and oxcarbazepine. A clinical trial using tamoxifen,<sup>6</sup> a protein kinase C (PKC) inhibitor successfully used in refractory mania, was reviewed and a decision made to try it. Clonazepam, lithium and gabapentin were continued. Lithium was eventually titrated up to 450 mg/day, likewise gabapentin was titrated up to 1500 mg/day and clonazepam to 3 mg/day.

## OUTCOME AND FOLLOW-UP

The patient was titrated to tamoxifen 80 mg/day (40 mg two times per day) without return of any hypothermia, now for 7 months. The tamoxifen appeared to dramatically reduce the severity of her mania, as the other psychiatric medications had allowed continued aggression, hypersexual behaviours and marked psychosis. With the new regimen including tamoxifen, she generally no longer experiences aggressive or hypersexual behaviours and is overall pleasant. At times, she has some mood lability, mild paranoia or verbally inappropriate statement but there are days where she is noted to have a normal mental state. This new regimen has not precipitated any further hypothermia, even with subsequent UTIs. She remains in the care of the chronic geriatric psychiatric unit.

## DISCUSSION

Our patient had multiple severe hypothermias associated with antipsychotics, VPA and oxcarbazepine.

Case reports exist of hypothermia associated with quetiapine and olanzapine.<sup>7–11</sup> In a report of data from the WHO, atypical antipsychotics were more likely than other psychiatric medications to induce hypothermia, especially following initiation or increase in dosing, as was the case in our patient. Olanzapine and quetiapine were the third and fifth most common psychoactive agents to cause hypothermia, and the third and fourth most common atypical antipsychotic agents, the most common being risperidone.<sup>1</sup> van Marum *et al* point out several other medications reported to induce hypothermia include aripiprazole, ziprasidone, chlorpromazine, haloperidol and so on,<sup>1</sup> though it is important to acknowledge the possibility of reporting bias.

Various mechanisms have been put forward. Antipsychotics with an affinity for 5-HT<sub>2</sub> receptors are thought to have an association with hypothermia.<sup>1</sup> Animal studies using *N*-phenylpiperazine, a similar structure as aripiprazole, demonstrated antagonism at 5-HT<sub>2</sub> receptors associated with their hypothermic effects.<sup>4</sup> Olanzapine is known to potentially block 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors, and has a mild selectivity for 5-HT<sub>2A</sub> receptors over dopamine D<sub>2</sub> receptors.<sup>2</sup> Quetiapine also has similar antagonistic effects at 5-HT<sub>2A</sub> receptors.<sup>3</sup>

Another mechanism is the interaction between antipsychotic agents with the neuropeptide, neurotensin (NT). Decreased levels

of NT may play a role in the psychopathology of schizophrenia. Typical antipsychotics increase synthesis of NT in the caudate nucleus and nucleus accumbens of dopamine terminal regions for the nigrostriatal and mesolimbic systems. Atypicals such as olanzapine increase NT in the nucleus accumbens.<sup>12 13</sup> NT plays a role in thermoregulation and in mice, stimulation with NT receptor agonists results in hypothermia.<sup>14</sup>

Next, we consider oxcarbazepine and VPA. A review of the literature revealed no cases of hypothermia associated with oxcarbazepine monotherapy. A single case report involving hypothermia in the setting of oxcarbazepine, topiramate and VPA multitherapy was found. In that case, the hypothermia was thought secondary to topiramate due to the return to normothermia on topiramate's discontinuation.<sup>15</sup>

On the other hand, VPA has numerous reports of hypothermia secondary to its use both with and without combination with antipsychotic agents, specifically pipamperone and zotepine.<sup>16–19</sup> In the cases of hypothermia with VPA in combination with antipsychotics, hypothermia resolved following discontinuation of the antipsychotic agents.<sup>18 19</sup> In the cases of hypothermia secondary to VPA without antipsychotics, normothermia was regained following VPA's discontinuation.<sup>16 17</sup>

In this case, the first hypothermia while clouded by a concurrent UTI, occurred in the setting of olanzapine, quetiapine and VPA combination therapy shortly after a temporary increase in the dose of VPA. We theorise VPA may have potentiated the ability of the atypical agents to induce hypothermia. There are reports in the literature noting increase in rare side effects following VPA coadministration with olanzapine and quetiapine, respectively.<sup>20</sup> VPA was noted to increase plasma concentration of quetiapine by 77% when coadministered.<sup>21</sup> An analysis on the interaction between VPA and olanzapine/quetiapine noted that VPA decreases plasma concentration of olanzapine and increases plasma concentration of quetiapine.<sup>20</sup>

In the fourth hypothermic event, VPA induced hypothermia without atypical antipsychotic agents. VPA is theorised to induce hypothermia via GABA.<sup>5</sup> Stimulation of GABA receptors is known to modulate thermoregulation and can induce hypothermia.<sup>22</sup> The current consensus in the literature is that while VPA does not directly bind GABA receptors, it increases GABA levels, although the exact mechanism has yet to be elucidated.<sup>5 23</sup> Of note, benzodiazepines interact with GABA receptors and induce hypothermia at high doses<sup>5</sup>; however, the doses in our patient were far too low to have caused her hypothermia. As for gabapentin, a GABA derivative, a review of its pharmacology states that it has no 'appreciable effect' on GABA A-receptors nor has the case been proven with regards to its effect on GABA B-receptor, while its effect on GABA turnover remains under investigation for clinical relevance.<sup>24</sup>

Advanced age is associated with a decline of autonomic nervous system function and ability to thermoregulate.<sup>25–28</sup> We speculate that while our patient's age may have been a factor, it was not the determinant factor given the fact that she has had no further hypothermias in the absence of antipsychotics and VPA.

There are also age-related changes in drug metabolism and clearance. The current literature has yet to find any appreciable change in the metabolism or clearance of VPA with increasing age.<sup>29–31</sup> There are some findings that suggest quetiapine and olanzapine have increased plasma concentration with advancing age.<sup>21 32</sup> Such changes could increase susceptibility to hypothermia following dose increases of these agents.

We also considered other drug–drug interactions, specifically aspirin and VPA, as aspirin is known to increase VPA-free serum levels.<sup>33</sup> While our patient took 325 mg/day aspirin throughout her treatment, her free serum VPA levels assessed on three separate occasions were all in the subtherapeutic range (4, <3 and <3 µg/mL; normal 5–25 µg/mL), ruling out this as a factor.

Next, medical conditions that could potentiate hypothermia were considered. Our patient has hypothyroidism, a medical condition known to cause hypothermia. However, her hypothyroidism was well controlled, normal TSH and free T4 levels were found repeatedly during and in-between episodes. Concerning environmental factors, the patient resided in a temperature-controlled environment and no other patients on the unit developed hypothermia which leads us to rule out this factor. Infection, another potential cause, was present. The first, fourth and fifth hypothermic events occurred with concurrent UTIs. However, no signs of systemic bacterial infections were found during these events. Additionally, the second and third hypothermic events occurred independent of UTIs or other infection. Lastly, she has had subsequent UTIs in the absence of the offending psychiatric medications without further hypothermia. We propose that UTIs may have played a role in disrupting thermoregulation and predisposing our patient to hypothermia but were not the determinant cause of her hypothermic events. As stated previously, primary adrenal insufficiency<sup>34</sup> was considered but ruled out in this case.

An MRI performed a month prior to the development of hypothermia revealed no evidence of lesions in the pituitary or hypothalamus, regions involved in thermoregulation. It is recognised that very small vascular lesions could have been present in either region without visibility on MRI, given the patient's vascular risk factors. Based on this, we postulate that such small vascular lesions in either area could have caused a change in her ability to tolerate the effects of the psychiatric medications which she had tolerated well without hypothermia for many years. To our knowledge, there is no literature reflecting this theory but we think it is a possibility.

With regards to the efficacy of tamoxifen as a treatment modality, in the trial reviewed, while pointing out the need for research replication, results yielded comparable improvements in mania rating to short-term trials of lithium carbonate and divalproex.<sup>6</sup> Subjects who participated in that trial were patients with a history of difficult to manage bipolar disorder. The proposed mechanism behind its efficacy is tamoxifen's inhibition of PKC. There is evidence that elevation in PKC activity is

### Learning points

- ▶ Re-emphasise hypothermia as a side effect, though rare, of atypical antipsychotics and valproic acid.
- ▶ Physicians should have an increased index of suspicion for these neuroleptic agents as hypothermia inducers, even in cases where patients have used the agents for an extensive period without such effects prior and especially in the elderly.
- ▶ Tamoxifen, as well as lithium, gabapentin and clonazepam, can be an alternative treatment options for refractory mania in patients where means of other conventional therapy are non-feasible.

present in persons with bipolar disorder and may play a role in some aspects of its manifestation.<sup>6</sup>

**Acknowledgements** We would like to acknowledge the excellent staff who take care of our patient.

**Contributors** OOA: primary author, responsible for acquisition and review of patient paper records to obtain essential data on hypothermic events and medications, responsible for literature review, drafting and revising the work for important intellectual content and provides approval for publication of content. SH: responsible for conception and design of case, made substantial/extensive contributions to drafting and revising work for important intellectual content and provides approval for publication of content.

**Competing interests** None declared.

**Patient consent** Guardian consent obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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