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Letter to the Editor

First generation antipsychotic-induced severe hypothermia: A case report and review of the literature

Hypothermia in patients on antipsychotics (APs) is an unpredictable, type B (idiosyncratic, often with low morbidity yet high mortality) adverse drug reaction (ADR) that commonly requires hospitalization, and sometimes even intensive care unit (ICU) admission (Van Marum et al., 2007). In the presence of other predisposing factors for hypothermia, such as advanced age, a cerebrovascular accident, hypothyroidism, sepsis, benzodiazepine use, alcohol intoxication, kidney or liver failure, this ADR could be life-threatening (Seeman and Emerita, 2017).

We report the case of Mrs. T, a 60-year-old Middle Eastern female patient, diagnosed with schizoaffective disorder, bipolar subtype. The patient had multiple somatic comorbidities, namely diabetes mellitus type II and hypertension (both controlled with lifestyle changes with no pharmacological interventions), subclinical hypothyroidism, generalized tonic clonic epilepsy, and gonarthrosis. She was bed-ridden, probably due to both psychiatric (apragmatism), and somatic (gonarthrosis) factors. For that reason, the patient was on enoxaparin 40 mg daily. As the patient was apragmatic, catatonia was considered, but the patient did not fulfill the DSM-5 criteria.

The patient was transferred from the residential nursing facility to an acute inpatient psychiatric hospital due to psychomotor agitation, auditory hallucinations, as well as persecutory delusions towards her family.

Upon admission, the patient was on haloperidol 10 mg/day, sodium valproate 1000 mg/day, levothyroxine 25 mcg/day, propranolol 10 mg/day, and zolpidem 5 mg/day. Her Brief Psychiatric Rating Scale (BPRS) score was 62.

On the day following admission, she was added chlorpromazine 200 mg at bedtime. On the fourth day of admission, haloperidol was increased to 13 mg/day, and lorazepam was given as PRN for agitation (1 mg at bedtime).

On the fifth day following admission, haloperidol was increased to 20 mg/day, and one day later, chlorpromazine was increased to 300 mg.

On the seventh day following admission, the patient developed bradycardia (38 beats per minute), along with hypothermia (35.1 °C), and hypotension (90/60 mm Hg). The ECG showed a junctional rhythm with the absence of P waves; QTc was 530 ms. The patient was transferred to the Emergency Department (ED). She remained hypotensive and bradycardic despite receiving 3 mg of atropine intravenously. Adrenaline was, thus, given. Intubation was considered but the arterial blood gases were normal at that time, suggesting adequate ventilation. Laboratory tests including thyroid function tests were grossly unremarkable. She was started on piperacillin/tazobactam 4.5 g every 6 h for several days as an empirical therapy for suspected sepsis. However, sepsis was not confirmed by microbiological cultures. Lumbar puncture was negative.

Over the following two days, the body temperature continued to decline, with values ranging between 31–34 °C. The patient was, thus, transferred to the ICU, and put under body warming machine. After sepsis was ruled out, the iatrogenic etiology was considered, and psychotropic medications were discontinued except for sodium valproate 1000 mg bedtime.

Hypothermia subsided 48–72 h after the psychotropic drugs were discontinued. All vital signs returned to normal.

Fig. 1 shows the timeline flowchart of the case.

The Naranjo Algorithm, or ADR Probability Scale, was used (Naranjo et al., 1981) and it yielded a score of 4 (possible). According to Hartwig's Severity Assessment Scale (Hartwig et al., 1992), the ADR can be classified as level 5 (severe).

AP-associated hypothermia appears to be less commonly reported and less studied than AP-associated hyperthermia, the latter being classically associated with the neuroleptic malignant syndrome (Zonnenberg et al., 2017).

Both conventional and atypical antipsychotics have been associated with hypothermia, but atypical antipsychotics may exhibit a lower risk for hypothermia (Zonnenberg et al., 2017).

Our patient developed hypothermia shortly following an increase in the dose of both haloperidol and chlorpromazine, suggesting the role of one or both of these drugs. Haloperidol and chlorpromazine are both among the APs most associated with hypothermia (Van Marum et al., 2007; Zonnenberg et al., 2017). Our patient had other factors that could have increased the risk for AP-related hypothermia, including: relatively old age, immobility (Zonnenberg et al., 2017), AP polypharmacy (Ajayi and Holroyd, 2017), as well as subclinical hypothyroidism (Kreuzer et al., 2012; Zonnenberg et al., 2017). Even though our patient was on levothyroxine with a normal TSH value, certain hypothyroidism symptoms might have still remained, possibly owing to insufficient conversion of T4 to T3 (Wiersinga et al., 2012). The diagnosis of schizophrenia, rather than other disorders for which APs may be prescribed, is another suggested risk factor for AP-related hypothermia cited by certain authors (Szota and Araszkiewicz, 2018). However, this can be argued against, since the data solely derives from case reports, and schizophrenia may simply be the indication par excellence for APs.

Management of AP-related hypothermia encompasses symptomatic treatment of hypothermia and its potential complications, as well as discontinuation of the incriminated drug (Zonnenberg et al., 2017). As it was the case with our patient, improvement usually occurs a few hours to days after the medication is withdrawn (Zonnenberg et al., 2017).

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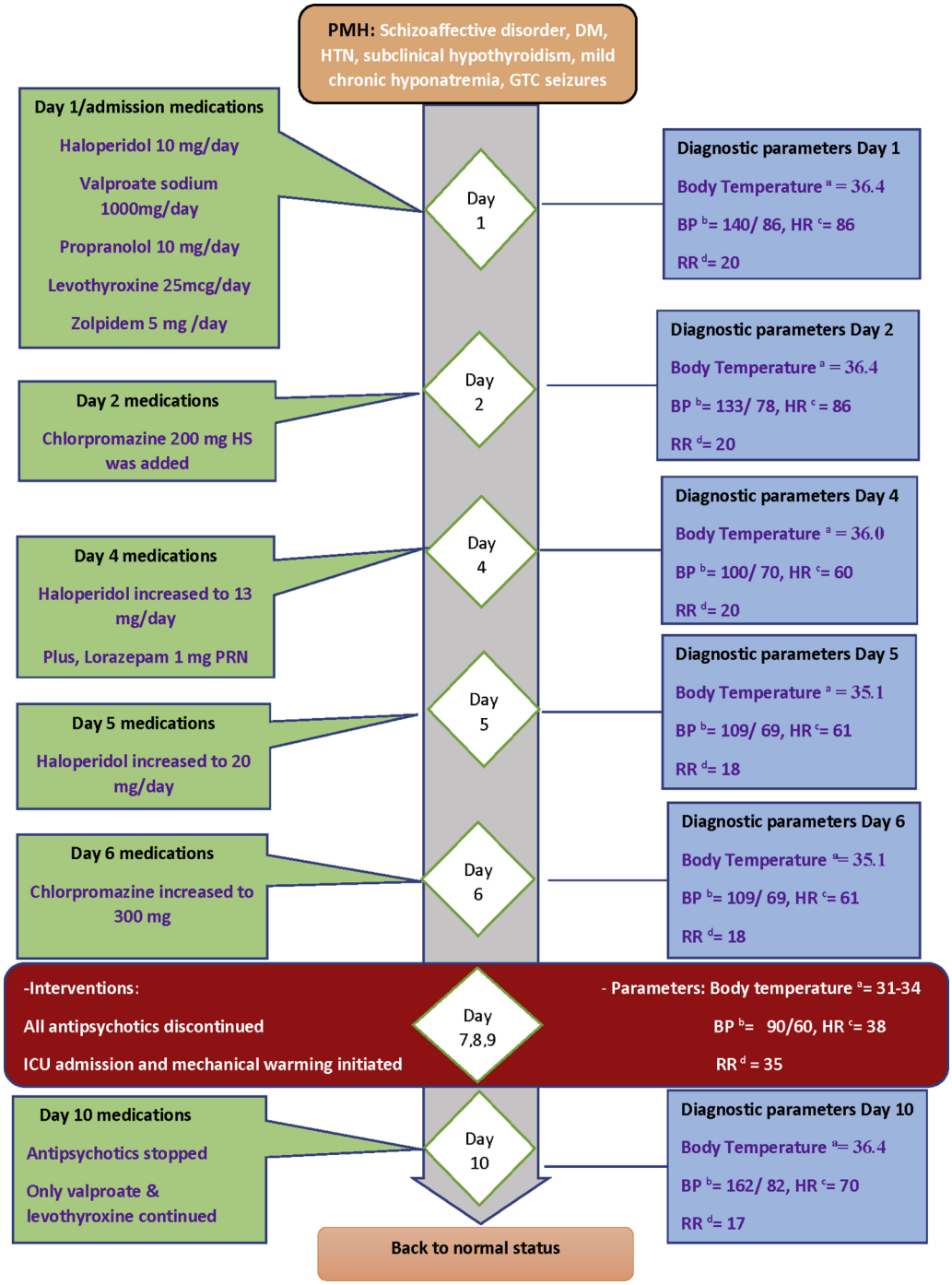

Fig. 1. Timeline of the case.
a: body temperature measured by Celsius (oC); b: blood pressure measured by mmHg; c: heart rate measured by beat/ minute; d: respiratory rate measured by breath/ minute; PMH: past medical history; DM: diabetes mellitus; HTN: hypertension; GTC: generalized tonic clonic

Declaration of Competing Interest

None.

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