Use of multiple anticholinergic medications can predispose patients to severe non-exertional hyperthermia

Ahila Manivannan,1 Dana Kabbani,2 Diane Levine2

SUMMARY
We present a case of a 64-year-old woman who developed severe non-exertional hyperthermia (NEHT) due to excessive anticholinergic effects from her psychiatric medications. The patient was found unresponsive in a non-air-conditioned room where the outside temperature was over 33°C. She presented with altered mental status, hypotension and an oral temperature of 42°C. Drug–drug interactions from her home medications for depression, bipolar disorder and seizures (amitriptyline, cyclobenzaprine, benzotropine, topiramate, clonazepam, trazodone) were suspected. Blood cultures grew Staphylococcus hominis. The patient quickly returned to baseline with supportive care in the intensive care unit. She was treated for the Staph hominis bacteraemia with a 7-day course of vancomycin. Due to her quick recovery and lack of neurological findings, severe NEHT with associated bacteraemia was determined to have caused her presenting symptoms. This patient’s multiple anticholinergic medications increased her susceptibility to develop NEHT by inhibited sweating, this patient’s natural cooling mechanism.

BACKGROUND
Severe non-exertional hyperthermia (NEHT) is defined as an elevated core body temperature above 40°C1 and can initially be difficult to distinguish from other heat illnesses such as neuroleptic malignant syndrome, serotonin syndrome or infection. When the ambient temperature is elevated, the body can only tolerate minor elevations in body temperature before systemic dysfunction begins to occur. Evaporation is the most effective way for the body to dissipate heat and there are serious consequences when that regulatory mechanism is suppressed, either through drug effects or through neural dysfunction. Failure of thermoregulatory mechanisms and exposure to hot ambient temperatures can be a potentially life-threatening combination, and this case demonstrates the need for physicians to be aware of this when prescribing multiple anticholinergic medications.

CASE PRESENTATION
A 64-year-old woman with bipolar depression, diabetes, migraine headaches and known seizure disorder was found unresponsive in a non-air-conditioned room by her husband. The ambient temperature outside was in excess of 90°F (33°C). Her home medications included amitriptyline 175 mg daily, cyclobenzaprine 10 mg daily, lurasidone 80 mg daily, benzotropine 1 mg three times a day, topiramate extended release 100 mg daily, clonazepam 0.5 mg daily, trazodone 100 mg daily, sitagliptin 25 mg daily and erenumab 70 mg injected monthly. Emergency medical service was called, and the patient was febrile on initial evaluation. Cool compresses were applied, and the patient was transported to the hospital.

On presentation to the emergency department, she was hypotensive (blood pressure 84/42) and febrile with a rectal temperature of 42°C. Skin was warm and dry. Mucous membranes were also dry. The remainder of the exam was normal with the exception of the neurological examination. The patient was only responsive to painful stimuli. She did not have any focal neurological deficits, hyperreflexia or rigidity. Initial labs were significant for leukocytosis (11 400). Creatine phosphokinase was normal. EKG was normal. The patient was admitted to the intensive care unit (ICU) and started on vancomycin and cefepime for possible sepsis. Blood cultures grew Staphylococcus hominis. During her ICU course, her core body temperature decreased to less than 38°C and her mentation returned to baseline. She was then transferred to the medical floor, where she was treated for the Staph hominis bacteraemia with a 7-day course of vancomycin. Toxicology recommended that she discontinue use of cyclobenzaprine on discharge to avoid excess anticholinergic effects. Due to her quick recovery and lack of neurological findings (ie, rigidity, tremors), severe NEHT with associated bacteraemia was determined to be the cause of her presenting symptoms.

DIFFERENTIAL DIAGNOSIS
When the patient first presented to the emergency department febrile with a high temperature, leukocytosis and hypotension, she was initially thought to be severely septic and was immediately started on broad spectrum antibiotics. However, once she was admitted to the ICU, due to her home medications there was concern for drug–drug interactions. Serotonin syndrome was also considered due to the serotonergic actions of trazodone,2 amitriptyline,3 lurasidone4 and cyclobenzaprine.4 However, there was low suspicion for this as she presented with no neurological deficits other than altered mental status. Blood cultures were obtained, and toxicology was consulted to assist the team in making a final diagnosis. Surprisingly, blood cultures were positive for S. hominis, which is part of the skin flora and
has mainly been found in nosocomial infections. Toxicology’s assessment stated that due to the high ambient temperature, NEHT was likely precipitated by the multiple home anticholinergic medications. Once the patient’s mentation improved to baseline, she revealed that she had been feeling overheated and fatigued at home for the past 2 weeks. No medication changes had been made in that time period.

OUTCOME AND FOLLOW-UP
In a 2-month postdischarge follow-up call, the patient revealed that her primary care physician advised her to continue her current medication regimen, including the cyclobenzaprine she was advised to stop per toxicology’s recommendation. She was encouraged to discuss with her physician if any of her current medications can be weaned due to the risk of a recurrence of NEHT. She was also educated about the risks of polypharmacy and the high likelihood of drug-drug interactions with her current medication regimen.

DISCUSSION
The combination of medications with anticholinergic medica
tions taken by this patient (amitriptyline, trazodone, cycloben-
zaprine and benzotropine) increased her susceptibility to develop
NEHT by inhibited sweating; this patient’s natural cooling
mechanisms. Topiramate further increased the risk of NEHT
by causing hyponatraemia. NEHT has been reported in patients
being treated with antipsychotic medications, and in at least
one elderly patient on oxybutynin. One case report described
the fatal outcome of NEHT in a patient with schizophrenia
who was prescribed risperidone and biperiden hydrochloride.
Despite the long history of the use of medications with anticho-
linergic effects by patients, reports of NEHT due to medica-
tions are few and physicians may not be aware of the risk of this
complication.

The current guidelines for NEHT management include initial
stabilisation, rapid cooling and measurement of rectal tempera-
ture. We suspect that if her core temperature had remained
elevated beyond her initial presentation, NEHT would have
been diagnosed earlier in her hospital course.

Our patient’s medication regiment put her at high risk for
hyperthermia. It is important to note that many of her home
medications were high dosages, which may have further
increased her risk for NEHT, although no literature could be
identified that correlated NEHT with medication dosage. The
Anticholinergic Risk Scale, developed by Randolph et al., was
used to quantify this patient’s anticholinergic burden. A score
of 3 or more increases the risk of central anticholinergic side
effects. Using their scoring system, our patient had a score of
3 or more increases the risk of central anticholinergic side
effects. This has thought to be partially due to the maladaptive effects of certain psychiatric medications. Further, a thorough history
including a detailed medication history is necessary to make
this diagnosis. Communication with the patient’s physician and
pharmacy may be necessary to obtain all relevant information.
Additionally, newer electronic health records with integrated
pharmacy fill histories are invaluable.

Learning points

- Severe non-exertional hyperthermia (NEHT) can be caused by anticholinergic medication use and is associated with serious
  sequela, including death.
- Patients with multiple psychiatric disorders and older adults are particularly vulnerable and may be at increased risk for adverse
drug events. Patients on multiple anticholinergic medications should be counselled on the risk of NEHT, particularly during hot
summer months. They should be advised to remain hydrated and avoid high temperature environments.
- This case highlights the importance of a medication reconciliation with each patient encounter to avoid the adverse effects associated with polypharmacy.

Contributors All authors have contributed to conception and design; contributed to acquisition, analysis and interpretation; drafted the manuscript; critically reviewed the manuscript; gave final approval; agree to be accountable for all aspects of work ensuring integrity and accuracy.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which
permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work
is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD
Ahlia Manivannan http://orcid.org/0000-0001-6757-7048

REFERENCES
Case report

Copyright 2021 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit https://www.bmj.com/company/products-services/rights-and-licensing/permissions/

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:
- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

Customer Service
If you have any further queries about your subscription, please contact our customer services team on +44 (0) 207111 1105 or via email at support@bmj.com.

Visit casereports.bmj.com for more articles like this and to become a Fellow