Ravjit Kaur *et al*, International Journal of Pharmaceutical Sciences and Medicine (IJPSM),
Vol.9 Issue. 6, June- 2024, pg. 141-147

ISSN: 2519-9889
Impact Factor: 5.9

Drugs that May Increase Risk of 'Heat-Related Illness' During Hot Weather

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DOI: 10.47760/ijpsm.2024.v09i06.012

Abstract:

The increasing frequency and intensity of heat waves due to global warming pose significant risks to human health, with vulnerable populations, such as the elderly and those with chronic conditions, being particularly affected. The hypothalamus plays a crucial role in thermoregulation, maintaining homeostasis through mechanisms like sweating and blood vessel dilation. However, extreme heat can disrupt these processes, leading to dehydration and heat-related illnesses such as heatstroke, heat rash, heat cramps, and heat exhaustion. Certain medications can exacerbate these risks by impairing the body's ability to regulate temperature. Antipsychotics, for example, disrupt hypothalamic function, while diuretics and beta-blockers affect fluid balance and vasodilation, respectively. Antidepressants may increase sweating and dehydration, and illicit drugs like amphetamines can induce severe hyperthermia. These drug-induced impairments highlight the interconnectedness of pharmacology and environmental health, emphasizing the need for heightened awareness and precautionary measures during heat waves, particularly for those on medications that impact thermoregulation. This review underscores the importance of understanding drug interactions with heat exposure to mitigate the risks of heat-related illnesses in a warming climate.

Keywords: Heat-related illnesses, thermoregulation, drug-induced hyperthermia, dehydration.

1. Introduction

Over the last 50 years, the earth's surface warming has resulted in increasingly frequent and severe extreme heat events (Haines & Ebi, 2019), which are anticipated to expand in frequency, length, and severity in the following decades. The frequency and intensity of heat wave occurrences have grown and are projected to keep increasing due to global warming, according to the Intergovernmental Panel on Climate Change (IPCC) ([H.-O. Pörtner, 2022). The negative consequences of global warming provide a clear illustration of the interconnectedness of environmental and human health (Arya et al., 2020). The intensity, and frequency of high heat events are predicted to rise in the next years, and rising temperatures are already detrimental to human health. The hypothalamus, which regulates thermoregulation, is one of the most vital bodily functions. Its primary goal is to keep the brain and major organs at a consistent temperature, crucial for maintaining homeostasis It has an impact on the autonomic nerve system, which regulates the body's vital functions such as breathing, blood pressure, and heart rate to maintain homeostasis. To dissipate body heat, the hypothalamus also controls sweating and dilates blood vessels in the skin, arms, feet, and face as part of its thermoregulatory activity. This process can be uncomfortable and drive the body to seek out shade, drink, or rest. When extreme heat conditions disrupt homeostasis, pathological conditions can develop. (Gamboa et al., 2023).

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Exposure to high temperatures may result in dehydration. Dehydration, from mild to moderate, decreases the amount of fluid available for sweating and increases cardiac effort. Increased risk of injury, heat-related illnesses, and cognitive decline are linked to dehydration. Overheating can directly cause some illnesses or ailments. These include heatstroke (a medical emergency), heat rash, heat cramps, and heat exhaustion. Everyone is at risk of heat-related illness but due to their advanced age and increased risk of disease, older people are 'more vulnerable' to extreme heat events. Furthermore, this population's capacity for thermolysis is reduced. There is a reduction in the ability for capillary vasodilation and fibrosis of many sweat glands. In addition, they may have various comorbidities that necessitate concurrent drug use (Bradley Layton et al., 2020). Certain drugs may become less effective or more harmful when kept at high temperatures, or they may raise the risk of heat-related illnesses. Consequently, taking medicine that may interfere with the body's various temperature-regulating systems, such as antipsychotics, serotoninergic medications, or anticholinergic drugs, may raise the risk of illness during heat waves. Even though a specific drug treatment by itself is not usually considered the main triggering factor of heat conditions, it can exacerbate heat-induced pathological illnesses including heat exhaustion and heat stroke. Based on their mechanism of action, some drugs should be considered as a risk factor in vulnerable individuals, considering they can exacerbate heat exhaustion and heat stroke (*Extreme Heat - Information for Clinicians. Victoria, Australia.*, 2022), (Westaway et al., 2015). Research has demonstrated that individuals with chronic conditions including schizophrenia, diabetes, cardiovascular or respiratory diseases, are often more susceptible to overheating—and that the medications they require may exacerbate this risk. A study discovered that several frequently prescribed medications impair the body's capacity to sense and defend against heat, raising the likelihood of hospitalization. Diuretics, beta-blockers, stimulants, antihypertensives, antipsychotics, and anticholinergic drugs are a few of these.

2. Thermoregulation in the human body

In the human body, the typical core temperature hovers around 37 degrees Celsius, stability upheld by a delicate interplay of heat generation through metabolic processes and environmental heat acquisition, counterbalanced by heat dissipation via conduction, radiation, and evaporation mechanisms such as sweating and insensible heat loss. The thermoregulatory center in the preoptic anterior hypothalamus is the central hub orchestrating this thermal equilibrium. Perturbations in this system, as seen in systemic hyperthermia and hypothermia, can profoundly influence bodily functions (Ishikawa & Maeda, 2013). Humans are susceptible to high temperatures when evaporative cooling is compromised by factors such as dehydration, restrictive clothing, rising humidity, or inadequate air circulation. Acetylcholine is a parasympathetic neurotransmitter, while norepinephrine is referred to as the sympathetic neurotransmitter. An important exception to this rule is the sympathetic postganglionic neurons that regulate the acetylcholine-secreting sweat glands. This explains why perspiration occurs during a sympathetic or adrenergic fight-or-flight response. Sweating helps to keep the body temperature maintained by releasing heat generated by increased motor activity (Hayes et al., 2013).

The essential concept of human thermoregulation is the desire to attain heat balance. A thermo-neutral heat balance equation is one where heat production equals heat loss, represented by the following equation:

$$\mathbf{S = (H_m - W_e) \pm H_{evap} \pm H_{Conv} \pm H_{rad} \pm H_k \pm H} \qquad \mathbf{(1)}$$

Where S = Change in body heat content, Hm = Internal metabolic heat, W_e = External work performed, ($H_m - W_e$) = Heat to be dissipated to the surrounding ("Waste heat"), H_{evap} = Evaporative heat loss from the body, H_{Conv} = Convective heat loss, H_{rad} = Radiated heat loss, H_k = Conductive heat loss, H_r = Heat loss through respiration. For

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normal heat balance, $H_m - W_e$ ("Waste heat") equals $H_{evap} \pm H_{Conv} \pm H_{rad} \pm H_k \pm H_r$ When there is an imbalance, either due to an increase in Hm or a decrease in $H_{evap} \pm H_{Conv} \pm H_{rad} \pm H_k \pm H_r$, the body accumulates heat.

Hyperthermias are conditions characterized by elevated body temperature, which can be broadly categorized into fever and hyperthermic states. Heat-related illnesses stem from various physiological disruptions due to excessive heat exposure. Heat rash occurs when sweat glands become inflamed or blocked. Heat cramps result from a loss of salt through sweating, which impacts muscle relaxation. Heat exhaustion is caused by dehydration and poor blood flow, affecting the brain and heart. Finally, heatstroke is characterized by a significant rise in body temperature, leading to widespread organ damage.

3. Drug-induced hyperthermia (General mechanisms)

Both prescription and OTC drugs can affect blood pressure, heart rate, alertness, electrolyte balance, and thermoregulation. Drug pharmacokinetics may be impaired by heat exposure. Experts claim many drugs related to drug-induced hyperthermia have a feature in common i.e. they are anticholinergic (Chew et al., 2006). These medications stop the neurotransmitter acetylcholine from binding to cell receptors, essential for the autonomic nervous system and its responses to heat, including sweating. Urinary retention, or the sensation of having to urinate yet being unable to, and dry mouth might result from blocking its activity. Due to their ability to prevent sweat, some of these drugs may make you more sensitive to heat. The hypothalamic-pituitary-adrenal axis can become dysregulated because of drug usage, raising body temperature (Jamshidi & Dawson, 2019).

Certain medications have been observed to induce hyperthermia when abruptly stopped, for example, dopamine agonists (McAllen & Schwartz, 2010). These could lead to more exercise, heat generation, or retention by blocking cooling (Palmer & Clegg, 2020). There may be other lesser-known processes that are not associated with physical activity. Through vasoconstriction, amphetamines and other sympathomimetic agonists that have α2 effects on the peripheral blood vessels (such as cocaine) prevent conductive cooling (Hayes et al., 2013) Dopamine antagonists can increase the hypothalamic threshold or reduce the POAH's reaction to heat stress (Gillman, 2010). Among other drugs, diuretics can deplete volume and reduce blood flow to the skin, which results in a decline in conductive cooling (Horseman et al., 2022). Amphetamine and various illegal drugs might change body temperature (Bradley Layton et al., 2020) Certain chronic illnesses, such as diabetes mellitus and ischemic heart disease, obesity, and a history of infection or inflammation, might amplify the effects of medications. Drug-associated heat stroke is the term used to describe cases of heat stroke where drugs are a contributing factor but not the primary cause.

4. Specific medications that may raise the 'heat risk' (with clinical evidence)

4.1 Antipsychotics

Antipsychotics, which are frequently used to treat psychiatric illnesses like bipolar disorder and schizophrenia, work mainly by blocking dopamine receptors in the brain, especially D2 receptors. Because of this antagonistic relationship, dopamine activity is lowered, potentially mitigating psychotic symptoms. Antipsychotics, however, can also affect the body's capacity to control its temperature. They interfere with the hypothalamus, which affects sweating and vasodilation, among other thermoregulatory reactions. This disturbance can raise the chance of heat-related disorders, particularly in the summer when effective thermoregulation is essential (Patel, 2023). Prolonged QTc, hyperprolactinemia, and neuroleptic malignant syndrome are among the side effects. On the other hand, heat brought on by antipsychotic medication that intensifies a cerebrovascular accident (CVA) is an uncommon but uncommon adverse effect.

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A case report revealed that a 47-year-old male patient presented with altered mental status was unresponsive to naloxone and was tachycardic (HR 160s). He was taking risperidone and fluphenazine. After the hyperthermia was resolved, a right-sided facial paralysis suggested a cerebrovascular accident, which was confirmed by MRI as a right cerebellar infarction. Following treatment, he returned to baseline mental status The patient was a 47-year-old man who had altered mental status, was unresponsive to naloxone, and was tachycardic (HR 160s). He was taking medication, including risperidone and fluphenazine. After the hyperthermia resolved, a right-sided facial paralysis suggested a cerebrovascular accident, which an MRI confirmed to be a right cerebellar infarction. After treatment, the patient's mental state returned to baseline and was released without antipsychotics. Patients taking antipsychotics should be aware of the risk of severe hyperthermia and should stop using them if it should occur. Hence, Patients taking antipsychotics should be mindful of the risk of severe hyperthermia and should stop using them if it occurs (Best et al., 2021).

4.2 Diuretics

Diuretics assist the human body in reducing fluid through frequent urination and are prescribed by doctors to treat heart failure, kidney disease, or high blood pressure. However, they can also result in an imbalance of electrolytes (Puga et al., 2019). Since they effectively treat several illnesses, including hypertension, congestive heart failure (CHF), liver failure, nephrotic syndrome, and chronic kidney disease (CKD), diuretics have been a significant class of drugs in the therapeutic arsenal for well over 50 years. The most prevalent side effects are electrolyte imbalances, which can have serious clinical repercussions. Examples include delirium caused by hyponatremia or arrhythmias caused by hypokalemia (Sok et al., 2014).

According to a case report, anasarca and congestive heart failure were the complaints of a 66-year-old man's admission to the hospital. He dropped around 35 kg of fluid in 13 days after starting intravenous furosemide and hydration restriction. Then he suffered from dizziness and hyperthermia. The results of a thorough workup were unclear. An examination of his inpatient fluid balance chart demonstrated the coincidental relationship between severe fluid loss and fever. His fluid balance was corrected, considering the possibility of hyperthermia and volume constriction brought on by rapid diuresis. His fever returned to normal, and he became conscious again after two days (Maramattom et al., 2018).

4.3 Beta-blockers

Cardiovascular illnesses like tachycardia, hypertension, myocardial infarction, congestive heart failure, cardiac arrhythmias, coronary artery disease, and other conditions are indicated and approved for treatment with beta-blockers by the FDA are the main conditions treated with beta-blockers. Numerous physiological effects are induced by beta receptors, which are present throughout the body. When beta-blocker drugs inhibit these receptors, there can be many adverse effects. The side effects that are likely to occur are bradycardia and hypotension. There are also many reports of constipation, nausea, fatigue, and dizziness. One possible mechanism of heat-related illnesses among beta-blocker users is reduced superficial vasodilation, and electrolyte imbalance which has been linked to impaired ability to dissipate heat that leads to decreased sweating (Kalisch Ellett et al., 2016). So, when the weather gets hot, people on beta blockers may feel their body temperatures rising to cause a greater risk of heat exhaustion or heat stroke. These also may raise the risk of fainting and make it difficult to sweat.

A study showed that patients taking beta-blockers or antiplatelet medications had a higher chance of experiencing a heart attack on hot weather days compared to control days. The use of beta-blockers was 65% associated with increased risk and those who took both medications had a 75% risk. People who did not take those medications had a greater risk of not experiencing a heart attack on hot days. The results also revealed that the

ISSN: 2519-9889
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patient's underlying heart condition may account for both the prescription drugs and their increased vulnerability to heart attacks in hot weather, however, it's also reasonable that they did raise the chance of heart attacks brought on by the heat (Chen, 2022).

4.4 Antidepressants

Although they are the preferred medication for treating depression, antidepressants are also approved by the FDA to treat several other illnesses like post-traumatic stress disorder, social anxiety, panic disorder, generalized anxiety disorder (GAD), obsessive-compulsive disorder, etc. There are other off-label, non-FDA-approved uses for antidepressants (Sheffler ZM, 2023). Certain antidepressants can suppress thirst and increase sweating which can result in dehydration during heat waves. Studies have shown that several antidepressants increase a person's susceptibility to heat. These include TCAs like amitriptyline and SSRIs like sertraline. The anticholinergic effects of SSRIs may impair the normal function of the sweat glands. Furthermore, some antidepressant types disrupt the functions of the brain region in charge of controlling body temperature—the hypothalamus. Overheating can occur when the hypothalamus is unable to regulate body temperature. Antidepressants have the potential to heighten a person's sensitivity to heat and raise their body temperature above 106°F (41°C) (Horseman et al., 2022)

A case report once reported that a 45-year-old man in Israel suffered heatstroke after moderate work in high temperatures, having missed doses of lithium and fluoxetine for depression. Despite treatment, he was unconscious for five days and later experienced neurological symptoms, including nystagmus, slurred speech, and ataxia. Brain scans revealed severe cerebellar atrophy after a year. The heatstroke was likely due to drug-induced heat intolerance from the combined effects of lithium and fluoxetine on body temperature regulation. Patients on these medications should be warned about the risk of heatstroke during exertion in hot weather (Albukrek et al., n.d.).

4.5 Illicit drug use

Among the most common illegal substances that can cause hyperthermia are amphetamines, methamphetamine, methylenedioxymethamphetamine (MDMA), dinitrophenol (DNP), etc. After using illegal drugs, sympathomimetic and/or serotonin poisoning often results in hyperthermia. Environmental elements that can contribute to this condition include extended periods of high temperature and/or physical activity. Extreme psychotic and agitated behavior are among the symptoms, and if left untreated, they can quickly worsen and even cause death. Stimulants, such as amphetamines and other drugs used to treat attention deficit hyperactivity disorder, may increase the risk of heat-related illnesses by interacting with the central nervous system and brain to increase the body temperature. Certain illegal substances, including amphetamines, can result in rhabdomyolysis along with extreme hyperthermia (Ishikawa & Maeda, 2013). After using illegal substances, patients who have high body temperatures run the danger of developing severe illnesses and even death. In these patients, the rapid progression to multi-organ failure and cardiac arrest can be avoided by early detection and prompt-focused therapy of hyperthermia (NSW Ministry of Health Guidelines, 2019).

A prominent case report describes a severe case of methamphetamine-induced hyperthermia. The patient in this instance had a core temperature of 41°C and needed to be aggressively cooled immediately. His pockets held needles and a bag containing methamphetamine, a crystalline white drug. Sedation, intubation, and a variety of cooling methods, including ice packs, immersion in cold water, and chilled IV fluids, were used as part of the management. After the patient's condition was stabilized, the ICU was consulted for additional care (Chakraborty, 2022).

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5. Conclusion

The rising incidence and severity of heat waves, driven by global warming, necessitate a comprehensive understanding of the factors exacerbating heat-related illnesses. Medications, including antipsychotics, diuretics, beta-blockers, antidepressants, and certain illicit drugs, significantly impair the body's thermoregulatory functions, heightening the risk of dehydration, heat exhaustion, and heatstroke. Vulnerable populations, particularly the elderly and those with chronic conditions, are at increased risk due to these pharmacological effects. It is crucial for healthcare providers to be aware of these interactions and to educate patients on the potential dangers during periods of extreme heat. Proactive measures, such as medication adjustments and increased hydration, can mitigate these risks. This review highlights the urgent need for integrated health and environmental strategies to protect at-risk individuals from the compounded effects of heat waves and medication use. As global temperatures continue to rise, ongoing research and public health initiatives will be essential in adapting to these challenges and safeguarding public health.

Consent for publication: Not applicable.

Funding: None.

CRediT authorship contribution statement

Ravjit Kaur: Conceptualization, Writing – original draft & editing. MD Asif Mallick: Review & editing

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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