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REVIEW

Understanding drug-induced hyperthermia

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ABSTRACT:

Drug-induced hyperthermia encompasses a spectrum of potentially life-threatening syndromes caused by pharmacological agents. This review summarizes the current understanding about the disease pathophysiology, clinical manifestations, diagnostic challenges, and therapeutic strategies. Emphasis is placed on major syndromes, including neuroleptic malignant syndrome, serotonin syndrome, malignant hyperthermia, anticholinergic toxicity, and sympathomimetic toxicity. Early recognition and timely intervention are crucial for reducing morbidity and mortality.

Keywords: Drug-induced hyperthermia; Neuroleptic malignant syndrome; Serotonin syndrome; Malignant hyperthermia; Anticholinergic toxicity; Sympathomimetic toxicity

INTRODUCTION

Drug-induced hyperthermia (DIH) refers to a spectrum of conditions in which pharmacological agents disrupt normal thermoregulatory mechanisms, leading to an uncontrolled increase in core body temperature. Unlike fever, which reflects hypothalamic set-point resetting, DIH is driven by excessive metabolic heat production or impaired heat dissipation; if left unrecognized, it can rapidly progress to organ dysfunction [1-4]. Although relatively uncommon, its clinical importance is amplified in acute and critical care settings, where fever is a frequent but often misleading clinical sign. Up to half of patients admitted to the intensive care unit (ICU) develop fever during hospitalization; however, a substantial proportion of these episodes are unrelated to infection [5, 6]. Non-infectious causes are frequently overlooked, and their contribution to febrile presentations may be underestimated in daily practice [6]. Several well-described syndromes, including malignant hyperthermia (MH), neuroleptic malignant syndrome (NMS), serotonin syndrome (SS), anticholinergic syndrome, and sympathomimetic toxicity, fall within the DIH spectrum. These conditions may resemble sepsis or heat stroke and require distinct management strategies, including immediate discontinuation of the causative drug, use of specific antidotes when available, and supportive care [3, 6].

In this review, we aimed to integrate the current evidence on DIH, encompassing its pathophysiology, clinical characteristics, diagnostic challenges, and treatment strategies. Particularly, we emphasized bedside differentiation of DIH from sepsis and heat stroke for enhancing early recognition and optimal management in emergency and critical care settings.

Literature search and study selection

This narrative review based on a targeted literature search was conducted by searching PubMed and Scopus up to October 2025 to identify relevant studies on DIH. The key search terms included combinations of "drug-induced hyperthermia," "malignant hyperthermia," "neuroleptic malignant syndrome," "serotonin syndrome," "anticholinergic toxicity," and "sympathomimetic toxicity." Studies were selected for relevance to the pathophysiology, clinical features, diagnosis, and management of DIH, with a focus on emergency and critical care settings; studies lacking clinical relevance were excluded.

PATHOPHYSIOLOGY AND MECHANISMS

Thermoregulation

The core body temperature is maintained through a central network that links peripheral sensors to the hypothalamic pathways. This system coordinates mechanisms that either conserve heat, such as vasoconstriction and shivering, or promote heat dissipation via sweating and cutaneous vasodilation [2-4, 7]. Under normal conditions, these processes maintain the temperature within a narrow range of 36.5–37.5°C [6]. Fever refers to a regulated elevation in body temperature due to an upward resetting of the hypothalamic set-point, most often defined in critically ill adults as ≥38.0–38.3°C in consensus guidelines [4, 6, 8]. Hyperthermia occurs independently of hypothalamic control and results from excessive heat production, impaired dissipation, or both. It may be precipitated by drugs, environmental exposure, or intense physical exertion [3-6, 8].

Dysregulation: impaired heat dissipation and increased heat production

DIH may arise from either a failure of heat dissipation or excessive metabolic heat generation. Impaired cooling is observed when anticholinergic drugs suppress sweating or sympathomimetic agents provoke cutaneous vasoconstriction, both of which reduce evaporative and convective heat loss [9]. In contrast, syndromes such as MH and NMS primarily reflect uncontrolled heat production driven by sustained muscle contraction and hypermetabolism [2, 3].

Role of neurotransmitters and muscle metabolism

Disturbances in neurotransmitter signaling and muscle physiology underlie the various forms of DIH. Disruption in dopamine signaling by D_2 receptor blockade or abrupt withdrawal of dopaminergic therapy precipitates NMS, characterized by rigidity, thermoregulatory failure, and altered consciousness. Excessive serotonergic activity, particularly overstimulation of 5-HT_2A receptors, produces SS, characterized by clonus, autonomic instability, and neuromuscular excitation. Abnormal ryanodine receptor-mediated calcium release in skeletal muscle drives the uncontrolled metabolism and heat generation observed in MH, which is uniquely reversed by dantrolene. Impaired acetylcholine-mediated sweating limits evaporative cooling in patients with anticholinergic syndrome, whereas excessive adrenergic stimulation amplifies thermogenesis and sympathetic activation in sympathomimetic syndrome [2, 3].

KEY MESSAGES:

- Drug-induced hyperthermia includes various syndromes with distinct mechanisms and overlapping clinical presentations.
- Differentiating between infectious fever and heat-related illnesses is essential for patient safety.
- Management involves the immediate discontinuation of the offending agents, targeted antidotes, and supportive care.

CLINICAL SPECTRUM OF DRUG-INDUCED HYPERTHERMIA

The clinical spectrum of DIH comprises several distinct but overlapping syndromes, each characterized by specific pharmacologic triggers and pathophysiologic mechanisms. In this review, five major syndromes are highlighted: NMS, SS, MH, anticholinergic toxicity, and sympathomimetic toxicity. Although these entities share the common feature of unregulated hyperthermia, they differ in clinical manifestation, diagnostic features, and therapeutic approaches. Before discussing the clinical characteristics and management of each syndrome in detail, the following section outlines general principles that apply across the spectrum of DIH.

General principles of management

The cornerstone of management across all forms of DIH is prompt recognition of the condition and immediate discontinuation of the offending agent [1-4, 6]. Supportive care remains fundamental and includes close monitoring of airway, respiratory, and cardiovascular statuses; aggressive intravenous fluid resuscitation; and surveillance for complications such as rhabdomyolysis, metabolic acidosis, and acute kidney injury. Active temperature reduction using external cooling measures should be initiated early, with escalation to more invasive cooling strategies in severe or refractory cases [3-6]. Importantly, antipyretic agents such as acetaminophen and nonsteroidal anti-inflammatory drugs are ineffective in DIH and should be avoided, as temperature elevation results from unregulated heat production or impaired heat dissipation rather than hypothalamic set-point resetting [1-3, 6]. Syndrome-specific pharmacologic therapies and antidotes are discussed in the sections below.

Neuroleptic malignant syndrome (NMS)

Clinical

The term neuroleptic has been linked to antipsychotic medications that act as dopamine D_2 receptor antagonists rather than antidepressants or anxiolytic drugs [10]. NMS was initially described in patients receiving typical or atypical antipsychotics and may also emerge following the sudden discontinuation of dopaminergic therapies or after exposure to other dopamine-blocking agents [1, 11-13].

Symptoms usually evolve over hours to days following antipsychotic initiation or dose escalation but can occur after sudden discontinuation of dopamine agonists [3, 12].

The syndrome is classically described by the tetrad of fever, severe generalized rigidity, altered mental status, and autonomic dysfunction [1, 5, 14]. The earliest manifestations are typically muscle rigidity and labile blood pressure [5, 11].

In patients with NMS, muscle rigidity is thought to arise from abnormal calcium handling within the sarcoplasmic reticulum, mirroring the pathophysiology of MH [5]. Clinically, this rigidity represents an extrapyramidal manifestation, most often appearing as the hallmark "lead-pipe." On examination, it is characterized by continuous and uniform resistance to passive limb movements throughout the full range of motion [11].

Laboratory findings

Biochemical abnormalities support the diagnosis of NMS and help in assessing its severity. The most consistent marker is a marked elevation in serum creatine kinase (CK) levels, which reflects rhabdomyolysis [2, 12]. Additional findings may include leukocytosis, elevated transaminase levels, and electrolyte disturbances, such as hyperkalemia. In severe cases, complications such as myoglobinuria, acute kidney injury, metabolic acidosis, or disseminated intravascular coagulation may occur [12, 14].

Diagnostic criteria

The diagnosis of NMS is clinically supported by a structured diagnostic framework. The Levenson [12, 15] and the DSM-5 criteria [10, 13, 16] are summarized in Table 1.

Management

Early recognition and immediate discontinuation of the causative drug are essential [1-4, 10-14]. Regarding moderate-to-severe NMS, pharmacological therapy may be considered along with supportive care. Dopamine agonists, such as bromocriptine and amantadine, can help restore dopaminergic tone and reduce rigidity. Dantrolene can be used for decreasing muscle rigidity and metabolic heat production; however, its benefits remain controversial. Dantrolene is reserved for severe presentations due to concerns regarding its efficacy and risk of hepatotoxicity. Benzodiazepines may be administered to control agitation and provide additional muscle relaxation. In refractory cases, electroconvulsive therapy has been used as a salvage option [3, 10-13].

Prognosis and outcome

With earlier recognition and advances in critical care, the mortality rate of NMS has declined to below 10–15%, compared with rates exceeding 30% in older reports [12, 14]. Although prolonged courses may occur with long-acting neuroleptics, most patients recover within 1–2 weeks. Recurrence remains possible if antipsychotics are reintroduced; therefore, rechallenge should be delayed for at least 2 weeks after full recovery using lower-potency or atypical agents with careful monitoring [11–13]. Long-term sequelae are uncommon but may include renal impairment due to rhabdomyolysis or thromboembolic complications, highlighting the need for follow-up [10, 12].

Serotonin syndrome (SS)

Clinical

SS, also known as serotonin toxicity, is a potentially life-threatening adverse drug reaction caused by excessive serotonergic activity in the central nervous system [17-20]. It typically develops within hours of exposure to serotonergic agents or drug interactions involving selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, or other serotonergic drugs [17, 21]. The clinical triad consists of neuromuscular hyperactivity (tremor, hyperreflexia, clonus, and myoclonus), autonomic instability (fever, tachycardia, diaphoresis, hypertension, and diarrhea), and altered mental status (agitation, confusion, and coma) [1, 2, 4, 5]. Compared with NMS, SS has a more abrupt onset; moreover, the presence of hyperreflexia with clonus is a distinguishing feature [1, 2, 5].

Table 1. Summary of the Levenson [15] and the DSM-5 diagnostic criteria for neuroleptic malignant syndrome [16].

Criteria	Levenson Criteria (1985)	DSM-5 Criteria (2013)
Diagnostic threshold	≥3 major or 2 major + 4 minor features	Exposure to dopamine antagonist (or dopamine agonist withdrawal) + severe rigidity + hyperthermia + ≥2 associated features
Major features	• Fever • Rigidity • Elevated Creatine kinase (CK)	• Severe muscle rigidity • Hyperthermia
Minor features / Associated findings	• Tachycardia • Abnormal blood pressure • Tachypnea • Altered consciousness • Diaphoresis • Leukocytosis • Metabolic acidosis	• Altered mental status • Diaphoresis • Dysphagia • Tremor • Incontinence • Mutism • Tachycardia • Elevated or labile blood pressure • Leukocytosis • Elevated CK

Laboratory findings

No specific laboratory test can definitively be used for diagnosing SS. Investigations primarily provide supportive evidence and aid in identifying complications. Frequently observed abnormalities include elevated CK levels due to sustained muscle activity, leukocytosis, and mild metabolic acidosis [3, 19, 21]. In more severe presentations, patients may develop rhabdomyolysis, hyperkalemia, acute kidney injury, or disseminated intravascular coagulation, reflecting the systemic consequences of uncontrolled serotonergic overactivity [19].

Diagnostic criteria

The diagnosis of SS remains clinical, as no confirmatory biomarkers are available. Several diagnostic tools have been proposed; however, the Hunter Serotonin Toxicity Criteria are considered the most accurate and widely used [17-21]. Alternative diagnostic frameworks, such as Sternbach's criteria, are less specific and may lead to overdiagnosis [18-20]. A comparison of the diagnostic frameworks is presented in Table 2.

Management

Managing SS begins with immediate discontinuation of all serotonergic medications [2, 4, 5, 17, 19-21]. Benzodiazepines are recommended for controlling agitation and reducing neuromuscular hyperactivity. In moderate-to-severe cases, the serotonin antagonist cyproheptadine may be administered orally or via a nasogastric tube [2, 4, 20, 21]. Neuromuscular paralysis and mechanical ventilation may be required in life-threatening presentations with severe hyperthermia and marked rigidity [4, 20, 21].

Prognosis and outcome

When recognized promptly and managed appropriately, SS resolves within 24–72 h of the withdrawal of serotonergic drugs [19, 21]. Most patients recover without sequelae; however, severe untreated cases may lead to multi-organ failure and death. Compared with NMS or MH, the overall prognosis is more favorable with early recognition and intervention. Prevention through awareness about drug interactions, cautious prescription, and patient education is critical [17, 20, 21].

Malignant hyperthermia (MH)

Clinical

MH is a pharmacogenetic disorder of the skeletal muscle that is often precipitated by exposure to volatile anesthetics such as halothane, sevoflurane, or desflurane, or by depolarizing neuromuscular blockers such as succinylcholine [2, 3, 5, 22-25]. The syndrome typically presents with a rapid onset of hypercarbia, generalized muscle rigidity, tachycardia, and rapidly rising body temperature, which may increase by approximately 1°C every 5–10 min. Early features include unexplained elevation of end-tidal CO_2 despite adequate ventilation, masseter muscle rigidity, and sinus tachycardia. Without intervention, fulminant hyperthermia, arrhythmias, and hemodynamic collapse may develop [22-25].

Laboratory findings

Characteristic laboratory abnormalities include marked metabolic acidosis, hyperkalemia, and elevated CK levels, all of which reflect intense muscle breakdown. Myoglobinuria is a common condition that can progress to acute kidney injury. Rapid arterial blood gas analysis often reveals combined respiratory and metabolic acidosis due to increased CO_2 production and lactic acidosis caused by sustained muscle contraction [22, 23, 25].

Diagnostic criteria

The Clinical Grading Scale is frequently used for estimating the likelihood of MH, as presented in Table 3 [22, 24]. The caffeine-halothane contracture test remains the gold standard for confirming susceptibility, whereas genetic testing for RYR1 (Ryanodine receptor-1) and CACNA1S (calcium voltage-gated channel subunit alpha-1-S) mutations provides a less invasive alternative [23-25].

Management

Immediate management centers should discontinue triggering agents and implement aggressive supportive measures. The definitive treatment is dantrolene sodium, which inhibits calcium release from the sarcoplasmic reticulum, thereby reducing muscle rigidity and metabolic heat production [22, 23]. Intensive monitoring in a critical care unit is essential because recurrence may occur within 24 h [23, 25].

Table 2. Comparison of the Sternbach [2, 18, 20] and the Hunter diagnostic criteria for serotonin syndrome [18, 20].

Criteria	Sternbach's criteria (1991)	Hunter serotonin toxicity criteria (2003)
Diagnostic threshold	Expose to serotonergic agent and at least three of the associated finding	Expose to serotonergic agent and one of specific clinical features (focus on clonus and neuromuscular findings)
Associated findings	• Mental status changes (confusion, hypomania) • Agitation • Myoclonus • Hyperreflexia • Diaphoresis • Shivering • Tremor • Diarrhea • Incoordination • Fever	• Spontaneous clonus • Inducible clonus + agitation or diaphoresis • Ocular clonus + agitation or diaphoresis • Tremor + hyperreflexia • Hypertonia + temperature >38°C + ocular or inducible clonus

Table 3. Clinical grading scale of malignant hyperthermia [24].

Category	Clinical features	Points
Muscle rigidity	• Generalized rigidity	15 points
	• Masseter muscle rigidity after succinylcholine	15 points
Muscle breakdown	• CK >20,000 IU after succinylcholine	15 points
	• CK >10,000 IU without succinylcholine	15 points
	• Cola-colored urine	10 points
	• Urine myoglobin >60 mcg/L	5 points
	• Serum myoglobin >170 mcg/L	5 points
	• Hyperkalemia (serum K>6 meq/L without renal failure)	3 points
Respiratory acidosis	• $ETCO_2$ >55 with controlled ventilation	15 points
	• $PaCO_2$ >60 with controlled ventilation	15 points
	• $ETCO_2$ >60 with spontaneous ventilation	15 points
	• $PaCO_2$ >65 with spontaneous ventilation	15 points
	• Inappropriate hypercarbia (by judgement)	15 points
	• Inappropriate tachypnea (by judgement)	10 points
Temperature increase	• Inappropriate rapid rise of temperature	15 points
	• Inappropriate temperature increase >38.8°C	10 points
Cardiac involvement	• Inappropriate sinus tachycardia	3 points
	• In appropriate ventricular tachycardia/ ventricular fibrillation	3 points
Family history	• Family history of MH in first degree relative	15 points
	• Family history of MH in relative not of first degree	5 points
Other indicators	• Arterial base excess > -8 mEq/L	10 points
	• Arterial pH<7.25	10 points
	• Rapid reversal of MH sign after dantrolene treatment	5 points
	• Positive MH family history along with positive personal anesthetic history without elevated resting serum CK levels	10 points
	• Elevate resting serum CK and positive family history	10 points

Total score range	MH likelihood	MH rank
≥50	Almost certain	6
35–49	Very likely	5
20–34	Somewhat great than likely	4
10–19	Somewhat less than likely	3
3–9	Unlikely	2
0	Almost never	1

Prognosis and outcome

With early recognition and access to dantrolene, mortality has fallen dramatically, from over 70% in the pre-dantrolene era to less than 5% in modern practice [22]. Most patients recover without long-term sequelae if treated promptly; however, complications such as renal failure, arrhythmias, and disseminated intravascular coagulation may occur in severe cases [25]. Survivors remain at lifelong risk, and family members should be counseled about genetic testing and the need for avoiding anesthetic triggers [22].

Anticholinergic toxicity

Clinical

Anticholinergic toxicity results from excessive blockade of muscarinic receptors, most commonly following an overdose of medications such as antihistamines, tricyclic antidepressants, antipsychotics, or antispasmodics [2]. The clinical presentation has long been summarized by the mnemonic "red as a beet, dry as a bone, blind as a bat, mad as a hatter, hot as a hare, and full as a flask," which corresponds to cutaneous flushing, anhidrosis with hyperthermia, mydriasis with blurred vision, central anticholinergic delirium, and urinary retention [5]. Additional features included dry skin, hypoactive bowel sounds, tachycardia, and escalating psychomotor agitation. In cases of severe intoxication, seizures or coma may occur. Thermoregulatory failure in this toxidrome reflects impaired sweating and ineffective heat dissipation resulting from antimuscarinic activity, producing the characteristic "hot and dry" clinical phenotype [1, 2, 4, 26].

Laboratory findings

No single diagnostic laboratory marker was identified. Tests are used for staging the severity and identifying complications. Elevated CK levels due to agitation/rigidity, leukocytosis, electrolyte disturbances, and metabolic acidosis can occur in severe hyperthermia cases. If a tricyclic antidepressant (TCA) is implicated, electrocardiogram (ECG) monitoring is essential because QRS widening, QT prolongation, and malignant arrhythmias may develop [9, 26].

Diagnostic criteria

The diagnosis is clinical, based on compatible exposure and a constellation of central (delirium, agitation, and hallucinations) and peripheral (dry skin/mucosae, mydriasis, ileus, and urinary retention) antimuscarinic signs. Routine bedside toxicology screens are nonspecific and do not require confirmation [26].

Management

Management is primarily supportive of benzodiazepines as the first-line therapy for agitation or seizures and often requires relatively high doses. When diagnosis is confirmed, physostigmine, a tertiary acetylcholinesterase inhibitor, can rapidly reverse the delirium and peripheral manifestations. However, its use is contraindicated in the setting of a suspected TCA overdose or evidence of cardiac conduction abnormalities, such as a widened QRS complex, and should only be administered with continuous cardiac monitoring. Recent reviews and cohort studies have indicated that physostigmine is effective and safe when administered judiciously and titrated appropriately. Intravenous sodium bicarbonate is recommended for managing patients with TCA-associated QRS widening [2, 4, 9, 26].

Prognosis and outcome

With timely recognition and appropriate supportive care augmented by physostigmine in selected patients, most individuals with anticholinergic toxicity completely recover. Severe complications, including rhabdomyolysis, acute kidney injury, and cardiac dysrhythmias, are uncommon when hyperthermia and agitation are rapidly controlled. Mortality is rare in modern clinical practices [1, 7, 23, 25].

Sympathomimetic toxicity

Clinical

Sympathomimetic toxicity results from excessive stimulation of adrenergic pathways through enhanced release and inhibited reuptake of endogenous catecholamines, including norepinephrine, epinephrine, dopamine, and serotonin. This toxidrome is most often triggered by exposure to amphetamines, cocaine, synthetic cathinones, and other stimulant compounds that drive the hyperadrenergic state and its characteristic clinical presentation [1, 2].

Patients with sympathomimetic toxicity typically present with marked agitation, profuse diaphoresis, tachycardia, hypertension, mydriasis, and hyperthermia. Neurological manifestations may range from tremors and seizures to more severe complications such as hypertensive encephalopathy. Cardiovascular involvement is associated with the risk of arrhythmias, myocardial ischemia, and infarction. Sympathomimetic toxicity typically manifests with preserved or increased sweating, producing a characteristic "hot and wet" phenotype that contrasts with anticholinergic toxicity [2, 5].

Laboratory findings

Although no single laboratory test can definitively be used for establishing a diagnosis, investigations play an important role in assessing the severity and complications of sympathomimetic toxicity in patients. Common abnormalities include elevated CK levels due to muscle hyperactivity or rhabdomyolysis, metabolic acidosis, electrolyte disturbances, hyperglycemia, and leukocytosis. ECG is essential for evaluating ischemia, QT interval prolongation, and arrhythmias, particularly in cases of cocaine-associated toxicity, where cardiovascular complications are common [1, 2].

Diagnostic criteria

Diagnosis is made clinically and informed by a history of sympathomimetic exposure. The classic triad of agitation, diaphoresis, and hyperthermia, combined with tachycardia and hypertension, strongly suggests a diagnosis [1, 2, 4].

Management

Benzodiazepines are first-line agents for controlling agitation, hyperthermia, and hypertension [2, 4]. Pure beta-blockers are avoided due to the risk of unopposed alpha activity; instead, vasodilators such as nitroglycerin or nitroprusside may be used. In refractory hypertension, phentolamine (an α-blocker) can be cautiously considered if benzodiazepines and vasodilators fail and supportive evidence exists in controlled settings [4].

Prognosis and outcome

Most patients with sympathomimetic toxicity recover completely with prompt supportive care. Poor outcomes are associated with severe hyperthermia, arrhythmia, myocardial ischemia, and multiorgan dysfunction. Although acute mortality is low with timely treatment, complications such as rhabdomyolysis, renal injury, and chronic cardiovascular disease may occur, particularly with recurrent or high-dose stimulant use [2, 5].

SUMMARY OF THE CLINICAL SPECTRUM AND BEDSIDE DIFFERENTIATION

Although the major DIH syndromes share the common feature of unregulated hyperthermia, they differ in precipitating agents, clinical manifestations, diagnostic features, and management priorities. A structured bedside comparison of key distinguishing clinical features and syndrome-specific management considerations across these entities is summarized in Table 4.

DIFFERENTIAL DIAGNOSIS FROM OTHER CONDITIONS

Differentiating DIH from other critical conditions such as sepsis and heatstroke remains a significant diagnostic challenge in emergency and intensive care.

Table 4. Differential diagnosis and specific treatments for syndromes associated with hyperthermia.

Syndrome	Neuroleptic malignant syndrome	Serotonin syndrome	Malignant hyperthermia	Anticholinergic toxicity	Sympathomimetic toxicity
Drug class / triggers	Dopamine antagonists, withdrawal of dopamine agonist	Selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), other serotonergic drugs	Volatile anesthetics, succinylcholine	Antihistamines, tricyclic antidepressant (TCAs), antipsychotics, antispasmodics	Amphetamines, cocaine, cathinones
Mechanism	Dopamine blockade	Excess serotonin (5-HT2A)	Ryanodine receptor-1 (RYR1)/ Ca^{2+} release	Muscarinic blockade	Hyperadrenergic state
Onset	Hours–days	Hours (abrupt)	Minutes (peri-anesthetic)	Acute (overdose)	Acute (stimulant use)
Key features	Lead-pipe rigidity, fever, AMS, autonomic instability	Clonus, hyperreflexia, diaphoresis, diarrhea, agitation	Rapid $\uparrow ETCO_2$, rigidity, hyperthermia	Dry skin, mydriasis, delirium, urinary retention	Diaphoresis, mydriasis, agitation, hypertension, tachycardia
Diagnostic criteria	Levenson / DSM-5	Hunter (preferred) / Sternbach	Clinical grading scale, CHCT, genetics	Clinical toxidrome	Clinical toxidrome
Specific treatment / antidote	Stop drug; supportive care; **bromocriptine** or amantadine (dopamine agonists) benzodiazepine; **dantrolene** (reserved for severe cases)	Stop serotonergics; supportive; **cyproheptadine**, benzodiazepine; paralysis if severe	Stop triggers; O_2, cooling; **dantrolene IV**; intensive care unit (ICU) monitoring	Supportive; benzodiazepine; **physostigmine** (if safe); $NaHCO_3$ if TCA	Supportive; benzodiazepine first-line; vasodilators; avoid pure β-blockers; **phentolamine** if refractory

Distinguishing from sepsis

Sepsis and hospital-acquired infections are important differential diagnoses, as they are the most common causes of fever in the intensive care unit [5, 6, 8].

Sepsis is mediated by cytokine-driven hypothalamic set-point elevation and is usually accompanied by identifiable infectious foci, positive microbiological cultures, and elevated levels of inflammatory biomarkers [6, 8]. In contrast, DIH is characterized by unregulated hyperthermia independent of hypothalamic control and frequently accompanied by rhabdomyolysis, metabolic acidosis, and sterile cultures [1, 3, 4]. Although overlapping clinical features may complicate early recognition, accurate distinction is critical because the management strategies diverge substantially.

Laboratory findings may further complicate the differentiation between DIH and sepsis. Procalcitonin levels may be elevated in DIH as a consequence of systemic inflammation or rhabdomyolysis, thereby limiting their specificity for infection [1, 3, 5, 6]. Similarly, CK is frequently increased across hyperthermic toxidromes, and serial trends may be more informative than isolated measurements [2–4].

Sepsis requires urgent antimicrobial therapy and source control, whereas DIH mandates discontinuation of the offending drug, toxidrome-specific antidotes when available, and aggressive supportive care [1-5, 8].

Distinguishing from heat stroke

Heat stroke is precipitated by environmental exposure or exertion in hot climates and reflects the failure of thermoregulatory capacity, whereas DIH occurs temporally in association with specific pharmacological exposures and results from mechanisms such as dopaminergic blockade, serotonergic excess, impaired sweating, and uncontrolled muscle metabolism [1-5, 27]. Clinical indications that favor DIH include the presence of rigidity in NMS, clonus and hyperreflexia in SS, or anhidrosis in anticholinergic toxicity, which are not typical of heat stroke.

CONCLUSION

DIH is a heterogeneous but clinically significant condition. Promptly recognizing and accurately differentiating DIH from infectious or environmental causes are crucial, as management strategies vary based on the underlying pathophysiology. Effective treatment involves promptly discontinuing the offending agent, targeted antidotal therapy when available, and supportive care. A comprehensive understanding of these syndromes improves diagnostic accuracy and patient outcomes by guiding clinicians toward appropriate and timely intervention.

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AUTHORS' CONTRIBUTIONS

Conceptualization: Dujrath Somboonviboon. Literature review and writing – original draft: Sasathorn Tharapoom. Supervision and writing – review & editing: Dujrath Somboonviboon. Both authors have read and approved the final manuscript.

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