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Drug-Induced Hyperhidrosis and Hypohidrosis

Incidence, Prevention and Management

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Abstract

The human sweating response is subject to the influence of diverse classes of drugs. Some act centrally at the hypothalamus or at spinal thermoregulatory centres, while others act at sympathetic ganglia or at the eccrine-neuroeffector junction. Pharmacological disturbances of sweating have broad clinical implica-

tions. Drugs that induce hyperhidrosis, or sweating in excess of that needed to maintain thermoregulation, can cause patient discomfort and embarrassment, and include cholinesterase inhibitors, selective serotonin reuptake inhibitors, opioids and tricyclic antidepressants. Drugs that induce hypohidrosis, or deficient sweating, can increase the risk of heat exhaustion or heat stroke and include antimuscarinic anticholinergic agents, carbonic anhydrase inhibitors and tricyclic antidepressants. As acetylcholine is the principal neuroeccrine mediator, anhidrosis is one of the clinical hallmarks by which acute anticholinergic toxicity may be recognized. The symptom of dry mouth often accompanies the less apparent symptom of hypohidrosis because the muscarinic M_3 acetylcholine receptor type predominates at both sweat and salivary glands. Management options include dose reduction, drug substitution or discontinuation. When compelling medical indications require continuation of a drug causing hyperhidrosis, the addition of a pharmacological agent to suppress sweating can help to reduce symptoms. When hypohidrotic drugs must be continued, deficient sweating can be managed by avoiding situations of heat stress and cooling the skin with externally applied water. The availability of clinical tests for the assessment of sudomotor dysfunction in neurological disease has enhanced recognition of the complex effects of drugs on sweating. Advances in the understanding of drug-induced anhidrosis have also enlarged the therapeutic repertoire of effective treatments for hyperhidrosis.

Sweating is the principal means of thermoregulatory heat dissipation in response to heat stress in humans. Although numerous drugs can influence the sweating response, very few studies have evaluated the effects of medications specifically on sweat production.

It is important to consider the potential role of sweat-promoting drugs in patients who complain of unpleasant increased sweating, or of sweat-inhibiting drugs in patients who present with hyperthermia or heat-related illness. In patients without symptoms of altered sweating, it is also important to consider the potential effects of drugs when clinical tests of sweat function are undertaken in an autonomic laboratory for the purpose of evaluating autonomic disorders or detecting small fibre neuropathies. Knowledge of the effects of drugs on sweating is also useful in managing the patient with a sweating disorder.

1. Clinical Importance

The clinical importance of sweating falls into two distinct categories, hyperhidrosis and hypohidrosis.

1.1 Hyperhidrosis

Hyperhidrosis refers to sweating in excess of that needed to maintain a constant body temperature. Under normal conditions, when increased metabolic activity or exposure to high ambient temperatures raises the internal temperature of the body beyond the range of physiological tolerance, the sympathetic nervous system responds with a coordinated set of reflexes resulting in vasodilatation, hyperpnoea and generalized sweating.[1-3] In this way, evaporative heat loss lowers body temperature to restore thermal normality and maintain homeostasis.

Sweating in excess of thermoregulatory need or that occurs during routine daily activities usually does not lead to hypothermia but can be quite uncomfortable and socially embarrassing to the patient. In these patients, generalized sweating may occur at a lowered threshold with excessive loss of body fluids resulting in the potential for dehydration or electrolyte depletion. A number of common medications occasionally cause hyperhidrosis (table I).

Table I. Drugs that can cause hyperhidrosis

Drug Class	Common examples	Mechanism
Anticholinesterases	Pyridostigmine	Cholinesterase inhibition
Antidepressants: selective serotonin reuptake inhibitors	Citalopram Duloxetine Escitalopram Fluoxetine Fluvoxamine Mirtazapine Paroxetine Trazodone Venlafaxine	Serotonergic effect on hypothalamus or spinal cord
Antidepressants: tricyclics	Amitriptyline Desipramine Doxepin Imipramine Nortriptyline Protriptyline	Norepinephrine reuptake inhibition with stimulation of peripheral adrenergic receptors
Antiglaucoma agents	Physostigmine Pilocarpine	Physostigmine = cholinesterase inhibition Pilocarpine = muscarinic receptor agonism
Bladder stimulants	Bethanechol	Muscarinic receptor agonism
Opioids	Fentanyl Hydrocodone Methadone Morphine Oxycodone	Histamine release
Sialogogues	Cevimeline Pilocarpine	Muscarinic receptor agonism

A US survey estimated the prevalence of hyperhidrosis in the general population at 2.8% but did not assess whether, or to what degree, drugs might have contributed.[4] Although the incidence of drug-induced hyperhidrosis is unknown, it is probably less than that of essential hyperhidrosis.

There is no evidence that drugs that promote sweating facilitate acclimatization to high ambient temperatures[5] or enhance the thermoregulatory efficiency of sweating during exercise.[6]

1.2 Hypohidrosis

The second category is hypohidrosis, or decreased sweating in response to a proportionate thermal or pharmacological stimulus. Its complete form is termed anhidrosis, or the absence of sweating. Although patients are more likely to notice hyperhidrosis than hypohidrosis, the latter is potentially more hazardous to health, since the inability to generate a thermoregulatory sweating response can seriously challenge one's ability to maintain core temperature in conditions of strenuous physical activity or in hot environments. When evaporative cooling is impaired, heat stress is more likely to lead to hyperthermia, heat exhaustion or heat stroke. Core temperatures in excess of 38–40°C are not only unpleasant for the patient but, if sustained, can cause cellular dysfunction or death. The brain is especially vulnerable to hyperthermia, and summer heat waves have taken the lives of large numbers of people.[7]

Most patients remain unaware of hypohidrosis unless it renders them heat intolerant, in which case they are less likely to notice the absence of sweating than the positive symptoms of flushing, dizziness, exhaustion, dyspnoea and mild confusion resulting from overheating. Any drug that suppresses the patient's ability to acclimatize to a given heat exposure has practical thermoregulatory implications. Since drug questionnaires developed to survey anticholinergic symptoms do not routinely inquire about changes in sweating or heat intolerance, it is possible that studies surveying anticholinergic adverse

effects have underestimated the prevalence of symptomatic impairment in sweating.[8-10]

The epidemiology of heat-related deaths is strongly dependent on weather conditions. The Center for Disease Control and Prevention reported a mean annual incidence in the US of 688 deaths resulting from exposure to extreme heat from 1999 to 2003.[11] Drug-induced anhidrosis as a possible contributing factor has not been systematically studied, although a number of anecdotal reports have correlated heat-related illness to drugs that inhibit sweating.[12-17] An investigation of 1999 heat-related deaths in Cincinnati, Ohio, US, found a positive association with anticholinergic drugs (24% of case subjects compared with 9% of controls), although toxicological screening indicated that most case subjects were noncompliant in taking them.[18] Apart from heat stroke, the incidence and prevalence of hypohidrosis are unknown.

Hypohidrosis is a common, reversible adverse effect of anticholinergic medications in particular (table II).[19] Drugs with anticholinergic properties are commonly used therapeutically for a wide range of clinical disorders including overactive bladder, neuropathic pain, irritable bowel syndrome, reactive airway disease, Parkinson's disease, dizziness, depression, nausea and headache. Epidemiological studies of the prevalence of anticholinergic drug use in the elderly have reported rates of 44–60% among hospital inpatients[8,9] and 9–27% among outpatients.[8-10]

The degree of collateral inhibition of sweating can be noticeable or subtle, depending on the drug's anticholinergic potency, receptor specificity, dose, route of administration, elimination half-life and individual patient variability. The elderly are especially vulnerable, because elimination time of the anticholinergic drug may be increased, or because elderly patients are more likely to be taking other drugs that may interact or compete with one another, and there is a decline in sweating responses with normal aging.[2,20,21] Children may also be at increased risk due to the immature stage of development of their thermoregulatory mechanisms.[2,17]

2. Sites of Drug Action

An understanding of the components of the human thermoregulatory system is helpful towards categorizing the effects of drugs on sweating (figure 1). Drugs can influence sweating at multiple levels of the thermoregulatory pathway, which begins in the medial preoptic (MPO) area of the hypothalamus. The core temperature at which sweating commences, or the thermoregulatory set point, is finely regulated and subject to the influence of numerous centrally acting drugs. There is a circadian rhythm of body temperature in which the threshold for the onset of sweating is lowest around 2 am.[22] The timing of medication ingestion in relation to this circadian rhythm, as well as differences in a drug's bioavailability and pharmacodynamic half-life may result in variable alterations in an individual's sweating response.

The thermoregulatory pathway then descends through the spinal cord intermediolateral column to the sympathetic chain ganglia and to the peripheral sympathetic nerves, which innervate 2–5 million eccrine sweat glands distributed over the body surface. Along this pathway, the most clinically important neuroeccrine mediator is acetylcholine. Drugs with the greatest potential to alter sweat production act at the junction between the sympathetic nerve terminal and the eccrine sweat gland.[23,24]

Each sweat gland receives innervation from several nerve fibres. Confocal fluorescence microscopy has shown that these branch into delicate bands of one or more axons that run longitudinally and then encircle the sweat tubule.[25] A dense complement of capillaries interweaves among the sweat tubules.[25] The main axonal supply to the secretory tubules are unmyelinated sympathetic fibres that release acetylcholine in response to nerve impulses. Acetylcholine binds to cholinergic muscarinic (M_3) receptors in the basolateral membrane of the clear cell. Muscarinic receptors are G protein-coupled and mediate their responses by activating a cascade of intracellular pathways.[25] Because released acetylcholine leads to myoepithelial cell contraction, sweat production is designated as sudomotor activity.

Table II. Drugs that can cause hypohidrosis

Drug class	Common examples	Mechanism
Anticholinergics	Glycopyrrolate Hyoscyamine Scopolamine Propantheline Dicycloverine Belladonna Atropine	Antimuscarinic effect
Antidepressants: tricyclics	Amitriptyline Desipramine Doxepin Imipramine Nortriptyline Protriptyline	Antimuscarinic effect (high for amitriptyline, doxepin; moderate for imipramine and protriptyline; low for nortriptyline)
Antiepileptics	Topiramate Zonisamide Carbamazepine	Topiramate and zonisamide = carbonic anhydrase inhibition Carbamazepine = central anticholinergic effect
Antihistamines	Cyproheptadine Diphenhydramine Promethazine	Antimuscarinic effect
Antihypertensives	Clonidine	Central adrenergic effect
Antipsychotics and antiemetics	Chlorpromazine Clozapine Olanzapine Thioridazine Quetiapine	Antimuscarinic effect
Antivertigo drugs	Meclozine Scopolamine	Antimuscarinic effect
Bladder antispasmodics	Darifenacin Oxybutynin Solifenacin Tolterodine	Antimuscarinic effect
Gastric antisecretory drugs	Propantheline	Antimuscarinic effect
Muscle relaxants	Cyclobenzaprine Tizanidine	Uncertain, possibly inhibition of spinal excitatory interneurons; possibly central and peripheral antimuscarinic effect
Neuromuscular paralytics	Botulinum toxins	Cleavage of SNAP-25 inhibiting pre-synaptic release of acetylcholine
Opioids	Fentanyl Hydrocodone Methadone Morphine Oxycodone	Elevation of hypothalamic set point; calcium channel antagonism

SNAP-25 = synaptosome-associated protein 25 kDa.

The sweat gland itself can also be a target for drug action. The eccrine sweat gland comprises a secretory coil within the lower dermis and an intraepidermal sweat duct, which opens directly onto the skin surface. The secretory coil consists of clear, dark and myoepithelial cell types and produces an isotonic fluid that becomes hypotonic following active NaCl reabsorption in the sweat duct. Energy-dependent active transport of ions mediates sweat secretion. The oxidative metabolism of glucose is the major route of adenosine triphosphate (ATP) formation for secretory activity and takes place primarily in the clear cell.[2] Clear cells and apical duct cells also contain carbonic anhydrase II, an enzyme involved in sweat secretion.[12,17] The density of sweat glands varies from 600–700 glands/cm^2 on

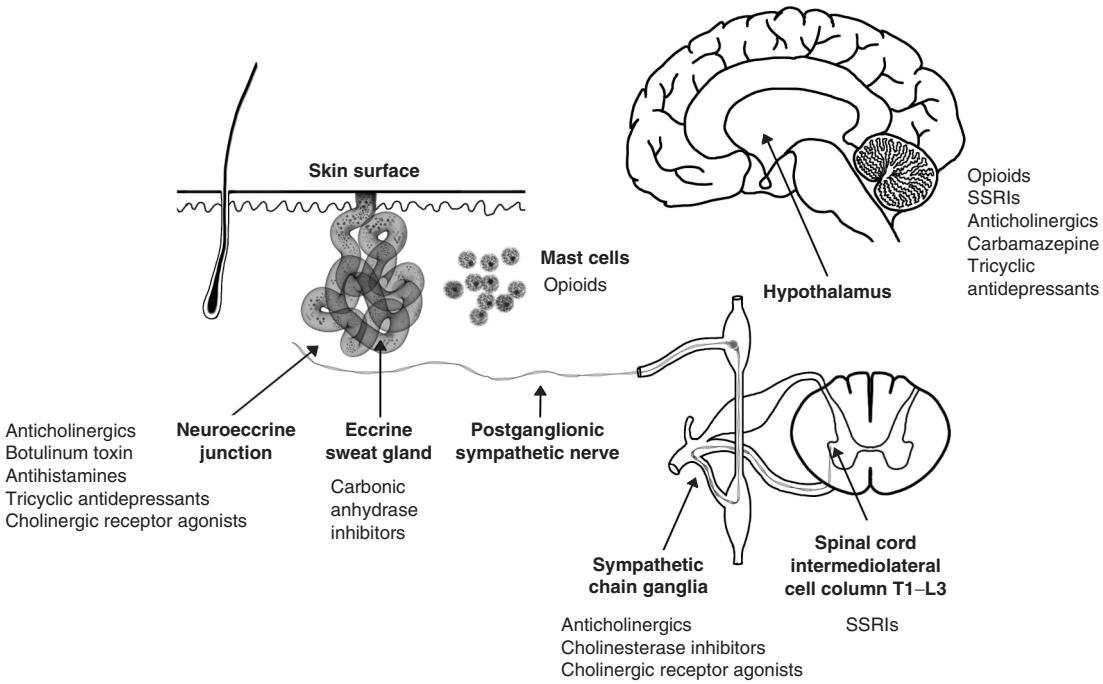

Fig. 1. Schematic representation showing the major sites of action of classes of drugs that commonly influence sweating. The sweating pathway begins in the hypothalamus and extends to the intermediolateral column, from which arise preganglionic sympathetic fibres that leave the spinal cord and synapse within the sympathetic chain ganglia. Postganglionic sympathetic nerves emerge from these ganglia and travel alongside arteries to reach their subdermal targets, the eccrine sweat glands. Drugs can interact with each level of this pathway. **SSRI** = selective serotonin reuptake inhibitor.

the soles of the feet, to 120 glands/cm^2 on the thighs and 60 glands/cm^2 on the back.[26,27] The rate of sweat secretion also varies by site, larger glands having greater rates, ranging from 2 to 20 nL/min/gland.[20] For the entire body, this amounts to 1.8 L/h of sweat to yield the capacity of dissipating 1000 kCal/h, which is approximately the amount of heat energy produced by an athlete vigorously and steadily exercising.[28]

3. Drug-Induced Hyperhidrosis

Since acetylcholine plays a key role at the neuroeccrine junction, drugs that augment cholinergic transmission may increase sweating. Cholinergic agonists are utilized in the treatment of dry mouth, glaucoma, tardive dyskinesia, gastroparesis and Alzheimer's disease. Additionally, drugs that interact with opioid receptors or affect serotonin or norepinephrine (noradrenaline) transmission can also influence sweating.

Classes of drugs that increase sweating may be divided into the following clinical categories.

3.1 Anticholinesterases

The reversible cholinesterase inhibitor pyridostigmine, which is used to treat myasthenia gravis and orthostatic hypotension as well as being used prophylactically to protect against nerve gas poisoning, increases sympathetic ganglion transmission and mildly increases sweating.[29]

3.2 Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) are associated with episodic or nocturnal general hyperhidrosis in about 10% of patients. Among the SSRIs, bupropion has the highest estimated incidence of hyperhidrosis and venlafaxine the next

highest. Paroxetine, fluoxetine, citalopram, sertraline and escitalopram are associated with an intermediate incidence. Trazodone and fluvoxamine appear to have the lowest estimated incidence of hyperhidrosis.[30-32]

A meta-analysis of 4016 subjects taking fluoxetine 20–80 mg daily for major depression found an incidence of increased sweating in 8.6% of patients compared with 3.5% of those taking placebo ($p < 0.001$).[33] The incidence of increased sweating was only 6.5% for those taking 20 mg daily ($p < 0.009$).[33] Of 558 patients who discontinued fluoxetine because of adverse effects, 3.7% did so because of sweating.[33] Similarly, in a safety and tolerability study of duloxetine prescribed for 84 patients with major depression, approximately 10% of patients taking 120 mg daily reported increased sweating, and one of the ten patients who subsequently discontinued the drug during open-label long-term treatment did so because of increased sweating.[34] A similar adverse effect profile is seen for SSRIs prescribed for indications other than depression.[35]

The tricyclic antidepressants occasionally cause hyperhidrosis despite their well recognized anticholinergic effects.[33] Imipramine, nortriptyline and amitriptyline have been implicated.[30] A meta-analysis of adverse effects among 84 randomized, controlled trials of SSRIs and tricyclic antidepressants in the treatment of major depression reported the incidence of increased sweating to be 10% for patients taking SSRIs and 14% for those taking tricyclic antidepressants at any therapeutic dose.[32]

Antidepressant-induced sweating can occur despite the concurrent use of anticholinergic medication,[30] but the mechanism is uncertain. Although paroxetine has been shown to inhibit norepinephrine reuptake, other SSRIs associated with hyperhidrosis have a minimal effect on norepinephrine.[30] The SSRIs may exert a direct effect on hypothalamic serotonin 5-HT receptors involved in thermoregulation.[30] Within the spinal cord, SSRIs can affect perineuronal transmitter levels of serotonin and enhance their action at 5-HT receptors. Studies of serotonin toxicity in humans have found an increase in core temperature and increased sweating indicating a complex action of serotonin on thermoregulatory pathways.[30,36] The complexity of the relationship between SSRIs and sweating is illustrated by the parodoxical observation that SSRIs are sometimes helpful in the treatment of postmenopausal hot flashes.[37]

The presumed mechanism of tricyclic-induced sweating is inhibited reuptake of norepinephrine leading to stimulation of peripheral adrenergic receptors and a generalized diaphoretic response.[30]

3.3 Antiglaucoma Agents

Increased sweating sometimes occurs with ophthalmic use of pilocarpine for the treatment of glaucoma. Heavy generalized sweating has also occasionally been reported as an adverse effect of latanoprost eyedrops used in the treatment of glaucoma.[38,39]

3.4 Bladder Stimulants

Bethanechol is an analogue of acetylcholine resistant to inactivation by cholinesterases. Increased sweating has been described in <1% of patients taking a dosage of 25 mg three times daily.[40]

3.5 Drugs for Dementia

Cholinergic drugs developed for the treatment of Alzheimer's disease are unlikely to affect sweating, since research has focused on developing centrally acting M_1 selective agonists.[19]

3.6 Opioids

Opioid drugs exert a range of effects on thermoregulation.[41] Opioid μ-receptor agonists inhibit warm-sensitive neurons in the MPO, raising the thermoregulatory set point, and they may also act at the spinal and peripheral nerve levels to reduce acetylcholine release at nicotinic and muscarinic synapses, thereby reducing sweat output.[42] Animal models have demonstrated a biphasic opioid response, such that low doses result in hyperthermia and higher doses result in hypothermia.[43] Opioid μ-receptors mediate the hyperthermic response while κ-receptors mediate the hypothermic response.[44]

The hyperhidrosis that commonly occurs during acute and chronic administration of opioids results from stimulation of mast cell degranulation with the release of histamine.[45,46] Excessive sweating can occur in as many as 45% of patients taking methadone.[46] Hyperhidrosis is also a recognized adverse effect of transdermal fentanyl.[47] Sweating in combination with hypertension, nausea and mydriasis characterize acute opioid withdrawal, which engages opioid neurons in the nucleus paragigantocellularis to stimulate activity in the nucleus tractus solitarius and locus coeruleus.[48,49]

The analgesic tramadol, although classified as a nonopioid, has weak opioid μ-receptor agonist properties that may elevate the hypothalamic set point. Tramadol also inhibits reuptake of serotonin and norepinephrine in the spinal cord, which can both increase the sweating response and decrease the intensity of the shivering response.[50]

3.7 Sialogogues

Increased sweating is the most common adverse effect of the sialogogues pilocarpine (typical dosage 20–30 mg daily), bethanechol (75–200 mg daily) and cevimeline (typical dosage 90 mg daily) in the treatment of xerostomia and keratoconjunctivitis sicca.[51-53] Of them, pilocarpine more frequently induces sweating.[6,51]

In a prospective study of oral pilocarpine in the treatment of dry mouth and dry eye symptoms in 256 patients with Sjögren's syndrome, 64% reported increased sweating. Of them, severe sweating occurred in three taking 5 mg and in another three taking 7.5 mg four times a day. The severity of the sweating was such that four patients withdrew from the study.[52] A smaller study of 45 patients receiving oral pilocarpine 5 mg for dry mouth symptoms due to Sjögren's syndrome or following irradiation found a 12% incidence of excessive sweating.[6]

In a heat acclimatization study, the administration of pilocarpine during controlled hyperthermia increased the rate of sweating by 9%, which was not a statistically significant increase over that of the controls.[5]

3.8 Rebound Effects

Withdrawal symptoms following discontinuation of alcohol, benzodiazepines, β-adrenergic receptor antagonists or opiates can include increased sweating.[54] Sweating in combination with paraesthesia, nausea and dizziness has been described as part of a drug withdrawal syndrome in a patient who ceased using transdermal scopolamine following 10 days of uninterrupted use.[55]

4. Drug-Induced Hypohidrosis

As the principle neurotransmitter at the neuroeccrine junction is acetylcholine,[56] the most clinically important sudomotor suppressants are anticholinergic drugs. Many drugs have hidden anticholinergic properties distinct from their therapeutic effects. Additionally, drugs that inhibit carbonic anhydrase, stimulate α_2-adrenergic receptors in the vasomotor centre of the medulla or block the presynaptic release of acetylcholine can interrupt the sweating response.

Conventional wisdom that drugs with weaker anticholinergic effects are safer in elderly patients at risk for cognitive adverse effects[57] would, in theory, seem to hold true also for patients susceptible to drug-induced anhidrosis. Individuals living in a hot climate whose capacity for thermoregulatory sweating is already impaired by neurological disease may be at a greater risk of symptomatic anhidrosis from taking anticholinergic drugs with the potential for developing hyperthermia.

Classes of drugs that decrease sweating may be divided into the following clinical categories.

4.1 Anticholinergics

Acetylcholine is a ubiquitous neurotransmitter present in many organs. Of the five types of muscarinic acetylcholine receptors, the M_3 receptor is the predominant receptor subtype in eccrine sweat glands.[56,58] M_3 receptors are also found in the bladder detrusor muscle, gastrointestinal smooth muscle, salivary glands, ciliary muscle of the eye and the brain. This is why muscarinic anticholinergic drugs that cause hypohidrosis may also cause dry mouth,

urinary retention, constipation, blurred vision or drowsiness, any one of which might be clinically more troublesome than hypohidrosis for the patient. M_1 receptors are found in the cerebral cortex and hippocampus and are important for memory. M_2 receptors are found in the detrusor and the heart. M_4 receptors are found in the neostriatum and M_5 receptors in the substantia nigra. There is also a minor nicotinic component to the eccrine sweat gland secretory response.[56] At the neuroeccrine junction, binding of acetylcholine to M_3 receptors causes an influx of extracellular Ca^{++}, an event required for subsequent efflux of K^+ and Cl^- ions and isotonic fluid egress from the luminal side of the clear cell.[56]

The organ-specific distribution of muscarinic receptor subtypes suggests that a drug's influence on salivation may be predictive of its anhidrotic effect. Tables exist in various publications[59-61] listing the frequency of occurrence of dry mouth for specific drugs. As cholinergic muscarinic M_3 receptors predominate on salivary glands as well as on sweat glands, data on control subjects experiencing dry mouth as an adverse effect may be highly relevant to the likelihood of sweat inhibition. As examples, tizanidine is associated with a 39% and oxybutynin a 60.8% incidence of dry mouth. Bupropion has a 17% incidence of dry mouth at 200 mg/day and 24% at 400 mg/day. Two-thirds of patients receiving anticholinergic drugs for overactive bladder may report symptoms of dry mouth.[62,63] Comparison of depressions in salivary flow and finger sweating have, in fact, shown close correlations in subjects given amitriptyline, desipramine or doxepin.[64] Similarly, drugs that cause increased salivation would be expected to be associated with the potential for hyperhidrosis.

Atropine administered intramuscularly or intravenously at doses sufficient to inhibit sweating does not significantly raise core temperature except under conditions of thermal stress.[24] The levorotatory form is the active isomer with regard to hypohidrosis.[24] The tertiary and quaternary salts of atropine exhibit similar potency.[24]

Scopolamine and hyoscyamine are well known to inhibit sweating.[5,24] Scopolamine is an M_1 receptor antagonist useful in preventing motion sickness, as an antiemetic, in drying the upper airway prior to instrumentation procedures, and as a cycloplegic and mydriatic in the treatment of iridocyclitis. In a heat acclimatization study, an oral dose of scopolamine 16 mg markedly depressed sweating by 43% compared with controls.[5] Its derivatives scopolamine butylbromide and methscopolamine are used as antispasmodic agents. Similarly, hyoscyamine, which decreases oral and gastric sections, gastrointestinal motility and urinary bladder contraction, is used to treat irritable bowel syndrome, peptic ulcer disease, overactive bladder syndrome, excessive sialorrhoea and rhinorrhoea.

The observation that atropine, scopolamine and methylatropine differ greatly in their potency in the central nervous system, yet are similar in their effects on the peripheral nervous system, indicates that their similar hypohidrotic effects occur primarily by antagonism of acetylcholine at the junction between sudomotor nerves and eccrine sweat glands.[24]

Whether an anticholinergic drug will exhibit central as well as peripheral nervous system effects depends not only on the drug and dose but also its lipid solubility.[65] Glycopyrrolate, for example, which is used as a preoperative antimuscarinic during induction of anaesthesia, an enteric antispasmodic agent and in the treatment of essential hyperhidrosis, has limited permeability across lipid membranes including the blood-brain barrier due to its highly polar quaternary ammonium group.

Drug design strategies have sought to develop anticholinergic compounds with greater selectivity for specific receptor types and hence with effects specific for selected organs.[38] Newer anticholinergic drugs for the treatment of overactive bladder syndrome, such as solifenacin and darifenacin, would be expected to have a hypohidrotic effect similar to that of their predecessors since they target the M_3 receptors common to the detrusor muscle and the sweat glands.[62,66] Future development of an anticholinergic drug specifically targeted to M_2 re-

ceptors, which are more abundant than M_3 receptors in the bladder and do not play a role in sweat glands, could conceivably treat overactive bladder syndrome while minimizing the adverse effects of dry mouth and hypohidrosis.[67] No anticholinergic drug has been identified that selectively inhibits just the sweat gland.[68]

4.2 Antidepressants

Among the antidepressants, amitriptyline is the most potent hypohidrotic agent. The muscarinic receptor affinity of amitryptiline *in vitro* is approximately five times that of doxepin and imipramine and eight times that of nortriptyline and desipramine.[69] The affinity amitriptyline has for muscarinic receptors is twice that of fluoxetine and four times that of trazodone.[9]

Amitriptyline is frequently prescribed for the treatment of neuropathic pain. For example, diabetes mellitus is one of the most prevelant chronic diseases in developed nations, affecting 6.9 per 1000 of the population in the US.[70] Of an estimated 2.4 million Americans with symptomatic diabetic peripheral neuropathy,[71] many have received symptomatic treatment with a tricyclic antidepressant. A retrospective review of a US health insurance claims database found that 84% of patients with diabetic peripheral neuropathy had been treated with amitriptyline.[72]

SSRI antidepressants such as citalopram[73] and paroxetine[74] do not have significant anticholinergic properties, but mixed agents such as venlafaxine and trazodone do. Chlorpromazine and similar medications used to control nausea have weak anticholinergic, hence hypohidrotic, effects.

Suppression of axon reflex sweating has been quantitatively documented in humans taking those tricyclic antidepressants and bladder antispasmodics that have the highest anticholinergic properties. These drugs affect both the M_3 receptors on sweat glands and cardiac M_2 receptors and can also impact adrenergic transmission. Moderate doses of amitriptyline as well as the antispasmodics tolterodine and oxybutynin commonly produce diffuse suppression of the sudomotor axon reflex as measured by the quantitative sudomotor axon reflex test (QSART). Amitriptyline is one of the few drugs studied for its effect on autonomic testing.[75] Low and Opfer-Gehrking[75] showed in healthy controls aged 20–40 years that a moderate dosage (75 mg daily) of amitriptyline resulted in greater inhibition of M_3 receptors than of M_2 receptors. QSART volumes were reduced by 47% while taking amitriptyline and recovered to 81% of pre-drug values 48 hours after withdrawal of the drug. The reduction in sweat volume occurred equally at proximal and distal limb sites and did not regress significantly with decreasing blood concentrations of amitriptyline.[75]

4.3 Antiepileptics

Carbonic anhydrase inhibitors such as zonisamide and topiramate can interfere with sweat production, probably at the level of the secretory coil clear cell or apex of ductal cells.[12,17] Impairment of pilocarpine-induced sweating resulting in heat intolerance and oligohidrosis has been reported in children taking topiramate.[12-14] A study of 13 children receiving topiramate reported reduced sweating activity in response to pilocarpine iontophoresis in nine of them, amongst whom only three had recognized symptoms of heat intolerance.[17] The risk of hypohidrosis in paediatric patients taking zonisamide has been estimated at 10-fold higher than that of adults.[14,76]

4.4 Antihistamines

Antihistamines exhibit binding affinity not only for histamine H_1 receptors but also for muscarinic cholinergic receptors. Functional bioassays have shown that cyproheptadine, promethazine and diphenhydramine exhibit the greatest M_3 receptor functional bioactivity, whereas loratadine, chlorpheniramine and hydroxyzine exhibited intermediate bioactivity, and cetirizine and fexofenadine exhibited no discernible bioactivity.[77] Meclozine has a relatively low affinity for muscarinic receptors.[78]

4.5 Antihypertensives

Whereas muscarinic acetylcholine receptor activation on sweat glands provides the major stimulus to sweating, β-adrenergic-mediated sweating also occurs.[79] The influence of β-adrenergic receptor antagonists on sweating is approximately 20% that of cholinergic receptor-mediated activation.[28,79] Peripheral α-adrenergic factors contribute a negligible component to sweating.[80] An interesting exception to this rule was described in a small study of patients with complex regional pain syndrome, in whom either increased α-adrenergic receptor density or sensitivity on presynaptic postganglionic sudomotor fibres augmented sweating.[81]

The central sympathetic inhibitory action of the α_2-adrenergic agonist clonidine at various doses has proved effective in ameliorating hyperhidrosis associated with episodes of sympathetic hyperexcitabilty.[23,82,83]

4.6 Antipsychotics and Antiemetics

Among the antipsychotic and antiemetic agents, clozapine has the greatest muscarinic receptor-binding affinity *in vitro*, being similar to that of amitriptyline.[84] Olanzapine and quetiapine also have high muscarinic receptor affinities, whereas thioridazine and chlorpromazine have intermediate affinity, and aripiprazole, risperidone, quetiapine and ziprasidone have very little affinity.[85]

4.7 Botulinum Toxins

Intradermal injection of botulinum toxins, which block the release of acetylcholine at the neuromuscular junction, similarly blocks the neuroeccrine junction, effectively inhibiting local sweating.[86] The anhidrotic effect of botulinum toxin A is dose-dependent and appears to be more sustained than that resulting from botulinum toxin B.[87]

4.8 Ganglionic Antagonists

Sympathetic ganglion activity influences the sensitivity of sweat glands to pharmacological agents. Accordingly, pharmacological studies have shown that the secretary response of sweat glands to intradermal injection of the cholinergic receptor agonist carbachol, which stimulates sweating locally, can be antagonized by sympathetic ganglion blockade by the muscarinic receptor antagonist atropine but not by the nicotinic receptor antagonists hexamethonium or tubocurarine.[88] These findings suggest that medications that affect muscarinic ganglionic transmission may also influence peripheral sweating responses. Some sympathetic ganglion antagonists that inhibit sweating include atropine, belladonna alkaloids and trimethaphan.[89]

4.9 Intoxication

Anticholinergic drugs in therapeutic and overdose ranges have been associated with hyperthermia and heat stroke in the elderly during hot summer conditions.[90-95] In these cases, hyperthermia develops as the result of a combination of factors including anhidrosis resulting from peripheral muscarinic receptor blockade, heat production by agitation with increased muscle activity, and impaired recognition of the need to seek cooling, due to altered mental status.[91]

Total anhidrosis, or complete suppression of sweat gland function, generally does not occur with therapeutic doses of systemically administered anticholinergic drugs but is more likely with overdose.[68] The cardinal signs and symptoms of poisoning with antimuscarinics consist of mydriasis, decreased secretions (sweating, salivation, lacrimation, bronchial fluid), ileus, urinary retention, hyperthermia, tachycardia and altered mental status. The skin may appear dry and flushed.[87] Classes of drugs most commonly associated with antimuscarinic poisoning include antihistamines, tricyclic antidepressants, antipsychotics and, less frequently, scopolamine,[96] cyclobenzaprine and carbamazepine.[15] Anticholinergic intoxication has also been reported with the use of the antiparkinsonian medications trihexyphenidyl and benzatropine, which are used less frequently in the treatment of Parkinson's disease now that dopamine receptor agonists and other classes of drugs have entered into common use.[15]

In a study of 213 patients presenting for emergency care with acute antimuscarinic poisoning, 73 were due to tricyclic antidepressants, of which amitriptyline was the most common agent; 66 cases were due to antihistamines, most commonly diphenhydramine; 25 to antipsychotics; 10 to carbamazepine; 5 to *Datura* herbs (described below); 4 to atropine; 2 to cyclobenzaprine and 1 to scopolamine.[15] In addition to the cardinal signs listed above, hallucinations the patients experienced tended to be visual, and they often demonstrated 'picking' behaviour, probing their intravenous lines, restraints and bedclothes with their fingers. Physostigmine was administered to 49 patients with improvement in mental status. Among the 213 patients, 75% had decreased oral or axillary secretions and 5% had temperatures >38°C.[15]

Antimuscarinic intoxication caused by plants of the *Datura* genus has been recognized since antiquity. Examples include jimson weed, thorn apple tea and moonflower seeds. *Datura* is hallucinogenic at toxic doses. Ten of its seeds can yield as much as 1 mg of atropine.[97] Signs and symptoms of *Datura* intoxication include confusion, tachycardia, dilated pupils and anhidrotic, flushed, hot skin.[98] Closely related is the South American burundanga, which contains scopolamine.[99]

5. Measurement of Hypohidrosis

The advent of routine clinical tests of sudomotor function has further enhanced interest in the influence of drugs on sweating. The ability to localize and quantify the hypohidrosis that accompanies neurological disorders has made it possible to predict increased susceptibility to heat stress, which has implications for identifying patients who may be less able to tolerate drugs that further inhibit sweating.[100] Reliable interpretation of these tests in the evaluation of neurological disorders also requires familiarity with the potential effects of concurrent medications on sudomotor responses.[101]

The laboratory evaluation of autonomic dysfunction and small fibre neuropathies has increasingly relied on non-invasive tests of sudomotor function. Colorimetric, evaporimetric and imprint techniques are in common use in clinical autonomic laboratories. The thermoregulatory sweating test and the starch iodine test, for example, combine a colorimetric indicator power with a controlled heat stimulus to assess anatomical patterns of sweating. The silastic imprint test measures the number and size of sweat beads produced over a selected area of skin. The QSART specifically evaluates postganglionic sympathetic sudomotor distal nerve function at standardized limb sites in response to iontophoresis of acetylcholine.[27,56,101-103] Because the sweating responses these tests measure can be strongly influenced by medications, the validity of these tests in assessing the severity of autonomic dysfunction or reaching a diagnosis of small fibre neuropathy can depend heavily on the presence of potentially confounding drugs. It may be difficult to ascertain, for example, whether the patient shown to have a reduced sweating response has a small fibre neuropathy impairing sudomotor fibres, or drug-induced hypohidrosis.[104] For this reason, anticholinergic medications are routinely withheld, if it is safe to do so, for several days prior to testing.[75]

Whereas application of these tests has focused primarily on autonomic dysfunction, they also provide a means of assessing how specific drugs alter the sweating response. The thermoregulatory sweating test[86] and QSART[105] have proven, for example, to be useful methods for monitoring the chemodenervative effect of botulinum toxin over time by assessing its parallel anhidrotic effect.

6. Management of Hyperhidrosis

Drug-induced hyperhidrosis may not be foreseeable in most cases, but it can be managed. Treatment options for drug-induced hyperhidrosis are outlined in figure 2. The first question to ask is whether the hyperhidrosis is drug-induced. Did the onset of hyperhidrosis coincide with the initial use of the drug or an escalation in its dosage? Is the particular drug known to increase sweating? Does the patient have a pre-existing history of essential hyperhidrosis or a separate medical reason for increased sweating?

Once a drug relationship is suspected, clinical options include a therapeutic dose reduction, drug

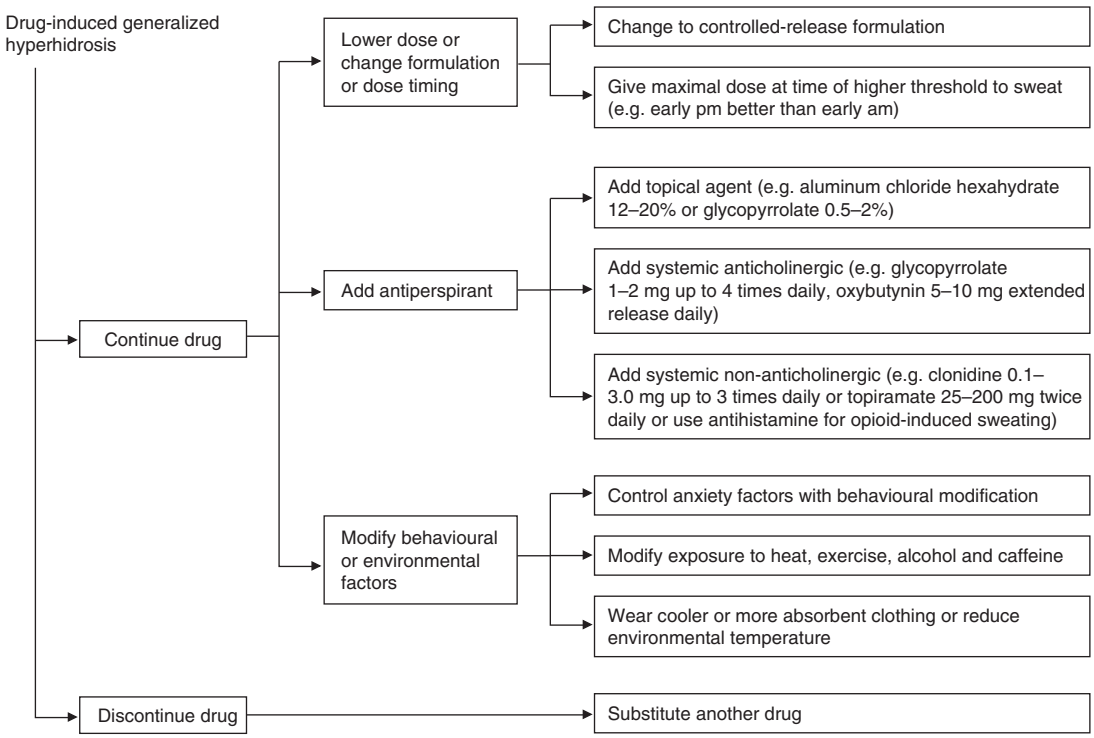

Fig. 2. Algorithm for managing drug-induced hyperhidrosis.

substitution or discontinuation. A drug substitution might involve switching to another drug within the same therapeutic class that has a lesser incidence of hyperhidrosis, or it might involve switching to an alternative class. If the hyperhidrosis is severe and outweighs the drug's therapeutic benefit, the patient may prefer to discontinue the drug.

If these strategies do not resolve the hyperhidrosis, or if the patient's medical condition does not allow a change in medication, then the addition of a pharmacological agent to suppress sweating may be preferable. Knowledge of the pharmacological action of drugs on the normal sweating response has proven useful toward developing treatments for disturbances of not only drug-induced sweating but also essential and neurological hyperhidrosis.[23,82,83,106-112]

Isolated reports have described successful management of opioid-induced sweating by rotating to a different opioid, switching to transdermal fentanyl, or by adding an antihistamine.[113] Scopolamine has been used to treat opioid-induced sweating.[114] Biperiden 2–4 mg daily has been reported as helpful in reducing the excessive sweating associated with methadone maintenance treatment for opioid dependence.[115]

Terazosin prescribed at a dose of 2 mg at bedtime resulted in complete resolution of hyperhidrosis caused by venlafaxine in one patient and sertraline in another.[116] The 5-HT_2 and 5-HT_3 receptor antagonist mirtazapine was reported to be effective at 15 mg daily in reducing hyperhidrosis in one patient with bipolar disorder whose excessive sweating whilst taking escitalopram 30 mg/day had required several changes of clothing daily.[117] Benzatropine, cyproheptadine and clonidine have been reported to decrease hyperhidrosis associated with SSRI use in anecdotal cases.[30,116]

The choice of a pharmacological agent for treating drug-induced hyperhidrosis takes into account the severity of the sweating and the potential risks and benefits of the treatment. Important variables

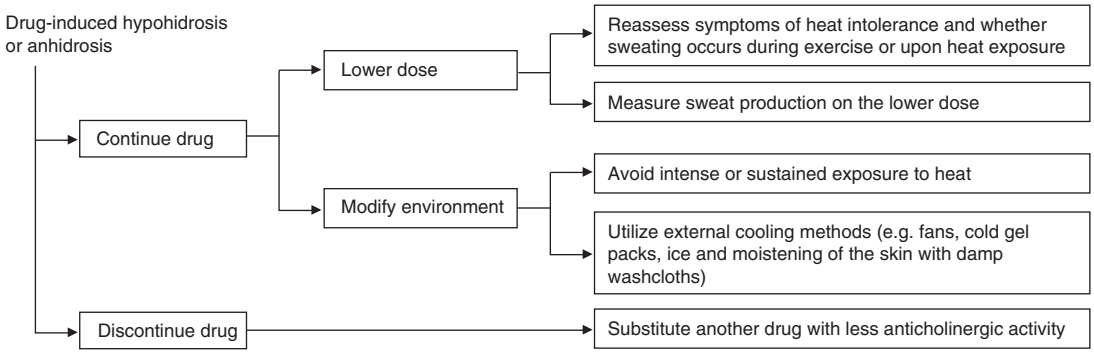

Fig. 3. Algorithm for managing drug-induced hypohidrosis.

include the body region involved, the frequency and volume of sweating, and the degree to which the sweating impairs the patient's daily functioning and sense of well-being. Also to be considered are the efficacy of the drug, ease of use or application, potential adverse effects such as dry mouth or constipation, and medical comorbidities such as glaucoma or dementia that may limit the patient's tolerance of anticholinergic medication.

Topical antiperspirants such as 12–20% aluminum chloride hexahydrate in an alcohol or water base can be effective for mild hyperhidrosis but may be difficult to apply to all the skin areas affected.[82] Oral anticholinergic drugs are often helpful in ameliorating drug-induced hyperhidrosis. Glycopyrrolate, 1–2 mg one to four times daily, is preferable to other anticholinergic drugs when it is desirable to minimize the potential adverse effects of sedation or confusion, since very little of the drug crosses the blood-brain barrier.[23,82] Additional oral anticholinergic drugs shown to be helpful in reducing hyperhidrosis, regardless of its cause, include oxybutynin 2.5 mg three times daily,[108] belladonna alkaloids 0.2 mg twice daily,[82] propantheline 15 mg three times daily,[109] thioridazine 10–25 mg at night[110] or scopolamine administered via 1.5-mg patch.[111] Anticholinergics such as glycopyrrolate, while not readily available in topical form, can be compounded in 0.5–2% concentrations in a noncomedogenic base for topical use.[82]

7. Management of Hypohidrosis

Drug-induced hypohidrosis also may not be foreseeable in most cases, but it should be suspected when patients taking anticholinergic agents or other drugs known to suppress the sweating response report symptoms of heat intolerance. Treatment options for drug-induced hypohidrosis are outlined in figure 3.

The first question to ask is whether a causal relationship exists linking the drug to the patient's heat intolerance. A temporal association may be difficult to establish, since hypohidrosis can go unnoticed in the absence of heat stress. Anhidrosis may remain inapparent through the winter months only to become symptomatic once the patient exercises and the heat of spring and summer arrive. Also to be considered are whether the particular drug is known to inhibit sweating and if there is a separate medical or neurological cause underlying the patient's hypohidrosis.

Numerous neurological and systemic illnesses can impair sweating, and tests of sudomotor function can be helpful towards determining the aetiology.[23] One of the most common causes of hypohidrosis is peripheral neuropathy, in which the degeneration of peripheral nerves can involve sudomotor fibres, either in combination with sensory and motor deficits[87] or selectively.[100] Patients with age-related decline in autonomic responses, existing anhidrosis due to neurological disease, Ross syndrome, Sjögren's syndrome, hypothyroidism or chronic idiopathic anhidrosis may be at increased

risk of the additional anhidrotic effect of drugs that inhibit sweating.[65]

Once a relationship to a drug is suspected, clinical options include a therapeutic dose reduction, drug substitution or discontinuation. Switching within a drug class to a drug with less potent anticholinergic properties or to a different drug class may restore the patient's ability to sweat.

Prevention of hyperthermia in patients who lack the capacity to sweat may require avoidance of prolonged direct sunlight or sustained vigorous exercise in hot climates. Many patients who become uncomfortably warm can manage mild overheating by applying a moist washcloth to skin surfaces exposed to the air as a substitute for thermoregulatory sweating. A portable fan is useful to enhance the evaporation of applied moisture.

Treatment of acute hyperthermia consists of rapid external cooling and cardiopulmonary support. Sedation is sometimes required to calm the agitated patient. Acetylcholinesterase inhibitors such as physostigmine are seldom needed and, if used, should be administered cautiously because of the potential for serious cardiac effects.[87,96]

8. Conclusion

Numerous common drugs can influence the pharmacologically complex system of thermoregulatory sweating in humans. Patients are more likely to complain of drug-induced hyperhidrosis, yet are more likely to experience adverse health effects from drug-induced hypohidrosis. Physicians who prescribe such drugs should, therefore, be familiar with both categories of drug effects. Understanding the neurological mechanisms underlying normal sweating and the ways in which drugs can stimulate or inhibit sweating, moreover, are proving increasingly helpful in the care of patients who perspire too much or too little.

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