Managing psychotropic-induced hyperhidrosis

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Ms. K, age 32, presents to the psychiatric clinic for a routine follow-up. Her history includes agoraphobia, attention-deficit/hyperactivity disorder, and schizoaffective disorder. Ms. K's current medications are oral hydroxyzine 50 mg 4 times daily as needed for anxiety and paliperidone palmitate 234 mg IM monthly. Since her last follow-up, she has been switched from oral sertraline 150 mg/d to oral paroxetine 20 mg/d. Ms. K reports having constipation (which improves by taking oral docusate 100 mg twice daily) and generalized hyperhidrosis. She wants to alleviate the hyperhidrosis without changing her paroxetine because that medication improved her symptoms.

Hyperhidrosis—excessive sweating not needed to maintain a normal body temperature—is an uncommon and uncomfortable adverse effect of many medications, including psychotropics.[1] This long-term adverse effect typically is not dose-related and does not remit with continued therapy.[2]

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Table 1[1-3] (***page 34***) lists psychotropic medications associated with hyperhidrosis as well as postulated mechanisms.

The incidence of medication-induced hyperhidrosis is unknown, but for psychotropic medications it is estimated to be 5% to 20%.[3] Patients may not report hyperhidrosis due to embarrassment; in clinical trials, reporting measures may be inconsistent and, in some cases, misleading. For example, it is possible hyperhidrosis that appears to be associated with buprenorphine is actually a symptom of the withdrawal syndrome rather than a direct effect of the medication. Also, some medications, including certain psychotropics (eg, paroxetine[4] and topiramate[3]) may cause either hyperhidrosis or hypohidrosis

Practice Points

- **If the inciting medication cannot be altered, medication-induced generalized hyperhidrosis should be treated with systemic oral therapy.** Topical agents should be considered only if the patient's hyperhidrosis is localized.
- **Oral anticholinergic medications** are considered first-line therapy for generalized hyperhidrosis, but in many cases **are inappropriate for psychotropic-induced hyperhidrosis** because they can increase the number and severity of adverse effects.
- When selecting treatment for hyperhidrosis, **consider the patient's chronic medical and psychiatric comorbidities, concurrent medications, and medication burden.**

Identifying the most appropriate treatment depends on patient tolerability, comorbidities, and the potential for adverse effects

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Table 1

Psychotropic medications associated with hyperhidrosis

Class	Medication	Proposed mechanism for hyperhidrosis
Agents for attention-deficit/hyperactivity disorder		
Stimulants	Dextroamphetamine/amphetamine, lisdexamfetamine	Increased serotonergic activity
Alpha-2 agonists	Guanfacine	
Agents for substance use disorders		
Alcohol use disorder	Acamprosate	
Opioid use disorder	Buprenorphine, buprenorphine/naloxone, methadone	
Agents for dementia	Donepezil, rivastigmine	Increased cholinergic activity
Agents for insomnia		
Benzodiazepines	Estazolam, flurazepam, temazepam	
Nonbenzodiazepine benzodiazepine receptor agonists	Eszopiclone, zaleplon, zolpidem	
Antidepressants		
MAOIs	Phenelzine, selegiline transdermal, tranylcypromine	Increased norepinephrinergic activity, increased serotonergic activity
TCAs	Amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline	Increased norepinephrinergic activity
SSRIs	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine,[a] sertraline	Increased serotonergic activity in hypothalamus
SNRIs	Desvenlafaxine, duloxetine, levomilnacipran, venlafaxine	Increased norepinephrinergic activity, increased serotonergic activity in hypothalamus
Other	Bupropion, vilazodone	Increased norepinephrinergic activity, increased serotonergic activity
Antipsychotics		
First-generation	Haloperidol, perphenazine, pimozide, thiothixene	Altered dopaminergic signaling
Second-generation	Aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone	Altered dopaminergic signaling
Other common CNS medications	Carbamazepine, divalproex sodium, modafinil, tiagabine, topiramate,[a] ropinirole, zonisamide[a]	

[a]Warning for hypohidrosis/oligohidrosis

MAOIs: monoamine oxidase inhibitors; SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants

Source: Adapted from references 1-3

(decreased sweating). Few medications carry labeled warnings for hypohidrosis; the condition generally is not of clinical concern unless patients experience heat intolerance or hyperthermia.[3]

Psychotropic-induced hyperhidrosis is likely an idiopathic effect. There are few known predisposing factors, but some medications carry a greater risk than others. In a meta-analysis, Beyer et al[2] found certain selective serotonin reuptake inhibitors (SSRIs), such as sertraline and paroxetine, had a higher risk of causing hyperhidrosis. Fluvoxamine, bupropion, and vortioxetine had the lowest risk. The class risk for SSRIs was comparable to that of serotonin-norepinephrine reuptake inhibitors (SNRIs), which all carried a comparable risk. In this analysis, neither indication nor dose were reliable

indicators of risk of causing hyperhidrosis. However, the study found that for both SSRIs and SNRIs, increased affinity for the dopamine transporter was correlated with an increased risk of hyperhidrosis.[2]

Treatment

Treatment of hyperhidrosis depends on its cause and presentation.[5] Hyperhidrosis may be categorized as primary (idiopathic) or secondary (also termed diaphoresis), and either focal or generalized.[6] Many treatment recommendations focus on primary or focal hyperhidrosis and prioritize topical therapies.[5] Because medication-induced hyperhidrosis most commonly presents as generalized[3] and thus affects a large body surface area, the use of topical therapies is precluded. Topical therapy for psychotropic-induced hyperhidrosis should be pursued only if the patient's sweating is localized.

Treating medication-induced hyperhidrosis becomes more complicated if it is not possible to alter the inciting medication (ie, because the medication is effective or the patient is resistant to change). In such scenarios, discontinuing the medication and initiating an alternative therapy may not be effective or feasible.[2] For generalized presentations of medication-induced hyperhidrosis, if the inciting medication cannot be altered, initiating an oral systemic therapy is the preferred treatment.[3,5]

Oral anticholinergic medications (eg, benztropine, glycopyrrolate, and oxybutynin),[4-6] act directly on muscarinic receptors within the eccrine sweat glands to decrease or stop sweating. They are considered first-line for generalized hyperhidrosis but may be inappropriate for psychotropic-induced hyperhidrosis because many psychotropics (eg, tricyclic antidepressants, paroxetine, olanzapine, quetiapine, and clozapine) have anticholinergic properties. Adding an anticholinergic medication to these patients' regimens may increase the adverse effect burden and worsen cognitive deficits. Additionally, approximately one-third of patients discontinue anticholinergic medications due to tolerability issues (eg, dry mouth).

However, anticholinergic medications may still have a role in treating psychotropic-induced hyperhidrosis. Benztropine[3,7,8] and cyproheptadine[2,3,9] may be effective options, though their role in treating psychotropic-induced hyperhidrosis should be limited and reserved for patients who have another compelling indication for these medications (eg, extrapyramidal symptoms) or when other treatment options are ineffective or intolerable.

Avoiding anticholinergic medications can also be justified based on the proposed mechanism of psychotropic-induced hyperhidrosis as an extension of the medication's toxic effects. Conceptualizing psychotropic-induced hyperhidrosis as similar to the diaphoresis and hyperthermia observed in neuroleptic malignant syndrome and serotonin syndrome offers a clearer target for treatment. Though the specifics of the mechanisms remain unknown,[2] many medications that cause hyperhidrosis do so by increasing sweat gland secretions, either directly by increasing cholinergic activity or indirectly via increased sympathetic transmission.

Considering this pathophysiology, another target for psychotropic-induced hyperhidrosis may be altered and/or excessive catecholamine activity. The use of medications such as clonidine,[3-6] propranolol,[4-6] or terazosin[2,3,10] should be considered given their beneficial effects on the activation of the sympathetic nervous system, although clonidine also possesses anticholinergic activity. The calcium channel blocker diltiazem can improve hyperhidrosis symptoms by interfering with the calcium signaling necessary for normal sweat gland function.[4,5] Comorbid cardiovascular diseases and tachycardia, an adverse effect of many psychotropic medications, may also be managed with these treatment options. Some research suggests using benzodiazepines to treat psychotropic-induced hyperhidrosis.[4-6] As is the case

Clinical Point

Topical therapy for psychotropic-induced hyperhidrosis should be pursued only if the patient's sweating is localized

Clinical Point

For generalized hyperhidrosis, if the inciting medication cannot be altered, initiating an oral systemic therapy is preferred

Table 2

Oral medications for treating psychotropic-induced hyperhidrosis

Medication	Common initial dosing	Mechanism	Drug interactions
Benztropine	0.5 mg twice daily scheduled or as needed	Muscarinic-1 antagonist. Direct inhibition of sweat gland secretions	Avoid combining with other anticholinergic medications due to increased risk of adverse effects
Clonidine	0.1 mg twice daily	Alpha-2 agonist. Reduction of sympathetic activity	Use with caution when combining with other CNS depressants. CYP1A2/2D6/3A4/5 substrate. Hypotensive effect can be exacerbated with concomitant use of inhibitors of CYP1A2/2D6/3A4/5
Cyproheptadine	Not well-defined; some case reports suggest 4 mg once or twice daily	Muscarinic-1 antagonist. Direct inhibition of sweat gland secretions	Avoid combining with other anticholinergic medications due to increased risk of adverse effects. Use with caution when combining with other CNS depressants
Diltiazem	30 to 60 mg 4 times daily	Calcium channel blocker. Interferes with calcium signaling needed for sweat gland functioning	CYP3A4 substrate and inhibitor. Hypotensive and bradycardic effect can be exacerbated with concomitant use of CYP3A4 inhibitors
Glycopyrrolate	1 to 4 mg twice daily	Muscarinic-1 antagonist. Direct inhibition of sweat gland secretions	Avoid combining with other anticholinergic medications due to increased risk of adverse effects
Oxybutynin	2.5 to 5 mg twice daily	Muscarinic-1 antagonist. Direct inhibition of sweat gland secretions	Avoid combining with other anticholinergic medications due to increased risk of adverse effects. Minor CYP3A4 substrate. Effects may be enhanced with concurrent use of other CYP3A4 inhibitors or substrates
Propranolol	5 to 20 mg 4 times daily scheduled or as needed	Nonselective beta-adrenergic antagonist. Reduction of sympathetic activity	CYP1A2/2C19/2D6 substrate. Hypotensive effect and bradycardia can be exacerbated with concomitant use of inhibitors of CYP1A2/2C19/2D6
Terazosin	1 to 2 mg daily	Alpha-1 antagonist. Reduction of sympathetic activity	Use with caution when combining with other CNS depressants or vasodilatory agents

[a]Evidence supporting use only available for immediate-release oral formulations

AV: atrioventricular; COPD: chronic obstructive pulmonary disease; CYP: cytochrome P450; EPS: extrapyramidal symptoms; ER: extended-release; GI: gastrointestinal; SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis

Source: Adapted from references 3,4,6-8,10

	Contraindications/ warnings	Common adverse effects	Comments
	May cause anhidrosis and/or hyperthermia; use with caution in glaucoma, obstructive GI disease, urinary stricture, prostatic hyperplasia	Dry mouth, blurred vision, tachycardia, constipation, urinary retention, impaired memory	May be beneficial in patients with EPS
	Abrupt discontinuation may cause withdrawal syndrome and rebound hypertension. Dosing adjustment recommended in severe renal impairment and dialysis	Dry mouth, sedation, constipation, blurred vision, urinary retention, orthostatic hypotension, bradycardia, dizziness, depression	ER and transdermal formulations available[a]
	Use with caution in cardiovascular disease, increased intraocular pressure, respiratory disease, thyroid dysfunction, and older adults	Sedation, weight gain, increased appetite, dry mouth, blurred vision, tachycardia, constipation, urinary retention, impaired memory	
	Avoid use in comorbid heart failure, as well as comorbid AV block and bradyarrhythmias. May cause AV block, bradycardia, and/or SJS/TEN. Use with caution in hepatic and renal impairment and with beta-blockers or digoxin	Peripheral edema, tachycardia, hypotension, headache, nausea, fatigue, rash	ER formulation available[a]
	May cause anhidrosis and/or hyperthermia. Use with caution in glaucoma, obstructive GI disease, or uropathy. Dosing adjustment required in renal impairment	Dry mouth, blurred vision, tachycardia, constipation, urinary retention, impaired memory, flushing, headache	Less centrally acting so lower adverse effect burden
	May cause anhidrosis and/or hyperthermia. Use with caution in glaucoma, obstructive GI disease, or uropathy	Dry mouth, blurred vision, tachycardia, constipation, urinary retention, impaired memory, dizziness	ER and transdermal formulations available[a]
	Avoid use in comorbid respiratory disease (ie, asthma/COPD), AV block, and heart failure. Use with caution in diabetes as it may mask most symptoms of hypoglycemia. May cause or worsen bradycardia. Use with caution in hepatic and renal impairment. Abrupt discontinuation can cause angina pectoris, arrhythmias, and acute myocardial infarction (dose-dependent)	Dizziness, drowsiness, fatigue, hypotension, bradycardia, cold extremities, Raynaud's phenomenon, erectile dysfunction	If situational: administer 60 min prior to known stressor to mitigate sweating. ER formulation available[a]
	Avoid use in comorbid heart failure. May cause orthostasis and/or syncope	Dizziness, drowsiness, orthostatic hypotension, vivid dreams, muscular weakness, tachycardia, peripheral edema, priapism, hypotension, dry mouth	Evaluated specifically for antidepressant-induced hyperhidrosis, but sample size was small (N = 64)

Clinical Point

Oral anticholinergics may not be appropriate for psychotropic-induced hyperhidrosis

Clinical Point

Clonidine, propranolol, or terazosin could be considered due to their effects on the sympathetic nervous system

Related Resources

- International Hyperhidrosis Society. Hyperhidrosis treatment overview. www.sweathelp.org/hyperhidrosis-treatments/treatment-overview.html

Drug Brand Names

Acamprosate • Campral
Aripiprazole • Abilify
Buprenorphine • Sublocade
Buprenorphine/naloxone • Zubsolv
Bupropion • Wellbutrin
Carbamazepine • Tegretol
Citalopram • Celexa
Clomipramine • Anafranil
Clonidine • Catapres
Clozapine • Clozaril
Desipramine • Norpramin
Desvenlafaxine • Pristiq
Dextroamphetamine/amphetamine • Adderall
Diltiazem • Cardizem
Divalproex • Depakote
Donepezil • Aricept
Doxepin • Silenor
Duloxetine • Cymbalta
Escitalopram • Lexapro
Eszopiclone • Lunesta
Fluoxetine • Prozac
Fluvoxamine • Luvox
Guanfacine • Intuniv
Glycopyrrolate • Cuvposa
Hydroxyzine • Vistaril
Imipramine • Tofranil
Levomilnacipran • Fetzima
Lisdexamfetamine • Vyvanse
Methadone • Dolophine, Methadose
Modafinil • Provigil
Nortriptyline • Pamelor
Olanzapine • Zyprexa
Paliperidone palmitate • Invega Sustenna
Paroxetine • Paxil
Phenelzine • Nardil
Pimozide • Orap
Protriptyline • Vivactil
Quetiapine • Seroquel
Rivastigmine • Exelon
Selegiline transdermal • Emsam
Sertraline • Zoloft
Temazepam • Restoril
Thiothixene • Navane
Tiagabine • Gabitril
Topiramate • Topamax
Tranylcypromine • Parnate
Vilazodone • Viibryd
Vortioxetine • Trintellix
Zaleplon • Sonata
Ziprasidone • Geodon
Zolpidem • Ambien
Zonisamide • Zonegran

for anticholinergic medications, the use of benzodiazepines would require another compelling indication for long-term use.

Table 2 (***page 36***)[3,4,6-8,10] provides recommended dosing and caveats for the use of these medications and other potentially appropriate medications.

Research of investigational treatments for generalized hyperhidrosis is ongoing. It is possible some of these medications may have a future role in the treatment of psychotropic-induced hyperhidrosis, with improved efficacy and better tolerability.

CASE CONTINUED

Because Ms. K's medication-induced hyperhidrosis is generalized and therefore ineligible for topical therapies, and because the inciting medication (paroxetine) cannot be switched to an alternative, the treatment team considers adding an oral medication. Treatment with an anticholinergic medication, such as benztropine, is not preferred due to the anticholinergic activity associated with paroxetine and Ms. K's history of constipation. After discussing other oral treatment options with Ms. K, the team ultimately decides to initiate propranolol at a low dose (5 mg twice daily) to minimize the chances of an interaction with paroxetine, and titrate based on efficacy and tolerability.

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