

Oral Medications



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KEYWORDS

- Systemic therapy • Anticholinergic • β -blocker • Glycopyrrolate • Oxybutynin • Propanolol
- Clonidine • Hyperhidrosis

KEY POINTS

- Localized treatments for hyperhidrosis are considered first-line therapy.
- Systemic therapy can be used as monotherapy or in combination with focally targeted treatments.
- Anticholinergic drugs are the most commonly used systemic therapy for hyperhidrosis.
- Side effect profiles of anticholinergic drugs vary based on their lipid solubility.
- β -Blockers can be useful for hyperhidrosis associated with performance tasks.
- There is a paucity of published literature on systemic treatment of hyperhidrosis.

INTRODUCTION

Hyperhidrosis (HH) is a disabling condition that impacts quality of life (QOL) and can cause significant emotional stress. Primary HH presents with focal areas of excess sweating, such as the axillae, palms, soles, scalp, face, and groin. Although some patients have only one focal area of excessive sweating, it is common for patients to have more than one body site producing excessive amounts of sweat.¹ In addition, patients may present with more generalized forms of HH, which are usually secondary in nature. In these cases, treatment or removal of the offending cause is beneficial, but may not always be feasible. Compensatory HH following sympathectomy varies significantly but occurs in 50% to 80% of patients who undergo sympathectomy.² It can affect very large areas, such as the chest, abdomen, and back, and is irreversible. Systemic therapy can be beneficial in all of these patients.

None of these agents have a Food and Drug Administration–approved indication to treat HH and there is a paucity of literature or studies on the use of these medications for the treatment of HH.

TREATMENT INDICATIONS

In general, treatment of primary HH should be as specific and focal or localized as possible to ensure good response and minimize side effects and interactions with other medications. Topical therapies are usually first-line treatment, and then more focally targeted therapies, such as botulinum toxin injections, iontophoresis, or microwave thermolysis, should be considered. However, when these treatments are ineffective, intolerable, or not feasible, systemic therapies are a good option. Oral medications can be added to the previously mentioned treatments to enhance improvements. This is especially beneficial when patients have multiple areas of HH. I might use botulinum toxin A injections for the axilla and iontophoresis for the hands and feet, but have to add an oral agent to manage such areas as the groin, face, or submammary sweating.

Generalized sweating presents a challenge. If a specific cause is identified, that agent or cause should be removed. However, it is common that an offending agent cannot be removed. Patients with psychiatric disease frequently cannot lower or change the medications that are controlling their

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mental illness. In these instances, other options, such as oral medications to treat the HH, have to be considered.³ Some patients have multiple confounding factors that can induce or worsen HH, and in these patients oral therapy may be very helpful.

There are groups of patients that should be considered very carefully before initiating therapy with oral medications, especially the oral anticholinergics, which decrease sweating from the entire body. Athletes and individuals who work or play a lot outdoors may become overheated if they are unable to cool their bodies without sweat evaporation, and may have an increased risk of hyperthermia and heat stroke. Small children or individuals who have difficulty self-monitoring their body temperature, mentation, and urine output may not be good candidates for oral anticholinergics. Allergies, other medications, or health issues need to be reviewed to avoid interactions or worsening of other diseases or health concerns. As an example, β -blockers are generally not given to patients with psoriasis.

It is very important to counsel patients on what therapy you are using, how it works, and what to monitor. It is also critical that patients are counseled on realistic expectations. Most patients can expect an improvement but not complete resolution of their HH symptoms. I counsel patients that they will most likely still have episodes of sweating when others around them do not, and that they will most likely still be the first to sweat and even sweat more than their counterparts during activity. Setting a step-wise plan for the patient can also be helpful so that they do not discontinue therapy and understand that if a plan is not providing enough improvement, then the next step will be added, especially with oral therapies. Improvement in symptoms is usually possible to achieve, but anhidrosis is not, nor is it desirable.

ANTICHOLINERGIC AGENTS

Because the sweat glands are innervated by the sympathetic postganglionic nerves and have acetylcholine as the primary neurotransmitter, the use of anticholinergic agents is a logical choice to treat HH.⁴ Anticholinergic agents work by competitive inhibition of acetylcholine at the muscarinic receptor. Muscarinic receptors are present throughout the central and autonomic nervous system, accounting for widespread and varied side effects that can develop.

There are several anticholinergic agents; however, there are differences in the side effect profile. Glycopyrrolate is a quaternary amine with limited passage across lipid membranes, such as the

blood-brain barrier. This is in contrast to such agents as atropine or scopolamine, which are tertiary amines and can easily penetrate lipid barriers. This is probably the reason why glycopyrrolate has fewer central nervous system side effects and may have less effect on the heart rate at lower doses.⁵ The most common side effect is dry mouth caused by inhibition of salivary glands. There are many potential side effects (**Box 1**) and concurrent use with other medications with anticholinergic activity, such as phenothiazines, antiparkinson drugs, or tricyclic antidepressants, intensifies the antimuscarinic effects and increases side effects. Anticholinergic therapy may be contraindicated in patients with glaucoma, obstructive uropathy, obstructive diseases of the gastrointestinal (GI) tract, paralytic ileus, severe ulcerative colitis, and myasthenia gravis.

Glycopyrrolate

Glycopyrrolate is the author's most commonly used anticholinergic drug to treat HH. Dosing is variable and is usually started at 1 to 2 mg twice daily (BID). The patient is asked to increase the dose by 1 mg per day at 2-week intervals based on the therapeutic response and side effects. Dry mouth is the most common side effect and usually the limiting factor in dosing. If side effects are minimal, management can allow patients to continue their medication. Managing dry mouth could include use of artificial saliva preparations, increasing water intake, and keeping candy or mints available; increased fiber consumption and light exercise can help to improve mild constipation. Over-the-counter eye drops can improve dry eye symptoms, but many patients have to discontinue therapy because of intolerable side effects. The efficacy and side effects of therapy are generally dose-dependent.

Walling⁶ published a retrospective review of 45 patients who used glycopyrrolate to treat HH of various body sites. Overall 67% were responders and 33% failed treatment. Of the treatment failures, 40% were nonresponders and the rest had adverse effects requiring medication cessation (xerostomia, GI disturbance, headache, rash, and mental status change). Only one-fourth of his patients used it as monotherapy, but others combined therapy with topical aluminum chloride, botulinum toxin, and iontophoresis. His patients most commonly took 1 mg daily and the highest dose that was used was 6 mg daily. Bajaj and Langtry⁵ reported on 19 patients treated with glycopyrrolate and found that 80% responded to therapy. The most common dose was 2 mg BID or three times daily (TID) but one patient took

Box 1**Anticholinergic therapy side effects***Gastrointestinal*

Dry mouth
 Constipation
 Nausea
 Vomiting
 Bloating feeling
 Loss of taste

Ocular

Mydriasis
 Cycloplegia
 Dry or gritty eyes
 Blurred vision
 Photophobia

Respiratory

Bronchodilation
 Reduced secretions

Genitourinary

Urinary retention
 Slow voiding
 Urinary hesitancy
 Erectile dysfunction
 Loss of libido

Cardiac

Bradycardia (lower doses)
 Tachycardia (higher doses)
 Arrhythmias
 Palpitations

Central nervous system

Headache
 Dizziness
 Insomnia
 Drowsiness
 Mental confusion and/or excitement (usually in elderly)
 Seizures

Skin

Decreased sweating
 Urticaria
 Pruritus

4 mg BID. Side effects were reported in 80% of the patients and about one-third of their patients had to stop the glycopyrrolate because of side effects. Typically my patients require daily maintenance, but a few take it on an “as-needed basis.” Doses range from 1 to 8 mg BID and do not seem to correlate significantly with age, gender, or body mass.

Oxybutynin

Oxybutynin is another common anticholinergic drug that is used to treat HH. It is classified as a tertiary amine. It comes in several different preparations including a tablet, slow-release tablet, topical gel, and transdermal patch. For oral administration, 5 to 10 mg daily is usually required for relief of HH, but doses up to 15 or 20 mg daily may be required.^{7,8} Wolosker and coworkers⁹ did a randomized placebo-controlled trial using oxybutynin for palmar and axillary HH. Fifty patients were enrolled, and the drug was initiated at 2.5 mg daily, increased to 2.5 mg BID during weeks 2 and 3, and then treated with 5 mg BID. Approximately 70% of the patients reported improvement in their axillary and palmar HH, whereas 90% of patients with plantar involvement reported improvement in their plantar sweating. Most of the treated patients reported improvement in their QOL, whereas one-fourth had no change in their QOL. Side effects were limited to dry mouth that was rated as moderate to severe by 30% of the subjects during the first 3 weeks (lower dose) and reached 35% by 6 weeks with the higher dose of oxybutynin. Tupker and coworkers⁸ reported 13 patients with generalized HH and 1 with drug-induced HH that were treated with oxybutynin (2.5 mg TID, and 5 mg TID), with all of the generalized HH patients responding (the paroxetine-induced HH patient did not respond). Therapy was well tolerated with the most common side effects being dry mouth, urinary difficulty, GI complaints, headache, and lassitude, although 30% had to discontinue therapy because of side effects. Therapy seems to work well in men and women, and overweight and obese individuals.^{10,11}

There are no guidelines to use when choosing which anticholinergic drug to use for HH. Because of the more limited penetration into the central nervous system, glycopyrrolate is a good option. Patients may respond to one anticholinergic drug better than another, or may experience fewer or different side effects with one drug compared with other anticholinergics.⁶ Additionally, there may be better compliance with the once-daily slow-release oxybutynin. It is reasonable to switch

anticholinergic drugs when faced with non-response. Another option is to try a topical formulation.

Other Anticholinergic Agents

Other drugs with antimuscarinic effects can be used to treat HH, and different options are available in various parts of the world. One of the best studied is methantheline bromide, which is a quaternary amine available in Germany. A large multicenter placebo-controlled randomized study of 339 patients with axillary or palmar-axillary HH was performed.¹² Methantheline, 50 mg, or placebo was used TID and gravimetric measurements of sweat, Hyperhidrosis Disease Severity Scale, and QOL were measured. At Day 28, there was a reduction of sweat production of 40% compared with the placebo, although the measured reduction in sweat production was greater in the axilla as compared with the palms. The researchers hypothesized that the decreased efficacy in the palmar sweating may be because a significant proportion of methantheline is excreted through the sebaceous glands and these are lacking in the palms. There was good tolerability with dry mouth, impaired accommodation, and dry eyes reported. There was a statistically significant decrease in the Hyperhidrosis Disease Severity Scale and an improvement in QOL in methantheline-treated subjects.

Anticholinergic Use in Pediatric Patients

In general, I avoid the use of systemic anticholinergic therapy for my young patients with HH because they have less control of their environment at school, may be exposed to heat stresses during playtime, and may not be able to monitor themselves for signs or symptoms of hyperthermia. However, Paller and coworkers¹³ reported on 31 pediatric patients that were treated with glycopyrrolate and found that 90% had improvement and 10% had no improvement in their HH. The average age of her patients at the time that the glycopyrrolate was prescribed was 14.8 years \pm 2.9. The mean dose for these teenagers was 2 mg daily but ranged from 1 to 6 mg daily. Approximately 30% had side effects including dry mouth, dry eyes, and blurred vision. One patient had to stop therapy because of palpitations. Oxybutynin has been studied extensively in children for urologic problems with a good safety profile, although there is a higher number of central nervous system adverse event cases reported in pediatric patients as compared with adult patients.^{14,15} Glycopyrrolate is approved by the Food and Drug Administration to treat children with sialorrhea and in this

population side effects are dose-dependent and include behavioral changes, constipation, excessively dry mouth, urinary retention, facial flushing, nasal congestion, vomiting, and diarrhea.¹⁶

β -ADRENERGIC BLOCKERS

The use of β -blockers to treat patients with HH stems from their use to improve symptoms of social phobias and performance anxiety.¹⁷ Episodes of HH may develop throughout the day, but many patients complain that the sweating develops at times of performance-related stress or just a perception that sweating may interfere with performance, such as meetings, public speaking, or school performance. In these instances the use of a β -blocker, such as propranolol, can be helpful. Propranolol is a highly lipophilic drug that binds to β_1 and β_2 receptors with equal affinity. Peak concentration is 1 to 1.5 hours postingestion, although food may delay peak concentration.¹⁸ Contraindications to therapy are numerous (**Box 2**) and a thorough history needs to be obtained, but low doses are generally used infrequently, making this therapy well tolerated. A resting blood pressure and heart rate should be taken in the office before prescribing the drug.

Commonly used doses are 10 to 20 mg of propranolol taken approximately 1 hour before the

Box 2

Contraindications for propranolol

Bradycardia^a
 AV block^a
 Asthma
 Chronic obstructive pulmonary disease
 Depression
 Diabetes mellitus
 Heart failure
 Hepatic disease
 Hypotension
 Hypoglycemia
 Cerebrovascular disease
 Myasthenia gravis
 Psoriasis
 Renal disease
 Thyroid disease
 Elderly
 Driving or operating machinery

^a Absolute contraindication.

planned performance. For patients with low resting blood pressure, slow baseline heart rates, or very small body mass index, 5 mg may be used initially. Patients should take a “test run” at home to monitor for hypotension, orthostatic hypotension, depressed cognition, or poor performance in general.

α -ADRENERGIC AGONIST

Clonidine is a sympatholytic medication used to treat hypertension and some anxiety/panic disorders. It is classified as a centrally acting α_2 -adrenergic agonist and has been successfully used to treat some patients with HH, and with flushing and sweating associated with menopause.^{6,19–21} Doses used to treat menopausal hot flashes were low, ranging from 0.025 to 0.1 mg BID. Walling’s⁶ reported dose in 13 patients with HH was 0.1 mg BID. Overall there was a 46% response rate and most of his patients used clonidine as monotherapy. Interestingly, the patients with craniofacial HH comprised most of his responders. Of the seven patients who failed treatment, three were nonresponders and four had to discontinue the medication because of side effects related to decreased blood pressure. Side effects most commonly seen with the use of clonidine are dry mouth, dizziness, constipation, and sedation.

As with propranolol, a thorough history and examination including blood pressure should be performed before initiating therapy. Doses of 0.1 mg BID are most commonly used and the drug can be combined with other therapies to treat HH.^{6,21} Anecdotally, I have found it most useful in my middle-aged patients with craniofacial HH and sweating associated with flushing. I have prescribed it for generalized HH especially when there are several factors contributing to the overall sweating.

BENZODIAZEPINES

Benzodiazepines are sometimes listed as a treatment of HH, social anxiety disorders, and performance anxiety.^{17,22} Diazepam, 5 to 20 mg/day, is recommended, but there is no real primary literature supporting the efficacy in patients with HH. Because HH is a chronic disease, one has to carefully weigh the risks of addiction or dependence. Propranolol is the author’s first choice to treat performance-based sweating. If anxiety seems to be the overriding problem, referral to psychiatry for cognitive therapy or other drug management is prudent.

OTHER SYSTEMIC AGENTS

There are a few anecdotal case reports using other systemic agents to help reduce sweating of

various etiologies, which may be of use in limited situations, or when other therapies have not produced satisfactory improvement.

The calcium channel blocker, diltiazem, was been reported to improve palmar sweating in two family members with autosomal-dominant emotional HH.²³ A woman with “lifelong generalized HH” reported resolution of sweating when treated with indomethacin, 25 mg TID, for her arthritis.²⁴ Gabapentin when used with probantheline improved sweating in a child suffering from HH after a spinal cord injury.²⁵ Gabapentin has also been used with limited success in social anxiety disorder.¹⁷

SUMMARY

Oral therapies can play an important role in treating HH of all types. Although monotherapy is sometimes useful, combining systemic treatments with more focally based therapy may provide superior results. Because of side effects and drug interactions, a thorough assessment should be performed before initiating systemic therapy, and working with other health care team members is valuable to monitor for and reduce the risks of systemic therapies.

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