

Systemic therapy for primary hyperhidrosis: A retrospective study of 59 patients treated with glycopyrrolate or clonidine

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Background: Data regarding systemic medications in the management of hyperhidrosis (HH) are limited.

Objective: The goal of this study was to provide evidence for the safety and efficacy of systemic medications for primary HH.

Methods: A retrospective chart review was conducted of patients seen at an academic dermatology department prescribed systemic medications for primary HH.

Results: A total of 71 patients were prescribed systemic agents. Twelve patients (17%) were lost to follow-up and were excluded from further analysis. A total of 59 patients with at least 2 months of follow-up data (mean age 28.9 ± 12.0 years; 37 women, 22 men; mean follow-up 19.5 months) were included in the analysis. Palmoplantar and/or axillary HH was most common (42/59; 71%); followed by generalized (9/59; 15%) and craniofacial (8/59; 14%) HH. Glycopyrrolate (generally 1-2 mg once or twice daily) was prescribed to 45 patients, with response rate of 67% (30/45). Fifteen treatment failures included 6 nonresponders and 9 with adverse effects, including xerostomia and gastrointestinal disturbance. Clonidine (0.1 mg twice daily) was prescribed to 13 patients, with a response rate of 46% (6/13). Seven treatment failures included 3 nonresponders and 4 with adverse effects, all relating to decreased blood pressure. One patient responded to oxybutynin at 5 mg twice daily. There were no significant differences in efficacy ($P = .21$; odds ratios 0.43, 95% confidence interval 0.12-1.5) or adverse effects ($P = .46$; odds ratios 1.78, 95% confidence interval 0.44-7.1) in comparing glycopyrrolate versus clonidine.

Limitations: This was a retrospective study from a single, university-based population.

Conclusion: Systemic therapy with glycopyrrolate or clonidine can be effective for HH. Nearly two-thirds responded to therapy, and less than a quarter had treatment-limiting adverse effects, all of which were self-limited and nonserious. (J Am Acad Dermatol 2012;66:387-92.)

Key words: anticholinergic; Catapres; craniofacial; hyperhidrosis; palmoplantar; Robinul; sweat.

Primary hyperhidrosis (HH) has an estimated prevalence of nearly 3% of the population.¹ HH increases the risk of cutaneous infection² and has a significant psychosocial burden and negative impact on quality of life.^{1,3} A variety of treatments are currently available for HH, including

Abbreviations used:

CI: confidence interval
HH: hyperhidrosis
OR: odds ratios

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nonsurgical and surgical options.⁴⁻⁶ Although oral medications may be considered as a second- or third-line treatment for HH, the authors of a recent clinical treatment guideline note that compelling evidence for the safety and efficacy of such agents is distinctly lacking.⁷ Moreover, the scant clinical data that are available are primarily in the form of individual case reports and small series, with no comparative studies or prospective trials. Finally, few data exist to

indicate which oral medications might be selected as best therapy options.

The purpose of this study was to systemically review a database of patients treated for primary HH at a single academic dermatology department during a 13-year period to identify patients who were prescribed systemic medications as HH therapy. Treatment outcomes were then assessed in the identified patients. The goal was to provide evidence for the safety and efficacy of systemic medications for HH affecting a variety of anatomic sites.

METHODS

Institutional review board approval was obtained from the university's human subjects committee to conduct a retrospective chart review. Charts were systematically reviewed for all dermatologic visits from 1993 to 2005 for all patients encountered for the *International Classification of Diseases, Ninth Revision* code corresponding to primary HH. Clinical data were reviewed to ensure that all patients met diagnostic criteria for primary HH,⁷ including at least 4 of the following 7 features: activity-impairing episodes of excess sweating occurring at least weekly and during waking hours, involving primarily a palmo-plantar, axillary, or craniofacial distribution in a bilateral and symmetric fashion, with onset before age 25 years, with positive family history. Patients with symptoms of HH for less than 6 months and/or patients with a diagnosis of secondary HH were excluded. Demographic information collected included age, gender, location of HH, current and past therapies, and response to therapy. The current study analyzed a subgroup of a previously reported database of 387 patients,² representing those patients who: (1) were prescribed oral medications; and (2) presented for clinical follow-up. Although 2 months of follow-up were required to categorize a patient as a responder, patients reporting intolerance to medications at any time were included in the analysis. A nonresponder was defined as a patient who reported "no," "slight," or "less than 50% improvement," or for whom specific adverse effects were not recorded but did not continue the medication and switched to another form of treatment. Absolute responses to therapy were recorded because degrees of response could be determined from

the clinical notes in only a minority of patient records. Patients were routinely instructed to attempt dose escalation of glycopyrrolate until adverse effects became bothersome, at which point they were instructed to decrease the dose back to the highest level for which any side effects were not problematic. A patient who was able to return to an effective and tolerable dose was considered a responder.

Categorical variables were compared by χ^2 testing (or the Fisher exact test for samples with $N < 5$), with P less than .05% considered statistically significant. Statistical testing, including odds ratios (OR) and 95% confidence intervals (CI) was performed using software (SPSS for Windows, SPSS Inc, Chicago, IL).

RESULTS

The retrospective chart review identified a total of 71 patients who were treated with oral medications for a diagnosis of primary HH. Of these 12 (17%) were lost to follow-up and were excluded from further analysis. The remaining 59 patients were included in the analysis, and had at least 2 months of follow-up data. Demographic and clinical characteristics are shown (Table I). The mean age was 28.9 years, with a female:male ratio of 1.7:1. The palms, soles, and/or axillae were primarily affected in the majority (42 of 59; 71%) of patients; fewer patients exhibited generalized HH (9 of 59; 15%) or craniofacial HH (8 of 59; 14%). Before starting the oral medications prescribed in this study, most patients (56 of 59; 95%) had previously failed other treatments, including topical aluminum chloride (55 of 59; 93%), iontophoresis (13 of 59; 22%), and other oral medications (13 of 59; 22%). Individual patients had tried and failed botulinum toxin injections and sympathectomy.

Among the 13 patients who had previously failed oral medications, a variety of different oral medications had been tried, per self-report or referral records from outside physicians (Table II). Antiadrenergic medications (eg, propranolol, clonidine) had been most frequently prescribed, followed by anticholinergic medications (glycopyrrolate, propantheline); benzodiazepines and antidepressants medications were prescribed less frequently. Five of these 13 patients had previously failed 3 or more oral medications.

CAPSULE SUMMARY

- Scant information is available regarding the use of systemic medications in the treatment of primary hyperhidrosis.
- This retrospective study found a response rate of 67% among 45 patients treated with glycopyrrolate, and a response rate of 43% among 13 patients treated with clonidine.
- Glycopyrrolate may be considered as second-line therapy for moderate to severe palmar-plantar, and/or axillary hyperhidrosis. Either glycopyrrolate or clonidine may be considered as first-line therapy for craniofacial or generalized hyperhidrosis.

Table I. Patient characteristics

No. of patients	59
Mean age, y	28.9 ± 12.0 (range 14-59)
Gender	37 Female (63%), 22 male (37%)
Sites affected	
Palmoplantar	18 (31)
Palmoplantar, axillary	14 (24)
Generalized	9 (15)
Craniofacial	8 (14)
Axillary	7 (12)
Palmar	2 (3)
Plantar	1 (2)
Mean follow-up duration after starting oral medication, mo	19.5 ± 12.2 (range 2-47)
Previously failed therapies (%)	56 (95)
Aluminum chloride	55 (93)
Iontophoresis	13 (22)
Oral medication	13 (22)
Botulinum toxin	1 (2)
Sympathectomy	1 (2)

Among the entire cohort of 59 patients, glycopyrrolate was the most common medication prescribed, with 45 patients treated (Table III). The overall response rate was 67% (30/45), including a 69% response rate (27/39) for patients with HH affecting the palms, soles, and/or axillae. Of responders, 90% took a dose of 1 to 2 mg once or twice daily. The most common dosing regimen used was 1 mg daily (N = 12), followed by 1 mg twice daily (N = 6), 2 mg twice daily (N = 5), and 2 mg once daily (N = 4). Two patients took 3 mg once daily, and one patient took 3 mg twice daily. This medication was effective in all HH distributions. There were no significant differences in dosing regimens between genders or between distributional patterns.

About a quarter of patients taking glycopyrrolate (11 of 45; 24%) used this medication as monotherapy for their HH. Three-quarters (34 of 45; 76%) took glycopyrrolate in combination with another form of therapy, including topical aluminum chloride (N = 16), botulinum toxin (N = 6), and iontophoresis (N = 1). Of the 30 patients with a positive response, 14 indicated a degree of improvement: 6 of 14 (42%) stated improvement was "great," "excellent," or ">75%"; 8 of 14 (59%) noted "some," "moderate," or ">50%" improvement.

Among the 15 patients (33%) who failed therapy with glycopyrrolate, 6 (13%) were nonresponders, and 9 (20%) had adverse effects requiring medication cessation.

Adverse effects requiring treatment cessation included xerostomia (4), gastrointestinal disturbance

Table II. Previously failed oral medications

Medication class	Medication (N)
Antiadrenergic (12)	Propranolol (5) Clonidine (4) Reserpine (1) Terazosin (1) Phenoxybenzamine (1)
Anticholinergic (8)	Glycopyrrolate (3) Proprantheline (3) Benztropine (1) Oxybutynin (1)
Benzodiazepines (6)	Lorazepam (3) Diazepam (2) Clonazepam (1)
Tricyclic antidepressants (2)	Imipramine (1) Nortriptyline (1)
Atypical antidepressant (1)	Bupropion
Selective serotonin reuptake inhibitor (1)	Fluoxetine

(2), headache (1), rash (1), and mental status changes (1).

Thirteen patients were prescribed clonidine, all at a dose of 0.1 mg twice daily (Table IV). Eleven of the 13 patients had craniofacial (N = 6) or generalized (N = 5) HH. The overall response rate was 46% (6/13). Of the 6 responders, 5 continued clonidine as monotherapy, including 4 of 6 patients with craniofacial HH. One patient continued to use topical aluminum chloride to his scalp after adding clonidine. Of the 7 patients who failed clonidine, 3 (23%) were nonresponders, and 4 (31%) had adverse effects requiring medication cessation, relating to decreased blood pressure in all cases. No patients took glycopyrrolate and clonidine simultaneously.

Overall, there were no significant differences in likelihood of efficacy comparing glycopyrrolate versus clonidine ($P = .21$; OR 0.43, 95% CI 0.12-1.5). Similarly, there were no significant differences in likelihood of treatment-limited adverse effects for glycopyrrolate versus clonidine ($P = .46$; OR 1.78, 95% CI 0.44-7.1). For both medications, adverse effects led to no serious consequences, required no additional medical intervention, and abated upon discontinuation. Eleven of 13 patients (85%) who were prescribed clonidine had craniofacial or generalized HH, whereas only 6 of 45 patients (13%) who were prescribed glycopyrrolate had craniofacial or generalized HH ($P < .00001$; OR 35.8, 95% CI 6.3-202.6).

One patient, a 25-year-old woman with palmoplantar and axillary HH, was treated successfully with oxybutynin 5 mg twice daily, which she continued as monotherapy with no reported adverse effects after 5 months of follow-up.

Table III. Glycopyrrolate efficacy

Site	Patients (N)	Nonresponder (%)*	Improved (%)	Monotherapy (%)
Palmoplantar	18	4 (22)	14 (78)	4 (22)
Palmoplantar, axillae	12	4 (33)	8 (67)	2 (17)
Axillae	7	3 (43)	4 (57)	3 (43)
Generalized	4	2 (50)	2 (50)	1 (25)
Palmar	2	1 (50)	1 (50)	0
Craniofacial	2	1 (50)	1 (50)	1 (50)
Total	45	15 (33)	30 (67)	11 (24)

*Seven nonresponders include patients showing no, slight, or <50% improvement (3; 43%) or those experiencing adverse effects resulting in treatment cessation (4; 57%). Adverse effects were symptoms relating to decreased blood pressure (orthostatic hypotension, dizziness).

DISCUSSION

Only limited data are available regarding use of oral medications in the management of HH. The HH disease severity scale defines moderate HH as sweating that is tolerable but sometimes interferes with daily activities, and severe HH as sweating that is barely tolerable to intolerable, that frequently to always interferes with daily activities.⁸ A 2007 practice guideline correctly states that "compelling evidence is lacking for the safety and efficacy of systemic anticholinergic agents" for the treatment of HH.⁷ This guideline recommends oral therapy with glycopyrrolate to be considered as third-line therapy for severe axillary HH (after topical agents or injected botulinum toxin), fourth-line therapy for severe palmar/plantar HH (after topical agents, botulinum toxin, or iontophoresis), and as first-line therapy for moderate to severe craniofacial HH.⁷ Insufficient evidence existed for the recommendation of glycopyrrolate for the treatment of palmoplantar/axillary HH of moderate severity, or for any other oral agents such as clonidine for HH at any site or of any severity.⁷ The level of evidence for these recommendations was of the weakest strength, based upon "opinions of respected authorities" rather than from randomized controlled trials, case-control or cohort studies, meta-analyses, or systematic reviews.⁷

The goal of this study was to provide evidence for the safety and efficacy of systemic medications for HH affecting a variety of anatomic sites. In the current study, 37 of 59 (63%) of patients with HH showed a positive response to systemic therapy. Treatment-limiting adverse effects occurred in 13 of 59 (22%) of patients. All adverse effects were self-limited and none were considered serious. Glycopyrrolate (N = 45) and clonidine (N = 13) were the most commonly prescribed medications.

Table IV. Clonidine efficacy

Site	Patients (N)	Nonresponder (%)*	Improved (%)	Monotherapy (%)
Craniofacial	6	2 (33)	4 (67)	4 (67)
Generalized	5	4 (80)	1 (20)	1 (20)
Palmoplantar, axillae	1	1	0	0
Plantar	1	0	1	0
Total	13	7 (54)	6 (46)	5 (38)

*Seven nonresponders include patients showing no, slight, or <50% improvement (3; 43%) or those experiencing adverse effects resulting in treatment cessation (4; 57%). Adverse effects were symptoms relating to decreased blood pressure (orthostatic hypotension, dizziness).

These results represent the largest reported data set regarding the systemic treatment of HH.

Only one previous report was identified regarding the use of systemic glycopyrrolate for HH. In a retrospective study, 15 of 19 patients (79%) with HH affecting a variety of body sites responded to glycopyrrolate, most commonly at a dose of 2 mg twice daily.⁹ In that study, 5 patients stopped the medication because of adverse effects and 4 patients discontinued for lack of efficacy,⁹ corresponding to a 53% (10/19) treatment success rate, similar to that reported in the current study.

The mechanism of action of glycopyrrolate is competitive inhibition of acetylcholine at muscarinic receptors. At least 5 subtypes of muscarinic receptors have been identified: M3 predominates in glandular tissue, whereas other types are found in neuronal tissue (M1, M4), the heart (M2), and the central nervous system (M5).⁹ Glycopyrrolate has a highly polar quaternary ammonium group that limits lipid solubility and may explain the relatively low incidence of central nervous system side effects compared with other anticholinergic agents.⁹ It is indicated for use as a perioperative antimuscarinic agent, as an adjunctive therapy for peptic ulcer disease, and to inhibit excessive salivation. Side effects relate to the anticholinergic mechanism and include xerostomia, urinary hesitancy, ocular effects (mydriasis leading to blurred vision and photophobia, cycloplegia, increased ocular pressure), tachycardia, dizziness, constipation, and rarely confusion. Glycopyrrolate is contraindicated in patients with myasthenia gravis, pyloric stenosis, and paralytic ileus, and should be used cautiously in patients with gastroesophageal reflux disease, glaucoma, bladder outflow obstruction, and cardiac insufficiency.⁹

Glycopyrrolate has also been effective as a non-systemic agent for HH therapy, both topically and with iontophoresis. In one study, 24 of 25 patients with craniofacial HH improved with application of

2% glycopyrrolate solution, with the improvement lasting 1 to 2 days for most subjects.¹⁰ In a double-blind, placebo-controlled crossover study, all of 13 patients with diabetes-related gustatory sweating responded to topical glycopyrrolate, experiencing reduction in the severity and frequency of episodes.¹¹ Eight of 10 patients with compensatory HH after sympathectomy responded to treatment with 2% glycopyrrolate solution.¹² In a single-blinded right-left comparison study in 20 patients with palmoplantar HH, glycopyrrolate iontophoresis was significantly more effective than tap water iontophoresis.¹³

Clonidine is indicated for treatment of hypertension, functioning as a centrally acting alpha-adrenergic receptor agonist that reduces sympathetic outflow. Side effects include dry mouth, dizziness, constipation, and sedation. Systemic clonidine has been reported as a treatment for HH in only a limited number of case reports^{14,15} and a series of 12 patients in the French literature.¹⁶ Clonidine administered as a transcutaneous patch (0.2 mg/d) was reported helpful in a single case of gustatory HH.¹⁷

In this study, 13 patients had previously tried and failed a total of 30 different medications prescribed to attempt to control the symptoms of HH. As these medications were not prescribed at the office visits reviewed in the study and in many cases would have been dependent upon patient recollection, little information was available on these medications as to the dosage and reasons for treatment failure (intolerance vs lack of efficacy).

There was no indication in the reviewed charts as to why the proportion of patients with craniofacial or generalized HH was greater in the clonidine-treated subjects compared with the glycopyrrolate treated subjects, nor why the proportion of patients with HH affecting palms, soles, and/or axillae was greater in the glycopyrrolate-treated subjects compared with the clonidine-treated subjects. No single attending physician was responsible for this trend. The numbers of patients in these distributional subgroups who responded to these treatments were not adequately powered to show a statistical difference. These observations likely represent a shared practice preference for this cohort of attending physicians.

This study is limited by the retrospective nature of the study. The amount of information available in the reviewed charts was limited by the thoroughness of clinical documentation at each patient visit and the variability among faculty and resident physicians caring for these patients during the 13-year period of the study. Moreover, patients did not routinely answer any standardized questions that would allow quantification of the disease severity or degree of

efficacy of the interventions. Some patients volunteered a degree of improvement to their symptoms, although others did not. However, it was generally possible to determine whether a medication was deemed effective enough to continue and whether it was sufficiently effective that other therapies were not necessary. Moreover, for patients using combination therapy (eg, topical plus oral medication) it was generally possible to attribute improved control of symptoms to the addition of oral medication, because at all visits in which an oral medication was started, this was the only variable changed in the therapy plan.

The percentage of patients prescribed oral medications and who were subsequently lost to follow-up (12 of 71; 17%) is not an unexpected rate for routine clinical care at a tertiary referral center, where patients often travel from great distances. It was not possible to determine whether these patients experienced improvement with the medication and had their local physician continue the prescription, whether they experienced lack of improvement or adverse effects, or whether they even filled the prescription. As such, these patients were noninformative and were excluded from further analysis. Finally, a prospective study with more patients would have greater statistical power to compare the relative efficacies of glycopyrrolate and clonidine.

In conclusion, this study indicates that systemic therapy, particularly with glycopyrrolate or clonidine, can be effective treatment for HH. Nearly two-thirds responded to therapy in this study, and less than a quarter had treatment-limiting adverse effects. As the adverse effects were generally mild and self-limited, the risk-benefit profile may be favorable for many patients in whom other therapies are ineffective or impractical. The information from this study may bolster the status of systemic medications in the HH therapeutic ladder. Based on these data, this author recommends consideration of glycopyrrolate as second-line therapy (after failure of or inadequate response to topical agents) for moderate to severe palmar, plantar, and/or axillary HH, and consideration of either glycopyrrolate or clonidine as first-line therapy for craniofacial or generalized HH. Although iontophoresis and botulinum toxin are highly effective for focal HH, ease of administration, cost, convenience, and availability may favor a trial of systemic medication in many individual cases. A prospective clinical trial of oral agents for HH is warranted to further study this therapy approach.

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