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Is prophylactic oxybutynin safe and effective in reducing the severity of palmar hyperhidrosis in adults?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

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Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine “Is prophylactic oxybutynin safe and effective in reducing the severity of palmar hyperhidrosis in adults?”

STUDY DESIGN: This review is based on two randomized controlled trials (RCTs) and one non-randomized crossover study published in 2008, 2011, and 2012. The studies compared the safety and efficacy of oxybutynin in reducing the severity of palmar hyperhidrosis.

DATA SOURCES: All articles used were published in English, in peer-reviewed journals, and found using PubMed, Ebscohost, and Cochrane Review databases.

OUTCOMES MEASURED: For all studies, the safety and effectiveness of oxybutynin on palmar hyperhidrosis was evaluated using post-treatment clinical questionnaires. For one study, symptom improvement was quantitatively measured using Transepidermal Water Loss (TEWL) measurements pre- and post-treatment.

RESULTS: Van Houte et al. (2008) found no statistical significance ($p > 0.05$) in effectiveness of sweat inhibition with oxybutynin at doses of 7.5 mg and 15 mg per day. Conversely, the Wolosker et al. studies (2011, 2012) saw statistically significant improvement (>80% of participants) in palmar hyperhidrosis symptoms (sudoresis) with the administration of oxybutynin at doses of 10 mg per day. None of the studies reported worsening symptoms with treatment. Noted side effects primarily included dry mouth, in which moderate to severe cases were reported in 34.8%-48.1% of participants. Despite the prevalence of dry mouth, it was not found to be an impeding factor in the use of oxybutynin for palmar hyperhidrosis.

CONCLUSIONS: Results of two of the three studies demonstrate that 10 mg of daily oxybutynin is safe and effective in the prophylactic management of palmar hyperhidrosis in those diagnosed with generalized hyperhidrosis (GH). Further comparative studies are warranted to investigate whether the long-term use of oxybutynin results in continued symptom improvement or tachyphylaxis.

KEY WORDS: Hyperhidrosis, oxybutynin, anticholinergic

INTRODUCTION

Hyperhidrosis is a somatic disorder of hyperactive sweat glands.^{1,2,3} Individuals with hyperhidrosis possess an autonomic neuronal dysfunction which causes the production of more sweat than what is needed to maintain thermoregulation.¹ This dysfunction most often occurs in areas with high concentrations of sweat-producing eccrine glands, most notably the axillae, soles, and palms.⁴ When not due to another disorder (e.g. endocrine dysfunction, cardiovascular disease, menopause, etc.), hyperhidrosis is known as primary hyperhidrosis (PH).^{1,2,3} Acetylcholine is the main neurotransmitter involved in sympathetic-induced sweat secretion;⁴ therefore, anticholinergic therapy is a logical choice when approaching symptomatic management of PH. Although surgical sympathectomy is the most definitive treatment, complications have lead patients and providers to seek less invasive treatment modalities.^{1,2,3} This paper evaluates two randomized controlled studies and a non-randomized crossover study, looking at the safety and efficacy of prophylactic oxybutynin, an oral anticholinergic medication, for improving symptoms of palmar hyperhidrosis.

The impact of PH on healthcare resources and costs has yet to be determined; however, it should not be ignored. In the United States, PH affects approximately 3% of adults---roughly 7.8 million Americans.⁵ The majority prevalence of those with PH are aged 25 to 64 years old, with reported age of onset younger than 25 years old.⁵ Due to the unpredictable and embarrassing nature of the disorder, many psychosocial problems develop as a consequence of hyperhidrosis. It is documented that those with PH have a lower quality of life as they suffer occupational, emotional, psychological, social, and physical impairment.^{2,3,5} It is estimated that only 38% of those with PH discuss their disorder with a healthcare provider. Due to this fact, an exact number of healthcare visits per year allocated to PH remains unknown.⁵ Furthermore, the total

healthcare cost of PH has not yet been identified. However, in accordance with this literature review, generic oxybutynin costs approximately \$636-\$954 per year, assuming self-pay pricing.⁶

The specific etiology of PH is unknown, but there are believed to be emotional factors as well as hereditary factors.^{2,3} Emotions, such as anxiety, excitement, fear, or anger, are often responsible for the exacerbation of hyperhidrosis symptoms.^{1,2,3} When triggered, the hypothalamus sends nerve impulses through pre- and postganglionic sympathetic nerves to sweat glands.^{1,4} Acetylcholine is the primary neurotransmitter responsible for inducing and amplifying sweat secretion during neuronal synapse.⁴ Hyperfunctioning of this sympathetic mechanism results in hyperhidrosis. Additionally, an abnormality of chromosome 14q has been linked to autosomal dominant inheritance of PH in some families.⁷

PH is most commonly diagnosed on history and physical examination⁸; however, an iodine and starch test can be done to test severity, foci of sweating, and response to treatments. Diagnosis requires a minimum of six months of sudoresis without a secondary cause,^{1,2,3,8} as well as at least two of the following: impairs daily activities, has a bilateral and relatively symmetric pattern occurring at least once weekly, age of onset younger than 25, cessation of focal sweating during sleep, or positive family history of PH.⁸ There is currently no definitive cure for PH, so treatment focuses on minimizing symptoms and improving quality of life.

Current treatments for palmar hyperhidrosis include tap-water iontophoresis, Botulinum toxin type A (Botox), anticholinergic medications, and endoscopic thoracic sympathectomy (ETS).⁹ Tap-water iontophoresis is the use of an electrical current through water to submerged hands in order to suppress sweat gland activity. Restrictions include limited efficacy and adverse reactions, such as skin cracking and blistering. Botox injections are being used for palmar hyperhidrosis and require regular treatments; however, may cause localized temporary weakness

and intense pain. ETS surgery is recommended for severe palmar cases and is effective by shutting down neuronal impulses to sweat glands; however, many patients experience compensatory hyperhidrosis after ETS surgery.² Although not routinely used, anticholinergic medications are being considered as they have been found to decrease sudoresis in patients treated for micturition disorders.^{2,3,9} These medications will be evaluated in this literature review.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not prophylactic oxybutynin is safe and effective in reducing the severity of palmar hyperhidrosis in adults.

METHODS

Two double blind, randomized controlled trials, and one non-randomized crossover study were included in this systematic review. Studies were selected based on various criteria including populations studied, interventions used, comparisons made, and outcomes measured. In all three included studies, the populations being measured consisted of healthy adults aged 18 and older. Van Houte et al.¹ included healthy men and women aged 18 to 50, whereas Wolosker et al.² included healthy men and women aged 18 to 56 years old, and Wolosker et al.³ included healthy men and women aged 18 and older. Additional inclusion criteria in the Wolosker et al. studies was a diagnosis of PH, which included palmar hyperhidrosis symptoms.

For all reviewed studies, the intervention applied was oral administration of oxybutynin. Van Houte et al.¹ performed two randomized, double-blind crossover studies in which participants received 2.5 mg oxybutynin TID (or placebo) for the first study, followed by 5 mg oxybutynin TID (or placebo) for the second study performed after a 7 day washout period. For both studies, oxybutynin was administered the day prior to testing with an additional dose the morning of testing. Both Wolosker et al.^{2,3} studies administered oxybutynin for 6-12 weeks at

incrementally increased doses, beginning with 2.5 mg QD, increasing to BID, then 5 mg BID.

All three studies compared the effects of oxybutynin to placebo (or no therapeutic treatment) on symptom improvement. However, in the van Houte et al.¹ study, additional crossover comparisons were made between dosages (2.5 mg TID versus 5 mg TID).

Articles were researched via PubMed, Ebscohost, Cochrane Review databases and were selected based on relevance to the clinical question and that measured outcomes included patient oriented evidence that matters (POEMS). Key words entered in the PubMed search included “hyperhidrosis,” “oxybutynin,” and “anticholinergic.” All three of the selected studies were peer-reviewed journal articles written in the English language published between 2008 and 2012.

The studies included in this systematic review were selected based on the following inclusion criteria: all were primary research studies (randomized controlled trials, cohort studies, crossover studies, etc.), all were published after 1998, all included relevant POEMs, and all evaluated efficacy of oxybutynin on palmar hyperhidrosis as one of the measured outcomes. Exclusion criteria included studies involving those under 18 years of age, those with secondary hyperhidrosis, and those whose hyperhidrosis was not palmar. Specific exclusion criteria varied slightly between studies but generally included patients whose past medical history revealed diseases where anticholinergic therapy was contraindicated, or diseases where anticholinergic therapy is a known treatment (e.g. micturition disorders). Statistics reported in the van Houte et al.¹ study included t-tests, means, standard deviations in Transepidermal Water Loss (TEWL) delta values, whereas the Wolosker et al.^{2,3} studies included NNT (Wolosker et al.³ only), t-tests, p-values, and mean change from baseline. See Table 1 below for Demographics and Characteristics of Included Studies.

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (yr)	Inclusion criteria	Exclusion Criteria	W/D	Intervention
vanHoute ¹ (2008)	RCT	8	20-46	Adults aged 18-50 years old	Subjects without: urinary obstruction, prostate hypertrophy, hiatal hernia, other GI disorder, myasthenia gravis, hyper- or hypotension, renal failure, liver failure, glaucoma, hyperthyroidism, heart disease (any); must be a non-smoker, not pregnant, and not use any medication that might interact with oxybutynin	0	Therapeutic oxybutynin 2.5 mg TID OR Therapeutic oxybutynin 5 mg TID
Wolosker ² (2011)	Cross-over	180	18-56	Adults aged 18-56 w/ a complaint of palmar hyperhidrosis who may also have presented w/ hyperhidrosis on other body sites	Subjects without: glaucoma or any micturition disorder	41	Therapeutic oxybutynin x 12 wks with incrementally increased doses: - 2.5 mg QD HS initially - 2.5 mg BID days 8-42 - 5 mg BID days 43-84
Wolosker ³ (2012)	RCT	50	18-50	Adults aged ≥ 18 with a complaint of palmar or axillary hyperhidrosis with intention of using oxybutynin after being informed of risks and benefits	Subjects without: glaucoma, narrow-angle glaucoma, urinary retention, gastric retention, demonstrated hypersensitivity to the drug substance or other components of the drug	5	Therapeutic oxybutynin x 6 wks with incrementally increased doses: - 2.5 mg QD HS initially - 2.5 mg BID days 8-21 - 5 mg BID days 22-42

OUTCOMES MEASURED

All three studies measured palmar hyperhidrosis symptom improvement as well as side effects via post-treatment questionnaires completed by study participants. In van Houte et al.¹, participants' subjective impression of sweat inhibition was scored by a 100-mm visual analogue scale. Side effects were measured using a Likert scale, ranked 1-4, with "1" being low impact and "4" being extreme severe impact. Both Wolosker et al.^{2,3} studies used clinical questionnaires that addressed improvement in hyperhidrosis symptoms and severity of dry mouth (a known anticholinergic medication side effect) using scoring on a Likert scale. Symptom improvement was scored as "null," "slight improvement," "moderate improvement," or "great improvement." Severity of dry mouth was scored on a range from absence of side effect to severe side effect.

Additionally, the van Houte et al.¹ study used Transepidermal Water Loss (TEWL) measurements to evaluate quantitative improvements in sweating. A double-probe Tewameter (TM 300, Courage+Khazaka Cologne, Germany) was used to measure the degree of sweating on the central part of the left palm before and after exercise-induced sweating. Participants' sweating threshold was documented using a cycle ergometer, initially started at a level of 60W, then increased every 3 minutes by 30W until sweating occurred. Exercise was continued for an additional 6 minutes at the sweating threshold rate. TEWL measurements were taken before exercise and after the 6 minutes for each study in the crossover. Differences between pre- and post-exercise measurements were compared for each study and TEWL-delta values determined.¹

RESULTS

All three studies were performed using the methods previously outlined. In van Houte et al.¹, 8 healthy adult participants (4 male, 4 female), were randomly assigned to double-blind crossover studies. No participants were lost to follow-up. In Wolosker et al.², 180 healthy adult

participants (85 male, 95 female), were administered oxybutynin at incrementally increasing doses, then followed prospectively for 12 consecutive weeks. Of the 180 participants, 41 were lost to follow-up. In Wolosker et al.³, 50 healthy adult participants (unknown gender distribution), were randomly assigned to a double-blind study where they were administered oxybutynin (or placebo) at incrementally increasing doses, then followed prospectively for 6 consecutive weeks. Of the initial 50 participants, 5 were lost to follow-up (3 from placebo group, 2 from oxybutynin group).

Efficacy of Oxybutynin

In van Houte et al.¹, the degree of palmar sweating following oxybutynin administration was measured using the TEWL-delta value, which is the difference between pre-exercise TEWL measurements and TEWL measurements taken at the completion of the exercise test. Means and standard deviation of TEWL-delta values were given, and comparisons of values were done using two-sided paired t-tests; however, t-test values were not given. For both the 2.5 mg and 5 mg groups, the p-value was > 0.05 (exact value not specified), meaning neither treatment group had statistically significant results (Table 2). Conversely, in the 2.5 mg group, one out of the eight participants reported suppression of sweating in their impression of sweat inhibition evaluation. In the 5 mg group, no sweating suppression was reported.

Table 2: TEWL-delta values at oxybutynin dosages of 2.5 mg and 5 mg (van Houte et al.¹)

TEWL-delta (g/m ² per hr)		Oxybutynin 2.5 mg	Placebo	Oxybutynin 5 mg	Placebo
Palm	Mean	30.6	35.4	28.8	23.3
	Standard Deviation	10.09	14.72	12.21	10.93

In Wolosker et al.², improvement in symptoms of palmar hyperhidrosis was assessed using clinical questionnaires administered before treatment and after treatment completion. Of the 139 participants who completed the study, questionnaire data showed that nearly 90%

experienced improvement in palmar hyperhidrosis symptoms, with 54.5% of those having experienced “great” symptom improvement (Table 3).

Table 3: Evolution of hyperhidrosis with the use of oxybutynin (Wolosker et al.²)

Site	Improvement <i>n</i> (%)				
	Null	Slight	Moderate	Great	Total
Palm	16 (11.5)	8 (5.7)	48 (34.5)	67 (48.2)	139

Similarly, the Wolosker et al.³ study evaluated efficacy of oxybutynin on palmar hyperhidrosis via clinical questionnaires on symptom severity. Over 80% of participants in the treatment group experienced “moderate” or “great” symptoms improvement, with the majority being “great” improvement (47.8%). Of all participants with any improvement, 26% (n=6) were from the placebo group and only reported “moderate” improvement. Comparisons between the two groups were statistically significant ($P < 0.001$). Tables 4 and 5 summarize the results and efficacy of the Wolosker et al.³ study. The ABI shows an increase in treatment effect with the oxybutynin group compared to the placebo group. The RBI represents the effectiveness of oxybutynin and the relative probability of experiencing symptom improvement with oxybutynin treatment compared to placebo. The NNT is calculated to determine the number of patients that need to receive oxybutynin in order to benefit one patient with symptom improvement. In Wolosker et al.³, only three patients need treated to have one with symptom improvement.

Table 4: Evolution ion of hyperhidrosis with the use of oxybutynin (Wolosker et al.³)

Evolution	Placebo No. (%)	Oxybutynin No. (%)	P-value
Worse	0 (0.0)	0 (0.0)	<.001
Null/slight	16 (72.7)	6 (26.1)	
Moderate	6 (27.3)	6 (26.1)	
Great	0 (0.0)	11 (47.8)	
Total	22 (100)	23 (100)	

Table 5: Efficacy of oxybutynin on hyperhidrosis symptom improvement: NNT

Proportion of patients having symptom improvement on placebo (CER)	Proportion of patients having symptom improvement on oxybutynin (EER)	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
		$\frac{EER - CER}{CER}$	EER - CER	1/ABI
0.27	0.74	1.74	0.47	3

Safety of Oxybutynin

Known side effects of anticholinergic medication include diarrhea, dizziness, dry eyes, and dry mouth. Other side effects which were not seen in any of the reviewed studies include mydriasis, flushing, and rash.^{1,2,3,6}

In the van Houte et al.¹ study, of the participants who received 2.5 mg TID, 50% (n=2) reported adverse side effects, which included mild diarrhea and dizziness. Of the participants who received 5 mg TID, 37.5% (n=3) participants reported dry mouth and dry eyes which were moderate (n=2) or severe (n=1). No side effects were reported for the control group.

In the Wolosker et al.² study, headache (n=5), mild urinary retention (n=4), and dry mouth (n=98) were the only reported side effects at dosages of 10 mg oxybutynin QD, with dry mouth being the most reported side effect (70.5%). Dry mouth cases were further broke down to mild (22.3%), moderate (19.4%), or severe (28.7%). No other side effects were mentioned.

In Wolosker et al.³, dry mouth was the only noted side effect. Following administration of 10 mg oxybutynin QD (or placebo), moderate to severe dry mouth was reported in 34.8% of the treatment group and 9.1% of the control group (p-value of 0.038). Despite the prevalence of dry mouth, it was not an impeding factor in the use of oxybutynin as >50% of those from the treatment group in Wolosker et al.³ continued using oxybutynin after study completion.

Table 6 delineates the NNH for experiencing dry mouth as an adverse side effect to

treatment. For the studies being evaluated, the NNH indicated that for every 2-4 patients given oxybutynin for hyperhidrosis, one patient will develop moderate to severe dry mouth.

Table 6: Efficacy of oxybutynin on development of adverse events: NNH

	Proportion of patients having mod-severe dry mouth on placebo (CER)	Proportion of patients having mod-severe dry mouth on oxybutynin (EER)	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)
			$\frac{EER - CER}{CER}$	EER - CER	1/ARI
van Houte et al. ¹	0	0.38	0	0.38	3
Wolosker et al. ²	0	0.63	0	0.63	2
Wolosker et al. ³	0.09	0.35	2.89	0.26	4

DISCUSSION

Only the Wolosker et al. studies found statistical significance in the improvement of palmar hyperhidrosis with the use of prophylactic oxybutynin. This is perhaps because the van Houte et al. study used only normohidrotic participants whereas the Wolosker et al. studies used participants diagnosed with PH. The suspected pathologic difference in sympathetic outflow may provide a challenge when making comparisons between normohidrotic and hyperhidrotic individuals. Also, van Houte et al. measured severity of sweating after inducing exercise whereas the Wolosker et al. studies examined severity of spontaneous sweating as seen in PH. Although van Houte et al. was able to quantitatively measure the severity of palmar sweating, the results are not statistically significant for all the factors aforementioned.

The prevalence of anticholinergic side effects, specifically dry mouth, seemed somewhat inhibitory for continued use of oxybutynin; however, none of the studies lost participants due to adverse reactions. Furthermore, >50% of those from the treatment group in Wolosker et al.³ electively continued using oxybutynin after study completion. This would infer that the perceived benefit of taking oxybutynin exceeding that of the perceived risk of dry mouth.

Major limitations of all three studies included small sample size and a short study duration. Specifically, van Houte et al. had a significantly shorter intervention period of 2 days compared to the others of 6 and 12 weeks. Longer studies would provide data on the long-term efficacy and side effect profile of oxybutynin on palmar hyperhidrosis. Given that there is a known compensatory hyperhidrosis with sympathectomy surgery, it would be valuable to know if this same complication is seen with long-term use of anticholinergic medications. Despite dropout rates of 22% in Wolosker et al.² and 10% in Wolosker et al.³, results remained significant after an intention to treat analysis was applied.

CONCLUSION

Based on this systematic review, it can be concluded that there is improvement of palmar hyperhidrosis symptoms with 10 mg daily prophylactic oral oxybutynin. The greatest improvement in symptoms, seen in >80% of participants, was seen in those diagnosed with PH (Wolosker et al. studies) as there was no statistically significant improvement seen in the van Houte et al. study using normohidrotic individuals. The most burdensome side effect experienced in all studies included dry mouth; however, side effects were not severe enough for participants to abandon the study. Additionally, future studies are warranted to evaluate the long-term effects of prophylactic anticholinergic medications on hyperhidrosis symptom improvement as well as anticholinergic side effects as there is a concern for tachyphylaxis with continued use. Future studies should consider the addition of an objective means of measuring palmar hyperhidrosis, such as the TEWL or an iodine and starch test; however, given that hyperhidrosis is not life-threatening and results are measured in the patient's perception of symptom improvement, subjective measurements may be sufficient to determine the efficacy of oxybutynin for palmar hyperhidrosis.

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