CLINICS

CLINICAL SCIENCE

Randomized trial - oxybutynin for treatment of persistent plantar hyperhidrosis in women after sympathectomy

Altair da Silva Costa Jr.,[I] Luiz Eduardo Villaça Leão,[I] José Ernesto Succi,[I] Joao Aléssio Juliano Perfeito,[I] Adauto Castelo Filho,[II] Erika Rymkiewicz,[I] Marco Aurelio Marchetti Filho[I]

[I]Federal University of São Paulo, Paulista School of Medicine, Department of Thoracic Surgery, São Paulo/SP, Brazil. [II]Federal University of São Paulo, Paulista School of Medicine, Department of Infectious Diseases, São Paulo/SP, Brazil.

OBJECTIVE: Hyperhidrosis is a common disease, and thoracoscopic sympathectomy improves its symptoms in up to 95% of cases. Unfortunately, after surgery, plantar hyperhidrosis may remain in 50% of patients, and compensatory sweating may be observed in 70%. This clinical scenario remains a challenge. Our objective was to evaluate the effectiveness of oxybutynin in the treatment of persistent plantar hyperhidrosis and compensatory sweating and its effects on quality of life in women after thoracoscopic sympathectomy.

METHOD: We conducted a prospective, randomized study to compare the effects of oxybutynin at 10 mg daily and placebo in women with persistent plantar hyperhidrosis. The assessment was performed using a quality-of-life questionnaire for hyperhidrosis and sweating measurement with a device for quantifying transepidermal water loss. Clinicaltrials.gov: NCT01328015.

RESULTS: Sixteen patients were included in each group (placebo and oxybutynin). There were no significant differences between the groups prior to treatment. After oxybutynin treatment, there was a decrease in symptoms and clinical improvement based on the quality-of-life questionnaire (before treatment, 40.4 *vs.* after treatment, 17.5; $p = 0.001$). The placebo group showed modest improvement ($p = 0.09$). The outcomes of the transepidermal water loss measurements in the placebo group showed no differences ($p = 0.95$), whereas the oxybutynin group revealed a significant decrease ($p = 0.001$). The most common side effect was dry mouth (100% in the oxybutynin group *vs.* 43.8% in the placebo group; $p = 0.001$).

CONCLUSION: Oxybutynin was effective in the treatment of persistent plantar hyperhidrosis, resulting in a better quality of life in women who had undergone thoracoscopic sympathectomy.

KEYWORDS: Hyperhidrosis; Thoracic Surgery; Oxybutynin.

Costa Jr AS, Leão LE, Succi JE, Perfeito JA, Filho AC, Rymkiewicz E, et al. Randomized trial - oxybutynin for treatment of persistent plantar hyperhidrosis in women after sympathectomy. Clinics. 2014;69(2):101-105.

Received for publication on July 12, 2013; **First review completed on** July 27, 2013; **Accepted for publication on** July 27, 2013

E-mail: cirurgiatoracica@uol.com.br

Tel.: 55 11 5576-4295

INTRODUCTION

Hyperhidrosis is a relatively common disease, affecting nearly 1 to 3% of the population (1,2). This condition is characterized by excessive sweating in certain areas of the body, particularly the hands, face, feet and armpits. Thoracoscopic sympathectomy is effective for the treatment of palmar, axillary and craniofacial sweating. This procedure results in symptom improvement in 80% to 95% of cases (3). However, compensatory sweating occurs as a side effect, usually on the abdomen or back, in the majority of patients (70%) (4-6).

In patients who also present with plantar hyperhidrosis, foot sweating decreases after upper limb sympathectomy in approximately 50% of cases, and the mechanisms involved are not fully understood (7,8). This plantar sweating can be relatively severe, often becoming as troublesome as the original complaint, particularly in women who often wear open shoes (9).

Plantar hyperhidrosis can be treated by laparoscopic lumbar sympathectomy, but this invasive procedure risks an increase in compensatory hyperhidrosis (10,11). Other side effects can occur, such as vaginal dryness, retrograde ejaculation, impotence, neuralgia and constipation (8,10). Current assessment of hyperhidrosis is subjectively performed using questionnaires. The generic SF-36 assessment has been used; however, there is another questionnaire specifically validated for assessing hyperhidrosis that

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

No potential conflict of interest was reported.

DOI: 10.6061/clinics/2014(02)05

focuses on palmar hyperhidrosis (12,13). Transepidermal water loss (TEWL) can be measured as an objective assessment, but there have been few studies published on its use (14,15).

Because the sweat glands respond to cholinergic stimuli, there is a rationale for using anticholinergic drugs; nevertheless, published data on the use of oxybutynin are limited (16-19). A non-randomized, non-controlled study analyzed the effect of oxybutynin as an initial treatment for plantar hyperhidrosis, before thoracoscopic sympathectomy. The drug yielded good results and improved quality of life (QoL) (20). To the best of our knowledge, to date, there have been no studies evaluating the use of oxybutynin for the treatment of persistent hyperhidrosis in patients after thoracic sympathectomy.

The objective of this study was to evaluate the effectiveness of oxybutynin for the treatment of persistent plantar hyperhidrosis in women who had undergone thoracic sympathectomy.

MATERIALS AND METHODS

This study was a prospective, randomized, double blind clinical trial, with a control arm. Patient selection was performed by telephone interview and/or by e-mail. The selection criteria included female patients who had been submitted to G3 and G4 thoracic sympathectomy for palmar-plantar hyperhidrosis more than six months prior to the study. The included patients had persistent plantar hyperhidrosis that interfered with their usual activities. The exclusion criteria were pregnancy, breastfeeding, glaucoma, use of tricyclic drugs, BMI >25 Kg/m^2 and previous use of anticholinergic drugs. The patients were informed that oral dryness was a more frequent side effect than other symptoms. The study period was from March 2010 to June 2010.

The diagnosis of hyperhidrosis was based on each patient's clinical history, in addition to his or her social, emotional and psychological characteristics. Therefore, the assessment after treatment was performed subjectively, based on the patient's opinion and degree of satisfaction (20,21).

In this study, the subjective assessment was conducted using a validated QoL questionnaire for hyperhidrosis with scores ranging from 20 to 100 (13,14). This questionnaire measures the negative impact of hyperhidrosis. The higher the score is, the greater the impact on the patient's QoL. Given the 20- to 100-point variation in responses to the questionnaire, we applied the mathematical formula below to transform the score to a scale of 0 to 100, as in the SF-36, which has also been used to evaluate hyperhidrosis (Table 1) (12,22-24).

Formula for correction:

$$\frac{(Measured\ value - Minimum\ value)}{(Difference\ between\ the\ limits)} \times 100$$

Table 1 - Grades and values for the adjusted questionnaire on quality of life.

Questionnaire on quality of life	Adjusted questionnaire on quality of life	Grade
20-35	0-20	Excellent
36-51	21-40	Very Good
52-67	41-60	Good
68-83	61-80	Poor
84-100	81-100	Very Poor

Objective measurement of transpiration was performed with a device for assessing TEWL by evaporation. This ''Vapometer'' (Defin®, Finland) is a battery-operated portable device with a humidity sensor in a closed chamber that enables the measurement of evaporation on a 1-cm-diameter patch of skin. The unit of measurement is grams (g) per square meter (m^2) per hour (h) and ranges from 0 to 300 $g/m^2/h$ (14,15). Hyperhidrosis was evaluated in the feet, hands, back and abdomen.

The patients were randomized into two groups by drawing lots, and they received oxybutynin or placebo orally for 30 consecutive days. The patients were assessed before and after the intervention. Oxybutynin was started at 2.5 mg daily and increased to a maximum of 10 mg to prevent side effects (20).

During the statistical analysis, a power analysis showed that the sample size required was 28 patients divided evenly between the groups. The data for the analysis included the following: TEWL in the left foot: 60.37 $g/m^2/h$ (8); standard deviation (SD): 46.64 $g/m^2/h$ (8); number of controls per case: 1; and expected response: reduction of at least 30%. The necessary sample size was 14 patients per group. The Wilcoxon test was performed to analyze the numeric variables, and Fisher's exact test was used to compare the categorical variables. The significance level considered in all statistical tests was 0.05.

This study was approved by the ethics committee of the Federal University of São Paulo (number 0609/08). This clinical trial is registered at www.clinicaltrials.gov, number NCT01328015.

RESULTS

In total, 185 patients who had undergone sympathectomy at the G3 and G4 levels for the treatment of palm-plantar hyperhidrosis, more than six months prior to the study, were evaluated. Among these patients, 78 (42%) had persistent plantar hyperhidrosis, with discomfort in their daily activities. In this study, 32 randomly selected patients were enrolled and divided into two groups: oxybutynin and placebo (Table 2). The groups were matched, and no significant differences were found in any parameters before treatment. The null hypothesis was retained by an analysis of independent samples using the Mann Whitney U test, with a significance level of 0.05.

Table 2 - Descriptive analysis of the groups: age, months after sympathectomy and body mass index (mean and standard deviation).

Group	Age	Months after sympathectomy	Body mass index
Oxybutynin	25.5±6.1	60.4±31.9	21.3±1.3
Placebo	28±6.4	41.3±30.1	22.4±2.1

Subjective assessment: The questionnaire results for QoL are summarized in Table 3. In the placebo group, the improvement did not reach statistical significance, in contrast to the improvement in the oxybutynin group.

Objective assessment: TEWL showed a significant difference in the oxybutynin group and no changes after treatment in the placebo group (Table 4).

Table 3 - Oxybutynin and placebo groups - Means and standard deviations of the questionnaire results (measured and corrected) before and after the intervention.

Treatment		Before	After	*p*-value
Oxybutynin	QoL HH	52.3±11.5 ''Good''	34.0±9.5 ''Excellent''	0.001*
	A-QoL HH	40.4±14.4 ''Very Good''	17.5±11.9 ''Excellent''	0.001*
Placebo	QoL HH	47.8±13.0 ''Very Good''	46.5±12.2 ''Very Good''	0.099
	A-QoL HH	34.8±16.3 ''Very Good''	33.2±15.3 ''Very Good''	0.099

QoL: Quality-of-life questionnaire; HH: Hyperhidrosis; A: Adjusted.

Table 4 - Oxybutynin and placebo groups - Means and standard deviations of the transepidermal water loss measurements (g/m2/h) before and after the intervention.

Treatment		Before	After	*p*-value
Oxybutynin	Temperature (℃)	24.4±1.0	24.1±1.0	0.157
	R Ft (g/m2/h)	140.3±40.3	87.6±70.2	0.008*
	R Hd (g/m2/h)	61.7±43.9	28.6±20.5	0.001*
	Back (g/m2/h)	38.2±64.3	10.8±8.7	0.004*
	Abdomen (g/m2/h)	39.7±46.0	16.5±19.2	0.00*4
Placebo	Temperature (℃)	23.8±1.2	23.9±1.2	0.739
	R Ft (g/m2/h)	112.6±49.3	102.2±55.9	0.796
	R Hd (g/m2/h)	58.3±39.3	50.4±37.8	0.245
	Back (g/m2/h)	18.2±19.0	19.0±27.9	0.959
	Abdomen (g/m2/h)	24.0±18.1	26.8±31.4	0.501

R: Right; Ft: Foot; Hd: Hand; p: Wilcoxon test.

The most common side effect was dry mouth, which was present in all patients in the oxybutynin group and approximately half of the patients in the placebo group (43.8%; $p = 0.001$). The occurrence of other, less common side effects, such as constipation and drowsiness, was not significantly different between the groups (Table 5).

Table 5 - The presence of side effects in the placebo and oxybutynin groups.

Side effects	Placebo	Oxybutynin	*p*-value
Dry mouth	43.8%	100%	0.001*
Constipation	6.3%	31%	0.172
Drowsiness	6.3%	18%	0.6

Fisher's exact test.

DISCUSSION

The main goal of this study was to evaluate the effectiveness of oxybutynin in the treatment of persistent plantar hyperhidrosis and in the improvement of QoL in women who had undergone previous thoracic sympathectomy. The study sample consisted of a random selection of female patients presenting with disabling plantar hyperhidrosis after the operation.

A female target population was selected because of the meaningfulness of their symptoms. Although both genders experience compensatory sweating after sympathectomy, males tend to complain more about abdominal and back sweating. In contrast, females are more prone to being bothered by foot sweating (4,5,21,24). Further studies should be performed to evaluate such aspects and gender specificities.

We chose oxybutynin for the treatment of persistent plantar hyperhidrosis because of this drug's availability and low cost. The drug exerts anticholinergic effects via the muscarinic M3 receptor. Because the same receptor is expressed in the salivary glands, the most common side effect is dry mouth (3,9,16,18-20,25,26).

Oxybutynin has been widely studied for the management of overactive bladder (27,28). The idea of using an oral anticholinergic for the treatment of hyperhidrosis is not original, as it was first reported in 1951 (17). There are several clinical reports and case series on the use of oxybutynin to treat plantar sweating, but to the best of our knowledge, there have been no randomized clinical trials on the subject so far (16,18-20,26,29-32).

We used one of the recommended QoL questionnaires for hyperhidrosis (13). However, because its main focus is on hand sweating, this questionnaire does not address plantar hyperhidrosis, with only 2 of 20 questions asking about foot sweating. Only 10% of the questions in this survey address specific areas of the body other than the hands. Regarding the hands, there are six direct questions (related writing, performing crafts, holding objects, shaking hands, holding hands and touching). Therefore, the questionnaire does not adequately address either plantar hyperhidrosis or compensatory sweating. Such inadequate assessment may be the reason why the results of the survey used in our study showed a ''good'' or ''very good'' QoL despite the unequivocal discomfort reported by patients.

Because sweat is primarily composed of water, it can be measured based on TEWL (15,33). The device that we used provides a promising method for the objective measurement of sweat that has been used by cosmetics companies for new-product research (33,34). Measurement of TEWL has also been used to evaluate the therapeutic effect of botulin toxin type A on palmar hyperhidrosis (14,33-36). The method was sensitive because it managed to detect the decrease in palmar sweating and the compensatory sweating on the back and abdomen (14,15,24,34). The possibility of objective measurement for the evaluation of hyperhidrosis is promising, but unfortunately, the device is expensive and not widely available.

Surprisingly, in this study, we found a high subjective response in the placebo group. The ''beneficial effect'' of an inert substance in a randomized clinical trial is expected to be 35% on average, ranging from 10% to 60% (37). We acknowledge that anxiety and stress can exacerbate sweating in people with either normal sweating or hyperhidrosis. Such emotions might be mitigated by placebo. The present study showed that the use of an antimuscarinic agent yielded better results compared with placebo.

The presence of side effects differed between the groups. Dry mouth was the most frequent, occurring in all patients in the oxybutynin group and in 43.8% of patients in the

placebo group. Two other studies on oxybutynin in hyperhidrosis have reported dry mouth in 57% to 70% of cases (16,18,20). When used for urinary incontinence, oxybutynin causes dry mouth in 94% of patients (27,28). Such an incidence of side effects can be lessened by the use of transdermal oxybutynin (38) or other drugs, such as darifenacin, solifenacin and fesoterodine (27,28). Nevertheless, there are no studies on such promising drugs in hyperhidrosis.

Despite the limitations of the present study, such as the small sample size, the short follow-up and the limitations of the questionnaire, our results demonstrate the potential benefits of oxybutynin use in this clinical scenario.

In conclusion, this randomized clinical study showed that oxybutynin was effective and safe for the treatment of persistent plantar sweating in women who had undergone thoracic sympathectomy. Further studies will be needed to investigate new treatment regimens with this drug at lower doses and to minimize the frequency and intensity of the side effects.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge Paulo Francisco Guerreiro Cardoso, MD, for revising the manuscript.

■ AUTHOR CONTRIBUTIONS

Costa Jr. AS and Filho AC conceived the study, participated in its design and analyzed the data. Leão LE critically revised the manuscript for important intellectual content. Succi JE drafted the article and approved the final manuscript. Perfeito JA drafted the article. Rymkiewicz E and Filho MA collected the data.

■ REFERENCES

1. Leão LEV, de Oliveira R, Szulc R, Mari J de J, Crotti PLR, Gonçalves JJS. Role of video-assisted thoracoscopic sympathectomy in the treatment of primary hyperhidrosis. Sao Paulo Med J. 2003;121(5):191-7, http://dx.doi.org/10.1590/S1516-31802003000500003.
2. Strutton DR, Kowalski JW, PharmD, Glaser DA, Stang PE. US prevalence of hyperhidrosis and impact on individuals with axillary hyperhidrosis: Results from a national survey. J Am Acad Dermatol. 2004;51(2):241-8, http://dx.doi.org/10.1016/j.jaad.2003.12.040.
3. Wenzel FG, Horn TD. Nonneoplastic disorders of the eccrine glands. Am Acad Dermatol. 1998;38(1):1-17, http://dx.doi.org/10.1016/S0190-9622(98)70532-8.
4. Hsia JY, Chen CY, Hsu CP, Shai SE, Yang SS. Outpatient thoracoscopic limited sympathectomy for hyperhidrosis palmaris. Ann Thorac Surg. 1999;67(1):258-9, http://dx.doi.org/10.1016/S0003-4975(98)01208-9.
5. Gossot D, Galetta D, Pascal A, Debrosse D, Caliandro R, Girard P, et al. Long-Term Results of Endoscopic Thoracic Sympathectomy for Upper Limb Hyperhidrosis. Ann Thorac Surg. 2003;75(4):1075-9, http://dx.doi.org/10.1016/S0003-4975(02)04657-X.
6. Plas EG, Függer R, Herbst F, Fritsch A. Complications of endoscopic thoracic sympathectomy. Surgery. 1995;118(3):493-5, http://dx.doi.org/10.1016/S0039-6060(05)80364-2.
7. Rieger R, Pedevilla S. Retroperitoneoscopic lumbar sympathectomy for the treatment of plantar hyperhidrosis: technique and preliminary findings. Surg Endosc. 2007;21(1):129-35, http://dx.doi.org/10.1007/s00464-005-0690-8.
8. Loureiro M de P, de Campos JRM, Kauffman P, Jatene FB, Weigmann S, Fontana A. Endoscopic lumbar sympathectomy for women: effect on compensatory sweat. Clinics. 2008;63(2):189-96.
9. Henteleff HJ, Kalavrouziotis D. Evidence-based review of the surgical management of hyperhidrosis. Thoracic Surgery Clinics. 2008;18(2):209-16, http://dx.doi.org/10.1016/j.thorsurg.2008.01.008.
10. Jani K. Retroperitoneoscopic Lumbar Sympathectomy for Plantar Hyperhidrosis. J Am Coll Surg. 2009;209(2):e12-5, http://dx.doi.org/10.1016/j.jamcollsurg.2009.04.015.
11. Coelho M, Kondo W, Stunitz LC, Branco Filho AJ, Branco AW. Bilateral retroperitoneoscopic lumbar sympathectomy by unilateral access for plantar hyperhidrosis in women. J Laparoendosc Adv Surg Tech A. 2010;20(1):1-6, http://dx.doi.org/10.1089/lap.2009.0223.
12. Sayeed RA, Nyamekye I, Ghauri ASK, Poskitt KR. Quality of Life after Transthoracic Endoscopic Sympathectomy for Upper Limb Hyperhidrosis. Eur J Surg 1998;164(S1):39-42.
13. Milanez de Campos JR, Kauffman P, de Campos Werebe E, Andrade Filho LO, Kusniek S, Wolosker N, et al. Quality of life, before and after thoracic sympathectomy: report on 378 operated patients. Ann Thoracic Surg. 2003;76(3):886-91, http://dx.doi.org/10.1016/S0003-4975(03)00895-6.
14. Tetteh HA, Groth SS, Kast T, Whitson BA, Radosevich DM, Klopp AC, et al. Primary palmoplantar hyperhidrosis and thoracoscopic sympathectomy: a new objective assessment method. The Annals of Thoracic Surgery. 2009;87(1):267-74; discussion274-5.
15. Wolosker N, Ishy A, Yazbek G, Campos JR, Kauffman P, Puech-Leao P, et al. Objective evaluation of plantar hyperhidrosis after sympathectomy. Clinics. 2013;68(3):311-5, http://dx.doi.org/10.6061/clinics/2013(03)OA05.
16. Tupker RA, Harmsze AM, Deneer VHM. Oxybutynin therapy for generalized hyperhidrosis. Arch Dermatol. 2006;142(8):1065-6, http://dx.doi.org/10.1001/archderm.142.8.1065.
17. Hund M, Sinkgraven R, Rzany B. Randomised, placebo-controlled, double blind clinical trial for the evaluation of the efficacy and safety of oral methanthelinium bromide (Vagantin®) in the treatment of focal hyperhidrosis. J Dtsch Dermatol Ges. 2004;2(5):343-9, http://dx.doi.org/10.1046/j.1439-0353.2004.04765.x.
18. Schollhammer M, Misery L. Treatment of hyperhidrosis with oxybutynin. Arch Dermatol. 2007;143(4):544-5.
19. Kim W, Kii H, Yoon K, Yoo J. Treatment of generalized hyperhidrosis with oxybutynin in post-menopausal patients. Acta Derm Venereol. 2010;90(3):291-3.
20. Wolosker N, de Campos JRM, Kauffman P, Yazbek G, Neves S, Puech-Leão P. Use of oxybutynin for treating plantar hyperhidrosis. Int J Dermatol. 2013;52(5):620-3.
21. Araújo CA, Azevedo IM, Ferreira MA, Ferreira HP, Dantas JL, Medeiros AC. Compensatory sweating after thoracoscopic sympathectomy: characteristics, prevalence and influence on patient satisfaction. J Bras Pneumol. 2009;35(3):213-20.
22. Ciconelli R, Meinão I, Quaresma M, Ferraz M, Santos W. Tradução para a língua portuguesa e validação do questionário genérico de avaliação de qualidade de vida SF-36 (Brasil SF-36). Rev Bras Reumatol 1999;39(3):143-50.
23. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002;21(2):271-92, http://dx.doi.org/10.1016/S0167-6296(01)00130-8.
24. Wolosker N, Yazbek G, Milanez de Campos JR, Kauffman P, Ishy A, Puech-Leão P. Evaluation of plantar hyperhidrosis in patients undergoing video-assisted thoracoscopic sympathectomy. Clinical Autonomic Research. 2007;17(3):172-6, http://dx.doi.org/10.1007/s10286-007-0420-5.
25. Walling HW. Systemic therapy for primary hyperhidrosis: retrospective study of 59 patients treated with glycopyrrolate or clonidine. J Am Acad Dermatol. 2012;66(3):387-92, http://dx.doi.org/10.1016/j.jaad.2011.01.023.
26. van Houte M, Harmsze AM, Deneer VHM, Tupker RA. Effect of oxybutynin on exercise-induced sweating in healthy individuals. J Dermatolog Treat. 2008;19(2):101-4, http://dx.doi.org/10.1080/09546630701418754.
27. Novara G, Galfano A, Secco S, D Elia C, Cavalleri S, Ficarra V, et al. A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. Eur Urol. 2008;54(4):740-64, http://dx.doi.org/10.1016/j.eururo.2008.06.080.
28. Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. Eur Urol. 2008;54(3):543-62, http://dx.doi.org/10.1016/j.eururo.2008.06.047.
29. Mijnhout GS, Kloosterman H, Simsek S, Strack van Schijndel RJM, Netelenbos JC. Oxybutynin: dry days for patients with hyperhidrosis. Neth J Med. 2006;64(9):326-8.
30. Lefrandt JD, Maurer JM. Oxybutynin for hyperhidrosis. Neth J Med. 2007;65(9):356.
31. Bajaj V, Langtry JAA. Use of oral glycopyrronium bromide in hyperhidrosis. Br J Dermatol. 2007;157(1):118-21.
32. Wozniacki L, Zubilewicz T. Primary hyperhidrosis controlled with oxybutynin after unsuccessful surgical treatment. Clin Exp Dermatol. 2009;34(8):e990-1, http://dx.doi.org/10.1111/j.1365-2230.2009.03645.x.
33. Nuutinen J, Alanen E, Autio P, Lahtinen M-R, Harvima I, Lahtinen T. A closed unventilated chamber for the measurement of transepidermal water loss. Skin Res Technol. 2003;9(2):85-9, http://dx.doi.org/10.1034/j.1600-0846.2003.00025.x.
34. Krogstad A-L, Annika Skymne BS, Göran Pegenius BS, Elam M, Gunnar Wallin B. Evaluation of objective methods to diagnose palmar hyperhidrosis and monitor effects of botulinum toxin treatment. Clin Neurophysiol. 2004;115(8):1909-16, http://dx.doi.org/10.1016/j.clinph.2004.03.012.

35. Braune C, Erbguth F, Birklein F. Dose thresholds and duration of the local anhidrotic effect of botulinum toxin injections: measured by sudometry. Br J Dermatol. 2001;144(1):111-7.
36. Kreyden OP, Scheidegger EP. Anatomy of the sweat glands, pharmacology of botulinum toxin, and distinctive syndromes associated with hyperhidrosis. Clin Dermatol. 2004;22(1):40-4, http://dx.doi.org/10.1016/j.clindermatol.2003.12.029.
37. Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, Kerr CE, Jacobson EE, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ. 2008;336(7651):999-1003, http://dx.doi.org/10.1136/bmj.39524.439618.25.
38. Baldwin CM, Keating GM. Transdermal oxybutynin. Drugs. 2009; 69(3):327-37, http://dx.doi.org/10.2165/00003495-200969030-00008.