Botulinum Toxin Treatment of Social Anxiety Disorder With Hyperhidrosis: A Placebo-Controlled Double-Blind Trial

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Objective: Given the often prominent and persistent nature of hyperhidrosis in social anxiety disorder (SAD), to compare botulinum toxin type A to placebo for generalized SAD with hyperhidrosis, in combination with paroxetine.

Method: Adults with severe axillary hyperhidrosis who met DSM-IV criteria for generalized SAD were randomly assigned to receive 1-time, bilateral, intradermal injections with either botulinum toxin type A or placebo (50 units/axilla). All subjects also received 8 weeks of open-label treatment with paroxetine. The primary outcome measure was the Hyperhidrosis Disease Severity Scale (HDSS). Secondary measures included the Hyperhidrosis Impact Questionnaire, Brief Social Phobia Scale, Liebowitz Social Anxiety Scale, Social Phobia Inventory, and Sheehan Disability Scale. Enrollment occurred from June 2002 to July 2004.

Results: Forty subjects were randomly assigned to treatment and included in the analyses. Response rates were 75% (15/20) for botulinum toxin type A versus 15% (3/20) for placebo on the HDSS ($p < .001$). Botulinum toxin type A produced significantly more improvement in many daily activities that had been limited ($p < .01$), as well as greater improvement in work and social functioning and in overall disability ($p < .05$). Botulinum toxin type A was well tolerated, as was paroxetine.

Conclusion: Botulinum toxin is effective in reducing hyperhidrosis disability and limitations in everyday activities when given in association with paroxetine to subjects with SAD. While further assessment of botulinum toxin type A in SAD is recommended, including a trial of botulinum toxin type A monotherapy, the results suggest that this well-tolerated treatment deserves further consideration in overall management of SAD accompanied by hyperhidrosis.

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Focal hyperhidrosis affects 2.8% of the U.S. population[1]; is persistent, disabling, and distressing; and leads to devastating emotional, social, and functional problems.[2,3] Axillary hyperhidrosis affects 1.4% of the population, 32% of whom find it is barely tolerable and that it frequently interferes with daily activities. In the most severely affected group, 64% have marked emotional problems.[1] Individuals who suffer from hyperhidrosis often go to great lengths to obtain relief, including overseas travel for surgical intervention with endoscopic thoracic sympathectomy. For psychiatrists, hyperhidrosis has particular relevance since it is a common feature of social anxiety disorder (SAD), occurring in as many as 32% at a level of moderate or severe intensity.[4] In one survey, compared with SAD alone, hyperhidrosis with SAD was associated with greater disability and severity of symptoms with, at best, a modest response to treatments that are otherwise quite effective for SAD.[4]

A recently popularized anticholinergic treatment, botulinum toxin, may hold particular promise in treating hyperhidrosis. Botulinum toxin type A (BT-A) inhibits the release of acetylcholine from presynaptic nerve endings and blocks sympathetic cholinergic pathways that innervate sweat glands.[5,6] Two large trials have determined that botulinum toxin robustly reduces primary axillary hyperhidrosis, relative to placebo, with good tolerability and sustained benefit.[5,6] Moreover, quality of life improves after treatment with botulinum toxin.[7]

In light of these considerations, we conducted a randomized, double-blind, placebo-controlled trial of BT-A versus placebo in subjects with SAD accompanied by severe hyperhidrosis. Since we were uncertain whether BT-A alone would have appreciable therapeutic benefit in SAD beyond simply reducing hyperhidrosis, we evalu-

ated BT-A versus matching placebo, in combination with paroxetine, a known effective pharmacologic treatment for SAD.[8–11]

METHOD

Overall Design

In this single-site, randomized, double-blind, placebo-controlled study, BT-A with paroxetine was compared with placebo with paroxetine. Hyperhidrosis severity was measured using the self-rated Hyperhidrosis Disorder Severity Scale (HDSS).[1] After a screening assessment, eligible subjects returned for a baseline visit, at which time randomly assigned treatment was administered and open-label treatment with paroxetine was initiated. Follow-up visits took place every 2 weeks, except for visits 1 week after baseline and after the final dose of paroxetine was taken. Enrollment commenced June 13, 2002, and was completed by July 28, 2004. The study was approved by the Duke University Medical Center Institutional Review Board in conformity with the principles of the Declaration of Helsinki, and all subjects provided written informed consent after full explanation of the study procedures and of alternative treatment options.

Sample

Subjects were recruited through advertisement. Inclusion criteria were as follows: age 18 to 65 years; a primary DSM-IV diagnosis of generalized SAD, as confirmed by structured interview[12]; a score of 20 or greater on the Social Phobia Inventory (SPIN)[13]; axillary hyperhidrosis of at least moderate intensity on the HDSS at screen or baseline; fluency in English; and provision of informed consent. Exclusion criteria were as follows: lifetime history of psychosis, bipolar disorder, or organic brain disorder; alcohol or other substance use disorder within the last 6 months; primary diagnosis of another Axis I disorder; concurrent use, or use within 7 days of randomization, of cholinomimetics, anticholinergic drugs, prescription antiperspirants and deodorants, and herbal or other treatments for hyperhidrosis (use of over-the-counter deodorants and antiperspirants was permitted except within 24 hours prior to the randomization treatment visit); concomitant use of medications with psychoactive properties during the study, including prescription drugs, over-the-counter medications, herbs, or dietary supplements; previous treatment with botulinum toxin for hyperhidrosis; history of sympathectomy or surgical debulking of sweat glands; and uncontrolled hyperthyroidism.

Treatment Administration

Assignment to treatment with BT-A or placebo was determined by a computer-generated randomization code. Treatment was administered by the study dermatologist (J.L.C.) at a facility remote to the clinic where psychiatric assessments were conducted. Botulinum toxin type A (Botox, manufactured by Allergan, Inc.; Irvine, Calif.) or matching placebo was administered in a series of approximately 25 intradermal injections to each axilla (total of 50 units per axilla) according to an established protocol. Botulinum toxin type A and matching placebo were provided in the form of white powders, each of which was dissolved in 4 mL of unpreserved 0.9% sterile normal saline as per the manufacturer's recommendations and constituted immediately prior to administration. The solutions were prepared by the study nurse, who was unblinded to the treatment assignment. After the BT-A or placebo was prepared, the unlabeled syringes were given to the treating physician, who had no knowledge of the particular contents of any syringe used in the study.

All subjects received open-label treatment with paroxetine and were instructed to begin the medication after receiving the injections. Immediate-release paroxetine (paroxetine IR) was given to the first 4 patients at a dosage of 10 mg/day, increasing up to 20 mg/day after 1 week. After the approval of controlled-release paroxetine (paroxetine CR) for SAD, this formulation was given to the remaining 36 subjects, at an initial dosage of 12.5 mg/day, increasing to 25 mg/day after 1 week. The dose could be lowered if troublesome adverse events emerged. Because assessment of BT-A was the primary goal of this study, our dosing strategy was to administer paroxetine at a minimally effective dose, in order to minimize the likelihood of confounding adverse events or possible attrition from side effects.

All staff involved with patients remained blinded to treatment assignment throughout the study, with the exception of the study nurse who prepared the syringe containing the assigned treatment. The study nurse prepared the BT-A or placebo syringes, but no information that would affect the blinded nature of the study was ever provided to the patient, to the treating physician, or to other study staff.

Assessments

The primary outcome was based upon the number of responders on the HDSS,[1] which rated the extent to which sweating was bothersome or distressing to the patient, from never (1) to intolerable (4). Additional aspects of hyperhidrosis were evaluated by means of the Hyperhidrosis Impact Questionnaire (HHIQ),[14] which assesses limitations in each of the following activities/situations due to hyperhidrosis and in the total of all: at work, being in public places, meeting or being introduced to people for the first time, on family occasions or with friends, when shaking hands, in developing personal relationships, in sexual activities, and in sport. Each item is scored from 0 to 4, where 0 = not limited, 1 = somewhat, 2 = moderately, 3 = quite a bit, and 4 = extremely limited. For these 8 items, the total score can range from 0 to 32.

Table 1. Sample Characteristics at Baseline[a,b]

Characteristic	Botulinum Toxin (N = 20)	Placebo (N = 20)
Demographics		
Male, N (%)	9 (45)	10 (50)
Nonwhite, N (%)	9 (45)	9 (45)
Married, N (%)	7 (35)	11 (55)
Age, y	30.8 (7.4)	34.4 (11.0)
Hyperhidrosis measures		
Hyperhidrosis severity (HDSS)	3.1 (0.4)	3.3 (0.5)
Limitation of activities (HHIQ)		
Total	13.2 (6.3)	16.1 (7.2)
Average item score	1.6 (0.8)	2.0 (0.9)
Social anxiety measures		
Brief Social Phobia Scale[c]		
Total	41.1 (8.4)	41.1 (10.3)
Physiologic subscale	7.3 (2.8)	7.9 (2.5)
Liebowitz Social Anxiety Scale	75.5 (22.8)	79.0 (21.3)
Social Phobia Inventory		
Total	39.8 (11.2)	41.6 (11.0)
Physiologic subscale	8.7 (3.7)	10.4 (3.2)
Sheehan Disability Inventory		
Total	13.1 (4.7)	14.9 (6.5)
Work subscale	4.7 (2.0)	4.8 (2.2)
Family subscale	3.0 (2.0)	3.9 (2.5)
Social subscale	5.4 (1.8)	6.1 (3.0)

[a]Data are shown as mean (SD) unless otherwise noted. Medians (25th, 75th quartiles) given in text.
[b]All between-group comparisons were nonsignificant.
[c]N = 19 for placebo, as a BSPS assessment was missing for 1 subject at baseline.
Abbreviations: HDSS = Hyperhidrosis Disease Severity Scale, HHIQ = Hyperhidrosis Impact Questionnaire.

Because some responses were not completed at baseline (e.g., the item of work limitation for someone who was not employed), they were recorded as "missing," and we therefore reported the total as an average score for each completed item. Other questions addressed on the HHIQ were the length of time spent per day in treating hyperhidrosis; frequency of changing clothes, showering, or bathing; number of days with restricted work attendance; and the influence of hyperhidrosis on work effectiveness.

Additional secondary outcomes consisted of final on-treatment scores for the Brief Social Phobia Scale (BSPS),[15] the SPIN,[13] their physiologic subscales and individual sweating item scores, the Liebowitz Social Anxiety Scale (LSAS),[16] and the Sheehan Disability Scale (SDS)[17] and its component parts (i.e., work, social, and family function).

Objectives and Statistical Analysis

We hypothesized that greater improvement in axillary hyperhidrosis would be reported by subjects who received BT-A than by those who received placebo. The sample size (N = 40) was determined a priori based upon assumed response rates of 65% for BT-A and 20% for placebo, which yielded a power of 0.85 to detect a difference at alpha = 0.05. Chi-square or Fisher exact tests were used to compare proportions of subjects who responded or remitted. Response was predefined according to a convention of a reduction of at least 2 points on the HDSS relative to an entry criterion score at screening or baseline. Remission was defined post hoc as a final score of 1 on the HDSS (i.e., sweating is never noticeable and never interferes with daily activities) and as a 70% or greater reduction in score from baseline on secondary measures. Continuous measures were analyzed by analysis of covariance (ANCOVA). On measures where data were not normally distributed, nonparametric statistical tests were performed. A last-observation-carried-forward analysis was conducted on all 40 randomly assigned subjects, including 1 subject in the BT-A group who failed to return after baseline. All tests were 2-tailed, with significance attained at $p < .05$.

Table 2. Hyperhidrosis Disease Severity Scale Ratings at Baseline and Final Visit

Rating	Botulinum Toxin (N = 20), N	Placebo (N = 20), N	χ^2	df	p Value
Baseline			2.80	2	NS
Tolerable	2	3			
Barely tolerable	15	10			
Intolerable	3	7			
Final visit			15.5	3	< .01
Barely noticeable	14	2			
Tolerable	2	9			
Barely tolerable	3	6			
Intolerable	1	3			

Abbreviation: NS = not significant.

RESULTS

Sixty-two potential subjects were screened, 22 of whom failed to meet study criteria. Of 40 randomly assigned subjects (N = 20 in each group), 5 withdrew from the BT-A group prematurely due to side effects, while 2 withdrew from the placebo group due to lack of efficacy or loss to follow-up. Thirty-three subjects (BT-A, N = 15; placebo, N = 18) completed the 8-week treatment trial.

The mean dosage of paroxetine CR at final visit was 20 mg/day in both the BT-A (N = 18) and placebo (N = 18) treatment groups. For paroxetine IR, the mean dosage was 20 mg/day in the BT-A group (N = 2), compared with 12.5 mg/day in the placebo group (N = 2).

Sample baseline demographic characteristics and symptom severity are shown in Table 1. No differences were found between the treatment groups at baseline.

Impact of Treatment on Hyperhidrosis

The impact of hyperhidrosis at baseline and at the final visit is shown in Table 2. A statistically significant difference was found at the final visit in favor of BT-A ($p < .01$). On the primary outcome, the HDSS, the number of responders was 15 (75%) for BT-A and 3 (15%) for placebo ($\chi^2 = 14.5$, df = 1, $p < .001$). Among HDSS

Table 3. Impact of Hyperhidrosis on Functioning in Various Situations by Treatment Group at Baseline and Final Visit

HHIQ Item[b]	Botulinum Toxin, Median (Q1, Q3)	Placebo, Median (Q1, Q3)	p Value[a] Final Visit	p Value[a] Change (baseline to final visit)
At work				
Baseline	2 (1, 3)	2 (2, 3)		
Final visit	0 (0, 0)	1 (0, 2)	< .01	.07
Being in public places				
Baseline	2 (1, 3)	3 (1, 4)		
Final visit	0 (0, 1)	1 (0, 3)	< .01	.09
When meeting or being introduced to people for the first time				
Baseline	2 (1, 3)	3 (2, 4)		
Final visit	0 (0, 1)	1 (0.5, 3)	< .01	.07
On family occasions or with friends				
Baseline	1 (0, 3)	2 (0.5, 3)		
Final visit	0 (0, 0)	1 (0, 2)	< .01	NS
When shaking hands				
Baseline	1 (1, 2)	1.5 (0, 2)		
Final visit	0 (0, 0)	1 (0, 1)	< .05	< .01
In developing personal relationships				
Baseline	2 (1, 2)	2 (1, 3)		
Final visit	0 (0, 0)	1 (0.5, 2.5)	< .001	NS
In sexual activities				
Baseline	1 (0, 2)	2 (0, 3)		
Final visit	0 (0, 0)	0 (0, 2.5)	< .01	NS
In sports				
Baseline	1 (0, 2)	1 (0, 2.5)		
Final visit	0 (0, 1)	0 (0, 2.5)	NS	NS
Average item score				
Baseline	1.6 (1.1, 2.3)	2.3 (1.3, 2.8)		
Final visit	0 (0, 0.6)	0.8 (0.3, 2.2)	.001	.09

[a]Kruskal-Wallis analysis of variance.
[b]Subjects were asked the following question from the HHIQ to which each item refers: "How limited do you feel you *currently* are in each of these activities/situations due to your hyperhidrosis?" HHIQ items were rated as follows: 0 = not limited, 1 = somewhat limited, 2 = moderately limited, 3 = quite a bit limited, 4 = extremely limited.
Abbreviations: HHIQ = Hyperhidrosis Impact Questionnaire, NS = not significant, Q1 = 25th quartile, Q3 = 75th quartile.

responders, rates of remission were 70% for BT-A (N = 14) versus 5% for placebo (N = 1) ($\chi^2 = 15.5$, df = 1, $p < .001$).

On the HHIQ, for which all item scores were non-normally distributed, no significant differences were found at baseline. For the final visit, statistically significant differences in favor of BT-A were noted on measures of limitation for working, being in public places, being introduced or making introductions to people for the first time, being with family or friends, shaking hands with someone, developing personal relationships, and participating in sexual activities, and for the total score (all $p < .05$), but were not significant for activities related to sport (Table 3). On the change in HHIQ scores from baseline to the final visit, a significant difference in favor of BT-A was noted for 1 item (i.e., shaking hands), while 4 items showed a trend toward significance. No differences were found with regard to length of time spent per day treating hyperhidrosis, frequency of changing clothes or taking a shower or bath, or number of days in which work attendance was down by 50%. However, a statistically significant difference was found in favor of BT-A on effectiveness at work ($p < .05$) at final visit and for change on this measure during treatment ($p < .01$).

Social Anxiety Symptoms

On the social phobia measures, no significant differences were found at posttreatment, when comparing either the mean (SD) or the median (25th and 75th quartiles) scores on the BSPS, LSAS, and SPIN scales. There were 20 subjects per treatment group for all comparisons except for the BSPS, for which 1 value was missing at baseline. Final mean (SD) and median (25th, 75th quartiles) scores on the BSPS by treatment group were as follows: BT-A, 20.6 (18.2) and 14 (4.5, 36.5); placebo, 22.5 (12.6) and 23.5 (13, 32.5). On the LSAS, mean and median posttreatment scores were as follows: BT-A, 39.2 (33.0) and 45.5 (5, 64); placebo, 45.9 (26.3) and 49.5 (31, 66). For the SPIN, final mean and median scores were as follows: BT-A, 18.2 (14.8) and 15 (3.5, 31.5); placebo, 22.8 (15.6) and 23 (9, 33.5).

No significant differences were noted between the treatment groups with regard to remission rates on the BSPS (BT-A, 45% [N = 9] vs. placebo, 26% [N = 5]),

LSAS (BT-A, 40% [N = 8] vs. placebo, 25% [N = 5]), or SPIN (BT-A, 35% [N = 7] vs. placebo, 35% [N = 7]).

Disability

The following posttreatment differences between BT-A and placebo were found on the SDS. With respect to total SDS score, mean (SD) and median (25th, 75th quartile) values for BT-A (N = 19; 1 missing baseline value) were 6.3 (4.9) and 4 (3, 8), compared with 10.1 (6.8) and 7 (5.5, 15) for placebo (N = 20) ($p < .05$, Kruskal-Wallis). On the SDS work impairment item, posttreatment scores for BT-A were 2.2 (2.0) and 1 (1, 2) while, for placebo, they were 3.4 (2.5) and 2.5 (1, 5) ($p < .05$, Kruskal-Wallis). On social functioning, posttreatment scores showed a nonsignificant difference in favor of BT-A, with scores for BT-A of 2.6 (2.1) and 2 (1, 3) and for placebo of 4.0 (2.6) and 3 (2, 6) ($p < .06$, Kruskal-Wallis). Regarding impairment at home or in family life, a nonsignificant difference was also noted in favor of BT-A, with BT-A scores of 1.6 (1.2) and 1 (1, 2) versus placebo scores of 2.6 (2.3) and 2 (1, 3), respectively ($p < .08$, Kruskal-Wallis).

No significant differences were noted between the treatment groups with regard to remission rates on the SDS total score (BT-A, 32% [N = 6] vs. placebo, 10% [N = 2]). However, significant differences were observed on both the SDS work functioning (BT-A, 39% [N = 7] vs. placebo, 10% [N = 2]; $\chi^2 = 4.04$, df = 1, $p < .05$) and SDS social functioning items (BT-A, 47% [N = 9] vs. placebo, 15% [N = 3]; $\chi^2 = 4.79$, df = 1, $p < .05$). No difference was found on the home and family life item (BT-A, 32% [N = 6] vs. placebo, 20% [N = 4]).

Side Effects

No serious or unexpected side effects occurred from BT-A or placebo. Five subjects (12.5%) withdrew because of side effects presumed related to paroxetine (headache [N = 2]; palpitations [N = 1]; sedation [N = 1]; nausea, insomnia [N = 1]). The most commonly observed side effects were as follows: insomnia (BT-A, 30% [N = 6] vs. placebo, 15% [N = 3]), drowsiness (BT-A, 15% [N = 3] vs. placebo, 20% [N = 4]), nausea (BT-A, 10% [N = 2] vs. placebo, 20% [N = 4]), and dry mouth and headaches (15% [N = 3] each group). Increased sweating was reported by 3 subjects (15%) in the placebo group.

DISCUSSION

Botulinum toxin produced greater benefit than placebo in this cohort of subjects with severe generalized SAD, all of whom were treated with paroxetine. Not only was the primary hypothesis confirmed (i.e., greater benefit on distress from axillary hyperhidrosis), but significantly greater improvement was noted in work and social functioning on the SDS and HHIQ measures. Situation-specific questions of the HHIQ revealed that botulinum toxin was associated with lifting of limitations in numerous areas of everyday function: working, being in public places, making introductions to new people, family occasions or being with friends, shaking hands, developing new relationships, and participating in sexual activities, although these differences were less evident on change scores. From this, we can readily appreciate the extent to which severe focal hyperhidrosis in SAD adversely impacted the lives of our subjects. Given the acknowledged persistence and treatment-refractory nature of hyperhidrosis in SAD,[4,18] we contend that it may warrant further attention in the overall management of SAD. In addition, further work is needed to identify the prevalence of comorbid SAD in patients with hyperhidrosis presenting for dermatologic evaluation.

One issue to be considered is whether paroxetine may exacerbate sweating, the neuroendocrine regulation of which is complex.[19] Eccrine gland innervation, which is cholinergic in nature, originates from the hypothalamic preoptic sweat center. However, significant cortical input is present for hypothalamic regulation of palmar and plantar sweating, but not of perspiration elsewhere. At all events, it is likely that focal hyperhidrosis is related to dysfunction of hypothalamic nuclei, prefrontal areas, or their connections.[20,21] Serotonin (5-HT) is a key hypothalamic thermoregulator, and activity at this site may be altered through reduced 5-HT activity, as well as by imbalance between 5-HT_{1A} and 5-HT_2 receptors.[22] Acute and chronic administration of selective serotonin reuptake inhibitor (SSRI) drugs can either enhance or reduce thermoregulatory response in ways that are time- and dose-dependent.[23–26] Given that altered 5-HT function is established in SAD,[27] it is conceivable that an additional contribution to the neurobiology of SAD comes from 5-HT–related dysregulation of the hypothalamic preoptic area, over and above the neuroendocrine alterations that have been described as integral to SAD.[28]

As far as paroxetine is concerned, 3 subjects (15%), all of whom received placebo, noted substantial intensification of sweating. On the other hand, there was an overall reduction in sweating associated with paroxetine, as noted by reductions in sweating item scores on the SAD measures—from 3.4 to 1.7 on the BSPS and from 3.3 to 1.6 on the SPIN. Thus, while paroxetine alone is associated with a modest reduction in hyperhidrosis, in a minority it is made worse, and, overall, this modest reduction is less than what was found with the combination of paroxetine and botulinum toxin. Our results suggest that this combination represents a promising therapeutic approach in the management of SAD with hyperhidrosis. It would be of considerable interest to determine whether botulinum toxin alone is a useful treatment of SAD with marked hyperhidrosis.

From a practical perspective, the duration of efficacy of botulinum toxin for axillary hyperhidrosis is about 7 months, though some patients may experience benefits for up to 16 months or more. An important yet unanswered question is if social anxiety remains under control, does hyperhidrosis return to the baseline level over time or are the gains maintained during continued SSRI treatment for SAD? The cost of treatment is approximately $1500 or more, depending on the community and the physician's experience and reputation. Other, less invasive treatments for axillary hyperhidrosis include topical antiperspirants and anticholinergic medications, though their effectiveness is limited and treatment can be associated with troublesome side effects. While botulinum toxin is approved for the treatment of axillary hyperhidrosis, the treatment may help to alleviate excessive perspiration in palmar and plantar regions. However, treatment to these areas is more complex, requiring nerve blocks and more cumbersome anesthetic techniques.

Several limitations of our study must be acknowledged. Firstly, we were unable to determine the possible effect of having one staff member who was aware of the treatment assigned. Whether in some way this information was subtly or covertly communicated to others cannot be completely ruled out, although all reasonable efforts were made to avoid this happening. Even if it had occurred, it would be a surprise if outcome were selective for some ratings more than others. In addition, the magnitude of the difference in response rates between botulinum toxin and placebo was below that reported in a major clinical trial.[2] The second limitation related to the relatively low dose of paroxetine. Higher doses may have led to greater benefit overall, including in hyperhidrosis; reduced benefit because of side effects or greater attrition, which is as high as 24% with paroxetine in SAD[10]; or no difference in outcome. The use of a subjective measure for the primary outcome may also be considered a limitation. Objective measures of sweating diminution are available (e.g., visual estimated change in starch-iodine staining patterns, volumetric analyses), and inclusion of such measures would have enhanced the rigor of the study design. However, due to logistical and financial considerations, we decided to use a subjective measure, the HDSS, as the primary outcome in this study. Lastly, the results reported in this study cannot be generalized to other formulations of botulinum toxin or to other botulinum toxin serotypes.

Our results are applicable only to that subgroup of men and women whose generalized SAD is accompanied by significant axillary hyperhidrosis that often presents a treatment challenge, but they do extend the potential application of botulinum toxin into a psychiatric population. However, we suggest that the administration of botulinum toxin be undertaken only by physicians with proper training in these procedures. We encourage further work with botulinum toxin in social anxiety. Moreover, for future trials in this area, we recommend a design modification, with reconstitution of the study treatment by a staff member who has no contact with subjects and no other role in the study. We also recommend that consideration be given to studying botulinum toxin as monotherapy in this population.

Drug name: paroxetine (Paxil, Pexeva, and others).

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