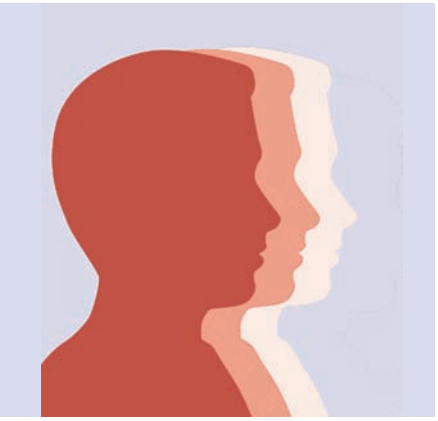

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ORIGINAL RESEARCH

Evaluating the Efficacy of Endoscopic Thoracic Sympathectomy for Generalized Social Anxiety Disorder with Blushing Complaints: A Comparison with Sertraline and No Treatment—Santiago de Chile 2003–2009

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ABSTRACT

Objective: No study has yet compared the efficacy of endoscopic thoracic sympathectomy for treating facial blushing with other treatment or no treatment. We conducted a prospective, observational, open-label, clinical study to compare endoscopic thoracic sympathectomy for blushing with generalized social anxiety disorder versus sertraline treatment and no treatment.

Method: Three-hundred and thirty consecutive patients seeking treatment for their blushing were assessed by psychiatric interview and patient-rated scales. The Brief Social Phobia Scale was the primary outcome measure. Patients meeting *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition* criteria for generalized social anxiety disorder, scoring 20 points or more in the Brief Social Phobia Scale and 19 points or more in the Social Phobia Inventory were considered eligible and followed up for a mean of 11 months (range 1–64) after endoscopic thoracic sympathectomy or initiation of sertraline.

Results: At baseline, 97 percent of the endoscopic thoracic sympathectomy-treated group, 87 percent of the sertraline-treated group, and 78 percent of the nontreated group rated their blushing as being "severe" or "extreme." At follow up, 16 percent of endoscopic thoracic sympathectomy-treated patients, 32 percent of sertraline-treated patients, and 57 percent of untreated patients reported this degree of

blushing. At endpoint, Brief Social Phobia Scale total scores exhibited a greater decline with either treatment than with no treatment. Nonetheless, in comparison to no treatment, only the results obtained with endoscopic thoracic sympathectomy achieved statistical significance (p=0.003). Compensatory sweating occurred in 99 percent of patients who underwent endoscopic thoracic sympathectomy. High degrees of satisfaction with treatment were reported by 89 percent of patients undergoing endoscopic thoracic sympathectomy and by 59 percent of patients taking medication.

Conclusion: Endoscopic thoracic sympathectomy was associated to a greater reduction of blushing and Brief Social Phobia Scale scores, and higher degrees of satisfaction with treatment, in comparison to sertraline and no treatment.

INTRODUCTION

Charles Darwin, in his book *The Expression of the Emotions in Man and Animals,* described blushing as "the most peculiar and the most human of all expressions."[1] He devoted an entire chapter to the topic, a phenomenon he described as consisting of a reddening of the face (especially the cheeks), ears, and neck, and occasionally other parts of the body, brought on by the "thinking of what others think of us." In a more recent review, blushing is defined as a "spontaneous reddening or darkening of the face, ears, neck, and upper chest that occurs in response to perceived social scrutiny or evaluation."[2] Contrary to reddening of the face caused by conditions such as heat, alcohol, or specific dermatological disease (e.g., rosacea), which should be called flushing as it is devoid of a psychological component, blushing is accompanied by feelings of embarrassment and disruption of mental function. Though facial blushing has been described as a specific symptom of social phobia, not all individuals afflicted with this condition complain of blushing. Thus, one study reported that only up to 50 percent of patients with social phobia say they blush frequently.[3]

Elsewhere, we have used the term *pathological blushing* to differentiate between normal, expected, nondebilitating blushing and too-easily triggered facial blushing that causes the person to suffer and interferes with his/her usual level of performance and/or social interactions.[4] The distinction is justified because while the experience of clinicians shows that abnormal blushing commonly occurs with social phobia, chronic blushers can suffer certain symptoms of social phobia without fulfilling all the criteria required for the diagnosis.

Thoracoscopic sympathectomy was first described in 1942 by Hughes,[5] and remained rare until the introduction of endoscopic thoracic sympathectomy (ETS) in the 1980s. Since then, it has become the preferred method of treatment of primary hyperhidrosis of the palms and hands. More recently, the possibility of using ETS to treat facial blushing has been raised, serendipitously borne from patients reporting incidental relief from facial blushing following ETS for hyperhydrosis.[6] Generalized social anxiety disorder (GSAD) sufferers, who, compared to controls, are more likely to blush,[7] exhibit heightened arousability as indicated by higher heart rates,[7] which is consistent with the notion that blushing is mainly caused by cervical sympathetic outflow.

Up to now, several follow-up studies report on the efficacy of ETS for treating facial blushing and even social phobia.[6,8–14] However, a recent review showed that so far no study has yet provided clear inclusion and exclusion criteria for patients, nor has any study compared ETS with other treatments or with no treatment or employed control samples.[15] The aim of this study was to carry out the first, to our knowledge, comparison of the efficacy of ETS for blushing with social anxiety disorder versus some other form of treatment. Although pharmacological treatments have not been tested specifically for social anxiety disorder with blushing complaints, for the comparison we chose sertraline because so far the only double-blind, placebo-controlled evidence for the efficacy of any treatment for blushing comes from a study by Connor et al[16] with this particular selective serotonin reuptake inhibitor (SSRI). Besides sympathetic activation,[7,17] there is some evidence that the serotonin system is also involved in the mediation of blushing. Cutaneous flushing in patients with serotonin-related carcinoid syndrome supports this view.[18]

In addition, we aimed at comparing the results of ETS with the results of no treatment, something that previous studies on blushing have not attempted to accomplish.

METHODS

Source of patients. A consecutive series of 330 patients seeking treatment for their blushing was assessed between August 2003 and November 2009. Most of these patients had consulted a thoracic surgeon (C.S.) and inquired about ETS following an internet search. They were then referred to one of the researchers (psychiatrist E.J.) by the surgeon in the context of an evaluation to improve the preoperative screening and to assist patients in considering alternative pharmacological treatment with sertraline or psychological treatment before pursuing surgery. A small minority of patients had sought help directly from the above mentioned psychiatrist after reading either the Spanish version[19] of a book of his authorship[4] or related press articles.

Procedure. This is a prospective, observational, open-label clinical study. All patients were blindly evaluated at baseline by means of measures commonly used to assess social anxiety. The Brief Social Phobia Scale (BSPS)[20] was the

primary outcome measure. It is an 18-item scale assessing GSAD symptoms of fear (7 items), avoidance (7 items), and physiological arousal (4 items: blushing, palpitations, trembling and sweating). Although this instrument was devised as a clinician-administered scale for assessing severity and treatment response in social phobia, we used it as a self-report measure. Pande et al[21] have previously used the BSPS in a somewhat similar form, requesting patients to enter their own ratings. Secondary outcome measures were also patient-rated measures: the self-report version of the Liebowitz Social Anxiety Scale (LSAS),[22] the Social Avoidance and Distress Scale (SADS),[23] and the Social Phobia Inventory (SPIN).[24] Subsequently, one of the researchers (E.J.), who was blind for the results of the scales, assessed all patients through a comprehensive clinical psychiatric interview.

Patients were considered eligible for the study if they fulfilled the following criteria: 1) were deemed to have a primary *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*)[25] diagnosis of GSAD; 2) rated the severity of the "blushing" item of the BSPS as 2 or more on a 5-point Likert-type scale (range 0=none to 4=extreme); 3) obtained a BSPS total score of 20 or more and a SPIN total score of 19 or more; 4) chose treatment with either T2 or T2-T3 ETS (i.e., second or second and third costa), if there were no contraindications to the procedure, or sertraline; and 5) had given informed consent to participate in the study (for those under 18 years of age additional consent of one of the parents was required).

A total BSPS score of 20 or more has been judged to reflect social phobia symptoms severe enough to warrant treatment[21] and a total SPIN score of 19 or more distinguishes between individuals with and without SAD with a diagnostic efficiency of 79 percent.[24]

Exclusion criteria were as follows: 1) being on antidepressants in the previous six months, 2) severity of current depressive symptoms clinically judged to be greater than mild, 3) considered to be suffering from flushing rather than blushing by one of the physicians involved in the study, and 4) chose treatment with another type of surgical sympathetic blocking (i.e., T2-T3-T4 ETS or ETS by clamping).

As most patients had been referred to mental health evaluation by the surgeon, they were already fully informed about ETS and possible complications by the time they were assessed by the psychiatrist. If patients consulted the psychiatrist first, clinical evaluation by the surgeon was deemed unnecessary before pursuing pharmacological or psychological treatment. The latter was neither provided by the principal investigator (a psychiatrist) nor by any other member of the research team. If patients expressed an initial preference for psychological treatment (hardly any did; on the contrary, many had received one or more courses of psychological treatment with no success), they were informed that they would have to obtain it elsewhere because the team lacked expertise in the field.

Patients opting for oral administration of sertraline had to initiate treatment with 12.5 to 25mg/day and had to reach a dose of 50mg/day at around the end of the first week. Thereafter, the dose had to be maintained indefinitely but could be increased, at the treating clinician's judgment, to 75 to 100mg/day, after four weeks. Patients opting for ETS were informed of expected effects, side effects, and risks of the procedure before acceptance for surgery. In particular, the irreversibility of compensatory sweating (CS), a side effect seen in almost all patients undergoing ETS,[26] was stressed. CS has been defined as perspiration in areas that did not present abnormal preoperative sweating and in higher quantities than those necessary for thermoregulation.[27] This complication is one of the reasons associated with the fact that approximately 10 percent of patients who undergo ETS for blushing regret the operation.[12] The study was approved by the local research ethics committee and written informed consent before the surgical procedure was mandatory (for those under 18 years of age, consent of both parents was requested).

Surgical technique. The operation is carried out under general anesthesia and takes about 45 minutes. The patient is placed supine with abduction of both arms for bilateral access. One, two, or three ports may be used to gain access to the chest. Our surgical team (led by C.S.) routinely uses two 5-mm ports. Either a sympathicotomy (transection of the sympathetic chain) or a sympathectomy (resection) was performed by an ultrasonic scalpel. In cases of isolated facial blushing, the sympathetic chain was interrupted at the level of T2 (T2 ETS); when palmar hyperhidrosis coexisted, a T2-T3 ETS was sometimes completed. The disadvantage with all these techniques is that they are irreversible. Because of this problem, some surgical teams are testing the use of clamps on the sympathetic trunk as an alternative approach for treating facial blushing since it supposedly allows for the possibility of reversing the operation if CS is disabling.[26]

Follow up. Follow-up assessments were blindly carried out by electronic mail at a mean of 11 months (range 1–64) after ETS or initiation of sertraline. Patients completed the same four measures administered at baseline plus a questionnaire to determine the degree of satisfaction with the elected treatment as measured by Pohjavaara et al,[28] and a questionnaire to assess severity of CS as used by the Brazilian Society of Thoracic Surgery[27]. Moreover,

patients were given the chance to qualitatively report on any other aspect of treatment they considered relevant.

The "no-treatment" group was composed by blushers who, for various reasons (mainly economical), had not undergone surgery by the time follow up was carried out or, if they had chosen sertraline, they had not responded to the drug and had discontinued it at least three months before follow-up assessment. Because the study was conducted in a real-life medical practice and subjects were help-seekers who were desperate for treatment, this group is numerically small and mixes subjects who were exploring financial options to pay for the operation and nonresponders to sertraline. It was considered unethical to keep the subjects off therapy for research purposes.

Data analyses. Descriptive distribution of continuous variables was performed by means and standard error of the mean. ANOVA and Scheffé multiple comparison test were performed in order to compare different groups.

RESULTS

All 330 patients seeking treatment for their blushing completed baseline assessments. Of those, 220 (66%) were eligible to take part in the study on the basis of the previously described inclusion and exclusion criteria. Reasons for exclusion were as follows: 29 patients had no data on treatment, 22 did not fulfil psychometric criteria for SAD (DSM-IV diagnosis of GSAD + facial blushing severity ≥2 + BSPS score ≥20 + SPIN score ≥19), 20 were prescribed other drugs for their blushing, 12 had a non-T2 or non-T2-T3 ETS, 10 refused to participate in the study, nine were already on antidepressants when seeking help for their blushing, four had depressive symptoms of greater than mild severity, three were judged to suffer from flushing, and one exhibited blushing in neck and chest only (Figure 1).

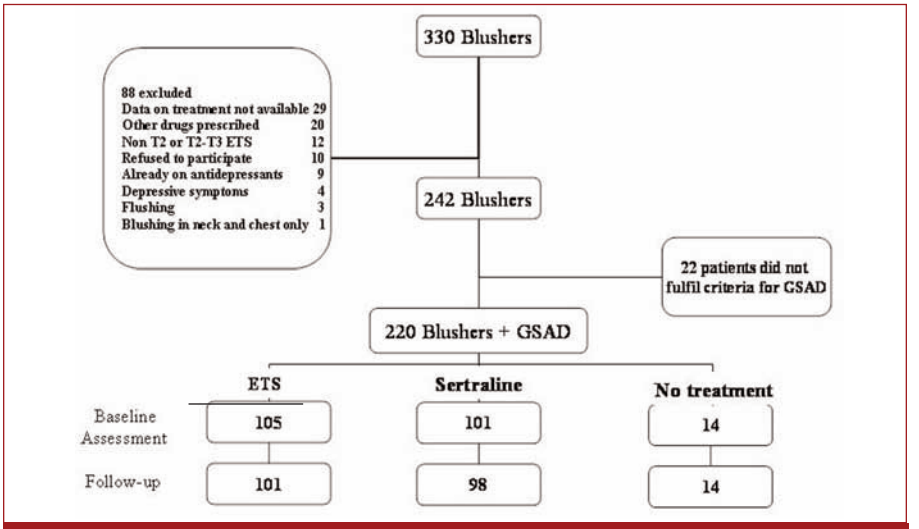

FIGURE 1. Study profile

ETS: endoscopic thoracic sympathectomy; GSAD: generalized social anxiety disorder

TABLE 1. Baseline sociodemographic characteristics in GSAD patients with blushing complaints

CHARACTERISTICS	ETS, n=105	SERTRALINE, n=101	NO TREATMENT, n=14
Age, 13–60 years	30 (8.4%)	30 (8.8%)	33 (7.2%)
Gender, % male	63 (60%)	26 (26%)	9 (64%)
Marital status			
Single	67 (64%)	54 (53%)	5 (36%)
Married/cohabiting	31 (30%)	40 (40%)	8 (57%)
Widowed	1 (1%)	0	0
Separated/divorced	6 (5%)	7 (7%)	1 (7%)
Education level/occupation			
Primary	0	1 (1%)	0
Secondary	19 (18%)	14 (14%)	2 (14%)
Technical	25 (24%)	22 (22%)	2 (14%)
University	58 (55%)	62 (61%)	10 (71%)
Entrepreneur	1 (1%)	0	0
Housewife	1 (1%)	1 (1%)	0
Other (eg, artisans, merchants)	0	1 (1%)	0

Data are number (%) or mean (SD); GSAD: generalized social anxiety disorder; ETS: endoscopic thoracic sympathectomy

TABLE 2. Baseline clinical characteristics in GSAD patients with blushing complaints

CHARACTERISTICS	ETS n=105	SERTRALINE n=101	NO TREATMENT n=14	*p* VALUE
Source of patient				
Referred by thoracic surgeon	97%	68%	93%	0.000
Spontaneous consultation to a psychiatrist (E.J.)	3%	32%	7%	0.000
Blushing severity: ≥3 on a 5-point Likert-type scale*	97%	87%	79%	0.003
Associated hyperhidrosis				
Blushing only	59%	61%	50%	0.711
Blushing + palmar hyperhidrosis	15%	8%	7%	0.223
Blushing + facial hyperhidrosis	6%	6%	7%	0.977
Blushing + facial/palmar hyperhidrosis	4%	5%	7%	0.824
Blushing + other types of hyperhidrosis	10%	15%	29%	0.112
Family history of excessive blushing or hyperhidrosis	71%	70%	79%	0.808

*Severe or extreme according to the Brief Social Phobia Scale; GSAD: generalized social anxiety disorder; ETS: endoscopic thoracic sympathectomy

Sixty-four percent of eligible patients (141/220) were women. Most patients (84%) had been referred to the psychiatrist by the thoracic surgeon, and only 16 percent had sought help directly from the mental health specialist. More men than women elected treatment with ETS, whereas there was a female predominance among those who chose sertraline (Table 1). The mean dose was 56mg/day.

At baseline, blushing intensity was severe or extreme in 97 percent of ETS patients, 87 percent of sertraline patients, and 79 percent of nontreated patients, as measured by the BSPS. Associated hyperhidrosis was considered to be present in 34 percent of ETS patients, 34 percent of sertraline patients, and 50 percent of nontreated patients. In all three groups, most patients reported a family history of excessive blushing or hyperhidrosis (Table 2). Baseline scores in measures of social anxiety were comparable in all three groups (Table 3).

Primary outcome measure. Compared to sertraline, ETS was associated with a significantly greater reduction in the number of patients reporting severe or extreme blush (score ≥3), according to the blush item of the BSPS. Whereas at baseline 97 percent of the patients in the ETS group reported suffering severe or extreme blushing, at follow up only 16 percent of the ETS-treated patients and twice this number among sertraline-treated patients reported this degree of blushing. The untreated group registered the least decrease in the number of patients reporting severe or extreme blushing (Figure 2).

At follow up, mean BSPS total scores exhibited a greater decline in both treatment groups versus the no-treatment group. This notwithstanding, in comparison to no-treatment, only the ETS results achieved statistically significant superiority (p=0.003). When the two treatments are compared, the difference in total score reduction did not reach statistical significance (p=0.093) (Table 4).

In comparison to no-treatment, ETS was associated with a significantly greater decrease in all three-symptom cluster: fear, avoidance, and physiological arousal. Among the individual physiological symptoms, statistically significant differences in favor of ETS were found for blushing (p=0.011) and palpitations (p=0.001) but not for trembling.

Patients on sertraline showed a greater, although nonsignificant, reduction in the three-symptom cluster (fear, avoidance, and physiological arousal) than nontreated patients. Among individual physiological symptoms, statistically significant differences in favor of sertraline were noted for blushing (p=0.035) and palpitations (p=0.003) but not for trembling and sweating.

When both treatments are compared, ETS-treated patients exhibited a greater, statistically significant decline in fear (p=0.025) than sertraline-treated patients. Among individual physiological symptoms, in all cases differences favored ETS but they were not statistically significant. Pre- and post-treatment scores in the blush item of the BSPS were 3.4 (0.7) and 1.5 (1.2), respectively, in the sertraline-treated group and 3.6 (0.5)

and 1.5 (1.2), respectively, in ETS-treated patients. Though the reduction in score in the blush item was greater with ETS, 2.2 (1.3) versus 1.9 (1.3), the difference did not reach statistical significance (p=0.063).

Secondary outcome measures. According to the LSAS, mean follow-up total scores showed a greater reduction in both treatment groups versus the untreated group. Yet, in comparison to the untreated group, only the ETS results were statistically significant (p=0.001). When the two treatments are compared, there is a statistically significant superiority of ETS (p=0.003) (Table 5).

At follow up, both ETS-treated patients and sertraline-treated patients exhibited a greater, statistically significant, decline in mean SADS total scores in comparison to the no-treatment group (p=0.013 and p=0.032, respectively). If the two treatments are compared, no statistically significant difference emerges (p=0.419) (Table 6).

For both treatment groups, mean follow-up SPIN total scores were considerably lower in comparison to the untreated group. However, in comparison to the untreated group, only the ETS results were statistically significant (p=0.037). Nonetheless, when the two treatment groups are compared, no statistically significant difference is detected (Table 7).

Adverse effects of ETS. There was no mortality or conversion to open thoracotomy. One patient developed a postoperative pneumothorax but recovered without sequelae. Two patients developed Horner's syndrome; one resolved after two days but the other had not resolved when the patient was contacted two and a half years later. One patient had sympathetic reinnervation with reappearance of blushing six months after the operation.

CS occurred in 99 percent of patients who underwent ETS. Among those experiencing this side effect, the majority (55%) had moderate CS, whereas 32 percent reported mild and 13 percent intense compensatory perspiration.

Gustatory sweating, a well-known side effect after sympathectomy particularly related to spicy foods or foods with moderate acidity (e.g., apples, oranges), was spontaneously reported by eight percent of ETS-treated patients.

Patient satisfaction with treatment. Among ETS-treated patients, the majority (53%) reported being "very satisfied" with the results of the procedure and 36 percent indicated they were "quite satisfied." Two patients who had ETS (2%) regretted the operation (Figure 3). In one case, this was because of intolerable CS and in the other because of postoperative maintenance of blushing.

By comparison, 37 percent of sertraline-treated patients reported that treatment was "somewhat

TABLE 3. Baseline mean scores (95% CI) in measures of social anxiety in GSAD patients with blushing complaints

MEASURE	ETS n=105	SERTRALINE n=101	NO TREATMENT n=14
BSPS	46.3 (44.3–48.3)	43.3 (41.3–45.3)	38.9 (33.0–44.7)
SPIN	40.8 (38.8–42.8)	38.6 (36.5–40.6)	36.9 (31.1–42.7)
LSAS	79.3 (74.6–84.1)	70.1 (65.5–74.8)	63.0 (50.9–75.1)
SADS	14.4 (13.9–14.8)	14.4 (13.9–14.8)	12.9 (11.4–14.5)
Blushing severity	3.6 (3.5–3.8)	3.4 (3.2–3.5)	3.1 (2.7–3.5)

GSAD: generalized social anxiety disorder; ETS: endoscopic thoracic sympathectomy; BSPS: Brief Social Phobia Scale; SPIN: Social Phobia Inventory; LSAS: Liebowitz Social Anxiety Scale; SADS: Social Avoidance and Distress Scale

TABLE 4. Comparison of pre- and post-treatment BSPS total scores by treatment group in GSAD patients with blushing complaints

BSPS TOTAL SCORE	ETS* n=101	NO TREATMENT n=14	*p* VALUE
Baseline	46.2 (10.2)	38.9 (11.1)	0.014
Endpoint	24.8 (13.4)	30.2 (16.8)	0.173
Change	- 21.5 (14.95)	- 8.6 (15.1)	0.003
BSPS TOTAL SCORE	**SERTRALINE n=98**	**NO TREATMENT n=14**	***p* VALUE**
Baseline	43.2 (10.1)	38.9 (11.1)	0.147
Endpoint	25.6 (13.4)	30.2 (16.8)	0.245
Change	- 17.6 (16.4)	- 8.6 (15.1)	0.058
BSPS TOTAL SCORE	**ETS* n=101**	**SERTRALINE n=98**	***p* VALUE**
Baseline	46.2 (10.2)	43.2 (10.1)	0.040
Endpoint	24.8 (13.4)	25.5 (13.4)	0.683
Change	-21.5 (15)	-17.6 (16.4)	0.093

Data are mean (SD).
BSPS: Brief Social Phobia Scale; GSAD: generalized social anxiety disorder; ETS: endoscopic thoracic sympathectomy
*ETS-treated patients: there is one missing value.

TABLE 5. Comparison of pre- and post-treatment LSAS total scores by treatment group in GSAD patients with blushing complaints

LSAS TOTAL SCORE	ETS n=101	NO TREATMENT n=14	*p* VALUE
Baseline	79.3 (24.0)	63.0 (22.9)	0.0190
Endpoint	34.7 (21.4)	50.7 (37.1)	0.0215
Change	- 44.6 (32.1)	- 12.3 (43.4)	0.0011
LSAS TOTAL SCORE	**SERTRALINE n=98**	**NO TREATMENT n=14**	***p* VALUE**
Baseline	70.1 (23.5)	63.0 (22.9)	0.2935
Endpoint	40.4 (27.1)	50.7 (37.1)	0.2118
Change	- 29.7 (35.9)	- 12.3 (43.6)	0.1041
LSAS TOTAL SCORE	**ETS n=101**	**SERTRALINE n=98**	***p* VALUE**
Baseline	79.3 (24.0)	70.1 (23.5)	0.0094
Endpoint	34.7 (21.4)	40.4 (27.1)	0.1147
Change	- 44.6 (32.1)	- 29.7 (35.9)	0.0034

Data are mean (SD).
BSPS: Brief Social Phobia Scale; GSAD: generalized social anxiety disorder; ETS: endoscopic thoracic sympathectomy

TABLE 6. Comparison of pre- and post-treatment SPIN total scores by treatment group in GSAD patients with blushing complaints

SPIN TOTAL SCORE	ETS* n=101	NO TREATMENT n=14	*p* VALUE
Baseline	40.8 (10.3)	36.9 (11.0)	0. 1932
Endpoint	20.8 (11.3)	26.5 (16.1)	0.1005
Change	- 20.0 (15.3)	- 10.4 (19.5)	0.0373
SPIN TOTAL SCORE	**SERTRALINE** n=98**	**NO TREATMENT n=14**	***p* VALUE**
Baseline	38.5 (10.3)	36.9 (11.0)	0.5929
Endpoint	22.5 (12.1)	26.5 (16.1)	0.2742
Change	- 16.0 (15.9)	- 10.4 (19.5)	0.2370
SPIN TOTAL SCORE	**ETS* n=101**	**SERTRALINE n=98**	***p* VALUE**
Baseline	40.8 (10.3)	38.5 (10.3)	0.1317
Endpoint	20.8 (11.3)	22.5 (12.1)	0.3258
Change	- 20.0 (15.3)	- 16.0 (15.9)	0.0837

Data are mean (SD).
BSPS: Brief Social Phobia Scale; GSAD: generalized social anxiety disorder; ETS: endoscopic thoracic sympathectomy
*ETS-treated patients: there are two missing values.
**Sertraline-treated patients: there are two missing values.

helpful," 35 percent were "quite satisfied," and 24 percent were "very satisfied." None of the pharmacologically treated patients regretted treatment (Figure 4).

If only the two most favorable outcomes are considered, high degrees of satisfaction are reported by 89 percent of ETS patients and 59 percent of their sertraline-treated counterparts.

From 1 to 5 (where 1 = "I regret the operation/ I regret pharmacological treatment" and 5 = I am very satisfied), mean satisfaction was 4.3 among ETS-treated patients and 3.7 among patients treated with sertraline.

DISCUSSION

Facial blushing. This is the first prospective, observational study on the efficacy of ETS for treating facial blushing, which includes a comparison group (actually two groups). To date, despite the fact that at least 16 previous prospective studies[6,8–14,29–36] show that blushing decreases after ETS, the lack of controlled studies implies that the efficacy of ETS for treating facial blushing is not yet firmly established. To that end, a randomized, double-blind, placebo-controlled trial, the now well-accepted gold standard in evaluating treatment efficacy and safety/tolerability, should ideally be carried out. However, in studies evaluating surgical procedures, the use of placebo poses a unique challenge.[37] For instance, assignment to the placebo group may involve risk since the subject undergoes all the preparations (including anaesthesia and surgical incision) that are essential to the true operation, but does not undergo the surgical procedure itself. Hence, it has been argued that placebo surgery poses ethical problems.[38] A reasonable alternative, although grossly inferior methodologically, is to use a standard treatment, if available, as comparator. No such standard treatment is nowadays available for the treatment of blushing.

Although our study does not control for the placebo effect of surgery, its results—arising from "real world" medical practice—are important because they include a small but valuable contrast group. The finding of a clear advantage of ETS for decreasing blushing in comparison to sertraline and no treatment (at follow up, the number of patients with blushing ≥3 in the last two groups was 2 and 3.6 times higher, respectively, than in the ETS-treated group) points to the therapeutic superiority of ETS treatment. A surgical placebo response is very unlikely because the beneficial effect of the placebo response in surgery has been estimated as being of the same

magnitude (about 35%) as that observed in clinical trials,[39] and our results show a response to surgery of greater magnitude and highly significant differences with no treatment. Besides, the durability of treatment effects is considered to question the hypothesis of placebo effect[40] and in our study the longest follow-up time exceeded five years.

So far, the longest follow up of ETS for facial blushing included 536 patients and exceeded 14 years, reporting a success rate of 72.8 percent with 73.5 percent of patients being satisfied with treatment. CS, the main side effect, was present in about 80 percent of patients, and for the majority remained unchanged along the years.[41]

The reduction in scores of blushing and social anxiety in the group of patients without treatment is not surprising as "no treatment" is perhaps a misnomer. First, access to healthcare personnel and being interviewed for research purposes might have a "therapeutic" effect. Nevertheless, all groups under evaluation are subjected to this effect. Next, baseline assessments were carried out when patients consulted, that is, at a time when symptoms bothered them most, to the point that they sought help. Therefore, another explanation for symptom reduction in the nontreated group of patients is timing of the assessments.

Neither authors of the 16 previous treatment studies already mentioned nor our research group used physiological recordings to assess blushing. This certainly is a weakness of all these studies.

Some earlier studies[42–45] found that nongeneralized social phobics with just public speaking fears showed greater autonomic responses to behavioral tests than generalized social phobics. This is in keeping with the clinical finding that beta blockers used on an as-needed basis tend to work better for nongeneralized social phobics. However, those studies were carried out before the emerging literature on fear of blushing and sweating had come out[46] and do not address the heterogeneity of GSAD patients from the viewpoint of the blushing response. Thus, as recent research shows,[47] patients who complain about blushing blush more and/or have a heightened general arousability in social situations than those who do not complaint about blushing. This opposes what several researchers had suggested in the past, namely that SA patients who complain mainly about blushing have a distorted view concerning their blush but do not show actual physiological blushing problems.[48] In addition, recent evidence suggests a possible influence of the less active serotonin transporter (5-HTT) genetic variants on blushing propensity in SAD and therefore strengthens the hypothesis of serotonergic dysfunction in the pathogenesis of SAD and psychophysiological arousal in particular.[49]

Interestingly, it has been shown that the vasodilator niacin may provoke greater flushing, anxiety, autonomic activity, and temperature in patients with SAD compared with normal controls.[50] Taking this into consideration, it would be worth studying the relationship between nicotinic acid and blushing propensity. It may well be that a higher hypersensitivity to niacin differentiates SAD patients with blushing complaints from SAD non-blushers.

TABLE 7. Comparison of pre- and post-treatment SADS total scores by treatment group in GSAD patients with blushing complaints

SADS TOTAL SCORE	ETS* n=101	NO TREATMENT n=14	*p* VALUE
Baseline	14.4 (2.3)	12.9 (2.8)	0.0293
Endpoint	13.4 (2.5)	14.4 (2.7)	0.1702
Change	- 1.0 (3.4)	-1.5 (3.9)	0.0134
SADS TOTAL SCORE	**SERTRALINE** n=98**	**NO TREATMENT n=14**	***p* VALUE**
Baseline	14.4 (2.2)	12.9 (2.8)	0.0239
Endpoint	13.8 (2.4)	14.4 (2.7)	0.3928
Change	- 0.6 (3.3)	- 1.5 (3.9)	0.0325
SADS TOTAL SCORE	**ETS* n=101**	**SERTRALINE n=98**	***p* VALUE**
Baseline	14.4 (2.3)	14.4 (2.2)	1.0000
Endpoint	13.4 (2.5)	13.8 (2.4)	0.2699
Change	- 1.0 (3.4)	- 0.6 (3.3)	0.4193

Data are mean (SD).
BSPS: Brief Social Phobia Scale; GSAD: generalized social anxiety disorder; ETS: endoscopic thoracic sympathectomy
*ETS-treated patients: there are two missing values.
**Sertraline-treated patients: there are two missing values.

Social anxiety disorder. Since sympathectomy has long been used to treat palmar and facial hyperhidrosis,[51] and in recent years also facial blushing, and because biological studies indicate that the sympathetic nervous system regulates these symptoms in social phobia,[52,53] it has been deemed ethical to extend studies of the possible effect of this surgery to social anxiety disorder cases with prominent autonomic symptoms, resistant to psychotherapy and medication. Previously, only one study, carried out in Finland, has assessed the efficacy of ETS in the treatment of social phobia.[9,10] A total of 164 social anxiety disorder patients diagnosed according to *DSM-IV* criteria, who had been suffering from the disorder for at least five years and had not responded to medication and/or

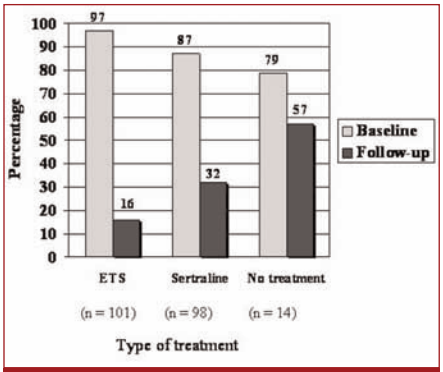

FIGURE 2. Frequency of severe or extreme blushing (score ≥3) according to the blush item of the BSPS in GSAD patients with blushing complaints.

BSPS: Brief Social Phobia Scale; GSAD: generalized social anxiety disorder

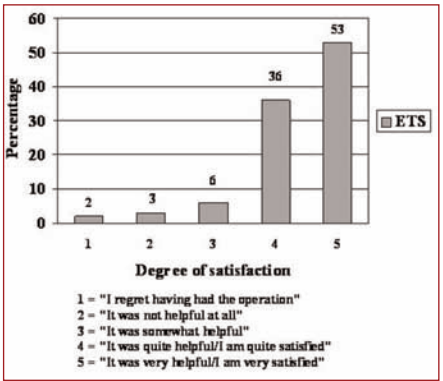

FIGURE 3. Degree of satisfaction with ETS treatment in GSAD patients with blushing complaints (n=101). There are four missing values.

ETS: endoscopic thoracic sympathectomy; GSAD: generalized social anxiety disorder

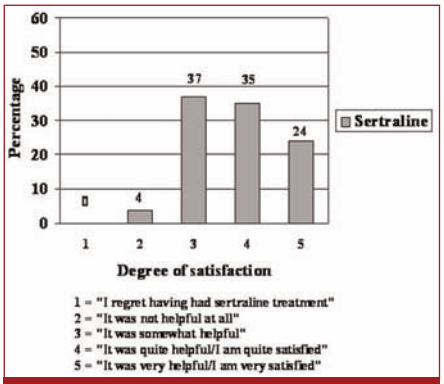

FIGURE 4. Degree of satisfaction with sertraline treatment in GSAD patients with blushing complaints (n=98). There are two missing values.

GSAD: generalized social anxiety disorder

psychotherapy, were included. Highly significant reductions in perceived physical symptoms (particularly blushing and palpitations) and psychic symptoms, as measured by a visual analog scale, were documented at follow up. Mean follow up was not specified but the longest follow-up time was more than 48 months. Patient´s satisfaction with treatment, assessed on a 5-point Likert-type scale (range from 1="I regret having the operation" to 5="It was very helpful/very satisfied"), was 3.5. Increase in sweating of the trunk was mentioned but described as being of low significance.

In comparison, in our Chilean follow up we found higher mean satisfaction, with values of 3.7 for sertraline and 4.4 for ETS, using the same measure as in the Finnish study. Satisfaction with sertraline, a well-known, first-line pharmacological treatment for social phobia, is not surprising. In contrast, the fact that most patients reported being satisfied with the operation despite the high prevalence of CS deserves attention. In our view, this is because in some individuals blushing is severe enough to become a debilitating disorder, with devastating consequences, both socially and in the workplace.[4] We have witnessed that patients are willing to tolerate bothersome CS and face the risks of complications as long as they feel liberated from their too-easily triggered facial blushing. We have seen that patients feel less sensitive about CS than about blushing. We hypothesize that this is because compensatory perspiration in most cases is less visible than blushing.

Worthy of note is that only two percent of ETS-treated patients regretted the operation in our study. This figure is identical to that reported by Drott[6] and compares favorably with the 10-percent rate found in other studies.[12]

We agree that it is only reasonable to ask if clinicians should recommend ETS to treat social anxiety disorder with blushing complaints. Our results indicate that ETS is effective, but, given the irreversibility of the surgical techniques currently in use, patients should be encouraged to try nonsurgical options first. Treatments that have been evaluated for social anxiety disorder patients with fear of anxiety symptoms include exposure,[53–55] cognitive therapy,[55–57] social skills training,[57] applied relaxation,[56] and task concentration training.[53,54,56] Results indicate that all these treatments are helpful, with task concentration training being somewhat more helpful than applied relaxation[56] or exposure.[53] As previously mentioned, pharmacological treatments have not been tested specifically for social anxiety disorder with blushing complaints. Nevertheless, our results confirm the findings by Connor et al[16] that social anxiety disorder patients report specific effects of sertraline on blushing, but not on trembling and sweating. These are encouraging results, and therefore studies addressing the efficacy of sertraline and also other SSRIs for disabling blushing should be carried out. The mean dose of 56mg per day used in our study is considerably less than what was used in the controlled trials that demonstrated the efficacy of sertraline in social anxiety disorder,[58–60] where doses went up to 200mg/day. However, the dose range we used is in accordance with the doses most commonly used in clinical practice by Chilean psychiatrists who, when prescribing psychotropic drugs, tend to use lower doses than those employed in the northern hemisphere.[61] Though Connor et al[16] state they employed sertraline in the 50 to 200mg per day range, they do not specify the mean dose they used. Still, the possibility that our results may underestimate the efficacy of sertraline for GSAD patients with blushing complaints cannot be excluded. Hence, future studies should consider using higher doses.

There is lack of data as to whether blushers who request sympathetic

surgery for their blushing suffer from isolated blushing, without any other signs of social anxiety disorder or if, on the contrary, they fulfil some or all the criteria for the disorder. Licht[26] has stated that most of the patients who are offered ETS for blushing in Denmark suffer from isolated facial blushing. In contrast, our results, using rather strict diagnostic criteria, show that 91 percent (220 out of 242) of patients who sought help for their blushing fulfilled criteria for social anxiety disorder. One reason for this discrepancy might be that most studies on the efficacy of ETS for blushing do not systematically screen for social anxiety disorder. Linked to this is the fact that blushing is a symptom that has not attracted much attention from mainstream psychiatry, a discipline that can contribute much to this topic.

The clinical histories and chronological development of symptoms in many of the patients we have assessed and treated suggest that social anxiety disorder might arise as a secondary maladaptive response to repeated embarrassing blushing experiences. This is in line with the recent proposition made by Pelissolo et al[62] that a social anxiety disorder form secondary to facial blushing should be considered. Indeed, in our view, an ideal approach would be to treat in a timely manner, by nonsurgical means first, patients seeking help for their blushing before they go on to develop social anxiety disorder.

Limitations of this study primarily relate to the selection of participants. Given the nature of the study, each patient decided his or her treatment, so in some aspects, such as blushing severity, the groups were not comparable at baseline. Next, the nontreated group had only 14 subjects, stressing statistical analysis; nevertheless, significant statistical differences between groups in some of the outcomes were found. It is plausible that other differences were not detected due to lack of statistical power of this small sample. Finally, a number of follow-up missing values for some of the study participants may bias the results; however, the amount of loss does not invalidate findings.

CONCLUSION

Reduction of blushing and BSPS scores in GSAD patients with blushing complaints was greater in ETS-treated patients than in sertraline-treated patients, who in turn exhibited a greater decline in blushing and BSPS scores than untreated patients. Despite a very high prevalence of CS associated with the surgical procedure, ETS patients reported higher degrees of satisfaction with treatment than sertraline patients. More research is necessary to determine outcomes for different types of treatment in patients with blushing only and in social anxiety disorder patients with blushing complaints. The nature of the association between blushing and social anxiety disorder also needs to be examined. We hope our study will stimulate further investigation into these two areas.

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