Long-term Therapy for Spasmodic Dysphonia

Acoustic and Aerodynamic Outcomes

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Objective: To evaluate the long-term aerodynamic, acoustic, and electromyographic effects of serial botulinum toxin (BT) injections in patients with adductor spasmodic dysphonia.

Design: Two-year, nonrandomized, controlled, before-after study.

Setting: Ambulatory care clinic at a single academic medical center.

Patients: A convenience sample of 91 patients with adductor spasmodic dysphonia evaluated and treated during 2 years and 64 age- and sex-matched controls.

Interventions: Injections of BT into the thyroarytenoid muscles in conjunction with electromyographic evaluation and acoustic and aerodynamic evaluation before and after serial BT injections.

Main Outcome Measures: Translaryngeal airflow, jitter, shimmer, signal-to-noise ratio, fundamental frequency, standard deviation of fundamental frequency, maximum phonation time, and inappropriate muscle activity by electromyography.

Results: Translaryngeal airflow, jitter, and shimmer improved significantly after serial BT treatments and showed sustained improvement over time. Fundamental frequency, standard deviation of fundamental frequency, and signal-to-noise ratio did not change significantly after BT treatment. Electromyographic data suggested decreased inappropriate muscle activity with repeated BT injections.

Conclusion: Treatment with BT provides ongoing relief of voice perturbations in patients with adductor spasmodic dysphonia who undergo long-term cumulative therapy.


Dystonias are disorders of central motor processing that lead to abnormal tonicity of muscles and thus dyskinetic movements or uncontrolled spasms. These movements can be slow and sustained or rapid and uncoordinated. Focal dystonias involve only one particular region of the body, whereas multifocal dystonias, as the name implies, involve several regions or muscle groups. In 1871, Traube first described the focal laryngeal dystonia known as spasmodic dysphonia (SD).

Spasmodic dysphonia is characterized by spasms of the laryngeal muscles that are active during vocal fold adduction (vocalis-thyroarytenoid muscle complex) or, less commonly, those involved in vocal fold abduction (posterior cricoarytenoid muscles). In the adductor type of SD, the voice is typically hoarse, soft, and strained, with abrupt initiation and termination of voicing causing breaks in phonation and variation in pitch. These symptoms are associated with increased approximation of the vocal folds and decreased transglottic airflow during phonation. The abductor variety of SD is characterized by a whispery or weak, breathy voice, especially at the onset of voicing, with associated decreased vocal fold approximation and increased airflow during phonation. In addition, some patients might exhibit characteristics of both forms of SD.

As with most dystonias, the cause of SD is unknown, although it is believed to originate in the basal ganglia, a well-known motor nucleus in the brain. It has also been determined that some forms of dystonia have a genetic origin. The incidence of SD is about 1 in 10000 adults and is more prevalent in women than in men. The average age of onset of the disorder is 40 to 50 years. Although there is no known cure for SD, therapeutic interventions have ranged from surgery to voice therapy to pharmacologic injections into the laryngeal musculature. The most common surgical treatment involves sectioning of the recurrent laryngeal nerve to in-
PATIENTS AND METHODS

PATIENTS

All patients with adductor SD evaluated at the University of California, San Diego Medical Center between September 1, 1995, and December 31, 1998, were invited to participate in this study. The diagnosis of SD was made by an otorhinolaryngologist (L.A.O.) in conjunction with a speech pathologist (S.N.G.) based on the results of a detailed clinical history, fiberoptic laryngoscopy with or without videostroboscopy, a complete neurological examination, and an acoustic and aerodynamic analysis of each patient’s voice. The fiberoptic laryngoscopy confirmed the presence of abnormal spasms and hyperfunction of the laryngeal musculature during speech. The voice analysis allowed an objective confirmation of the patient’s vocal symptoms. The proposed research protocol was approved by the Human Subjects Committee at the University of California, San Diego.

STUDY DESIGN

Patients who completed the entire protocol were studied for a minimum of 2 years at 6 points: T1, entry into the study (before treatment or retreatment); T2, 6 weeks after the first BT treatment or retreatment; T3, immediately before the first BT treatment that occurred 12 months or more after T1; T4, 6 weeks after the T3 measurement; T5, immediately before the first BT treatment that occurred 12 months or more after the T3 injection (approximately 2 years after study entry); and T6, 6 weeks after the T5 measurement. Some patients did not complete all 6 data collection sessions, as described in the “Results” section. Each pair of measurements (ie, T1 and T2, T3 and T4, and T5 and T6) represented a preinjection and postinjection set of data. In addition to patient data collection, normative data for all noninvasive aerodynamic and acoustic measurements were obtained from 64 age- and sex-matched control subjects without a voice disorder.

PROCEDURES

All BT injections were performed by one otorhinolaryngologist (L.A.O.) using a transcutaneous approach and EMG guidance into the laryngeal muscles. Immediately before BT injection, patients received subcutaneous 1% lidocaine injections to induce local anesthesia. Patients received unilateral or bilateral thyroarytenoid injections at doses ranging from 0.75 to 30.00 U of BT (botulinum toxin type A; Allergan Inc, Irvine, Calif) at each injection site. There are no concrete guidelines for dosage, and each patient’s injection dosage was determined by evaluating individual responses to injections. The first few injections for each patient typically varied in dose until an optimal therapeutic dose was determined based on perceptual evaluation of the patient’s vocal quality, degree and duration of symptom relief, and incidence of adverse effects such as breathiness, hoarseness, and dysphagia. There were no complications from BT injections.

DATA COLLECTION

Aerodynamic Data: Phonatory Airflow

Each patient was fitted with a standard anesthesia face mask covering the nose and mouth. Coupled to this mask was a pneumotachograph and a differential pressure transducer, which in turn connected to a laboratory computer and its accompanying software (Atlantic; Lakeshore Technologies, Chicago, Ill). The system was calibrated by passing a continuous airstream through a rotameter coupled to the pneumotachograph and differential pressure transducer. Airflow was measured for each patient’s sustained phonation of the vowel /a/. Three samples of the /a/ were obtained at each data collection point. The airflow rates of the first 3 seconds of each of the 3 samples were averaged, and this value was used for analysis.

In the second year of the study, a new device for measuring airflow, the Aerophone II model 6800 (Kay

RESULTS

Of 91 patients who underwent initial evaluation (T1), 70 were women and 21 were men (age range, 26-93 years; median age, 62 years). Of these 91 patients, 61 (67%) had been treated previously with BT and the remaining 30 (33%) had their first BT injection as part of the study. At T2, 65 patients had complete evaluations. At the remaining points, the following numbers of patients underwent measurements: T3, 52 patients; T4, 36 patients; T5, 34 patients; and T6, 21 patients. Patient accrual


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Table 1

<table>
<thead>
<tr>
<th>Acoustic Measure</th>
<th>Formula</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fundamental Frequency (F0)</td>
<td>f</td>
<td>Hz</td>
</tr>
<tr>
<td>Shimmer</td>
<td>(F0/F0')</td>
<td>%</td>
</tr>
<tr>
<td>Jitter</td>
<td>(ΔF0/mean F0)</td>
<td>ms</td>
</tr>
<tr>
<td>Signal-to-Noise Ratio (SNR)</td>
<td>SNR</td>
<td>dB</td>
</tr>
<tr>
<td>Signal Diversity Factor (SDF0)</td>
<td></td>
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</tbody>
</table>

The EMG signal observed was a function of the location of the needle tip within the muscle being injected, which might have varied from one injection to the next in a given patient. Nevertheless, effort was made at each injection to identify and inject the site of maximum IMA within the vocal fold.

**STANDARD ANALYSIS**

The aerodynamic and acoustic variables were analyzed using analysis of variance (ANOVA) at an overall significance level of P<.05. A Fisher protected least significant difference was computed for all possible pairwise comparisons using data from T1 through T6. In addition, a 1-factor repeated-measures ANOVA was performed on the subset of patients who had complete data at each data collection point (T1-T6). Patient data were compared with control data using an unpaired t test. A separate analysis was conducted to evaluate whether there were any significant differences between patients who had and those who had not been treated with BT before study entry. This analysis revealed no significant differences between the 2 groups in terms of the acoustic and aerodynamic variables evaluated. The results presented in the following section thus represent all patients in the study.

Data are given as mean ± SD.

Mean airflow at each data collection point is shown in Figure 1A and Table 1. Overall, patients showed improvement in airflow after BT treatment, with the overall difference between periods being statistically significant (P=.03). The most significant difference was between T1 and T2 (P=.008). When all pretreatment airflow measurements (T1, T3, and T5) were averaged and compared with an average of all posttreatment airflow measurements (T2, T4, and T6), the difference was statistically significant (P=.007) (Figure 1B).

Repeated-measures ANOVA for 16 patients who had data at all 6 data collection points (T1-T6) again showed the overall difference between periods to be statistically significant (P=.006) (Figure 1C).

Control data for airflow yielded mean airflow of 187.14 ± 96.91 mL/s. The overall difference between this value and patient values at any given data collection point (T1-T6) was not statistically significant. Comparing the control group average to the pretreatment airflow average (T1, T3, and T5), P>.10. Comparing average airflow for controls with the posttreatment airflow average (T2, T4, and T6), borderline significance was noted (P=.07). However, patients with SD showed a trend in which they initially started with lower-than-normal airflow but after BT treatment had higher-than-normal airflow, which was maintained with subsequent injections.

**ACOUSTIC MEASUREMENTS**

**Fundamental Frequency**

Data for F0 were analyzed separately by sex owing to the distinct difference in vocal pitch between men and women.
Overall differences between data collection points (ANOVA) and the repeated-measures ANOVA were not statistically significant for either sex. Control data indicated a mean F0 of 170±31.7 Hz for women and 127.9±36.5 Hz for men, which did not differ significantly from patient data (Table 2).

### Standard Deviation of F0

Differences in mean values for SDF0 at each data collection point were not statistically significant (Table 2). Control data, however, showed a mean SDF0 of 2.32±1.63 Hz, which was significantly lower than patient data at each data collection point (P<.001). Thus, patients with SD have a higher SDF0 than normal.

### Shimmer

Mean values for shimmer at each data collection point are shown in Figure 2A and Table 2. Neither differences between data collection points for all patients nor the repeated-measures ANOVA for the 14 patients with complete shimmer data from T1 through T6 were statistically significant. Control data for shimmer showed a mean value of 5.61%±3.83%. The overall difference between control data and patient data at each data collection point was highly statistically significant (P<.001). Thus, patients with SD had higher than normal values for shimmer. The trend from T1 through T6 suggests that shimmer tends to decrease after treatment with BT, although it never reaches normal values.

### Jitter

Mean values for jitter at each data collection point are shown in Figure 2B and Table 2. The overall difference between periods was of borderline statistical significance (P=.05). The pair contributing most to the significance level was T1 and T2 (P=.02). When all pretreatment jitter measurements (T1, T3, and T5) were averaged and compared with an average of all posttreatment jitter measurements (T2, T4, and T6), the difference was statistically significant (P=.02). Repeated-measures ANOVA for the 14 patients with complete jitter data from T1 through T6 did not show overall significance (P>.05).

Control data for jitter showed a mean value of 0.046±0.051 milliseconds. The overall difference between control data and patient data at each data collection point was highly statistically significant (P<.001). As with shimmer, patients with SD had much-higher-than-normal values of jitter that tended to decrease with treatment but never reached normal values.

### Signal-to-Noise Ratio

Mean values for SNR at each data collection point are shown in Figure 2C and Table 2. The overall difference between data collection points for all patients and the repeated-measures ANOVA for the subset of patients with complete SNR data from T1 through T6 were not statistically significant (P>.05). Control data showed a mean

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**Table 1. Mean Translaryngeal Airflow for Sustained Phonation of the Vowel /a/ for Controls and All Patients at Each Data Collection Point**

<table>
<thead>
<tr>
<th>Patients, No.</th>
<th>Mean ± SD Airflow, mL/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>64 187.14 ± 96.91</td>
</tr>
<tr>
<td>T1</td>
<td>91 165.94 ± 110.05</td>
</tr>
<tr>
<td>T2</td>
<td>65 221.28 ± 153.15</td>
</tr>
<tr>
<td>T3</td>
<td>52 179.07 ± 127.73</td>
</tr>
<tr>
<td>T4</td>
<td>36 228.45 ± 131.69</td>
</tr>
<tr>
<td>T5</td>
<td>34 225.05 ± 128.84</td>
</tr>
<tr>
<td>T6</td>
<td>21 216.13 ± 109.38</td>
</tr>
</tbody>
</table>

*See the “Study Design” section for definitions of the data collection points (T1-T6).
SNR of 17.50±3.63 dB. The overall difference between control data and patient data at each data collection point was statistically significant ($P < .005$). Patients with SD had lower-than-normal SNR values, and there was no significant increase in SNR after BT therapy.

**PHONATION TIME**

Mean MPT during sustained phonation of the vowel /a/ for each data collection point is shown in Figure 2D and Table 2. The overall ANOVA was not statistically significant. When all pretreatment MPT measurements (T1, T3, and T5) were averaged and compared with an average of all posttreatment MPT measurements (T2, T4, and T6), the difference was statistically significant ($P = .03$). The repeated-measures ANOVA for the subset of 14 patients with MPT data at each data collection point did not show a significant change ($P > .05$).

Control data showed a mean MPT of 15.46±6.15 seconds. Patient values at each data collection point were significantly lower than control values ($P < .05$). Thus, patients with SD tend to have lower-than-normal MPT values.

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**Table 2. Acoustic Data for Sustained Phonation of the Vowel /a/ for Controls and All Patients at Each Data Collection Point**

<table>
<thead>
<tr>
<th>Data Collection Point</th>
<th>F0, Hz</th>
<th>SDF0, Hz</th>
<th>Shimmer, %</th>
<th>Jitter, ms</th>
<th>SNR, dB</th>
<th>MPT, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>170 ± 31.7 (51)</td>
<td>127.9 ± 36.5 (13)</td>
<td>2.32 ± 1.63 (64)</td>
<td>5.61 ± 3.83 (64)</td>
<td>0.046 ± 0.051 (64)</td>
<td>17.50 ± 3.63 (64)</td>
</tr>
<tr>
<td>Men</td>
<td>172 ± 49.5 (69)</td>
<td>123 ± 38.8 (19)</td>
<td>8.87 ± 9.70 (14)</td>
<td>15.33 ± 16.61 (88)</td>
<td>0.318 ± 0.527 (88)</td>
<td>13.33 ± 5.75 (88)</td>
</tr>
<tr>
<td>T1</td>
<td>180 ± 35.7 (48)</td>
<td>130 ± 33.5 (16)</td>
<td>4.50 ± 3.95 (12)</td>
<td>13.72 ± 17.00 (64)</td>
<td>0.174 ± 0.273 (64)</td>
<td>14.99 ± 6.08 (64)</td>
</tr>
<tr>
<td>T2</td>
<td>188 ± 42.8 (42)</td>
<td>130 ± 29.3 (11)</td>
<td>11.32 ± 13.21 (15)</td>
<td>20.08 ± 23.56 (53)</td>
<td>0.324 ± 0.413 (53)</td>
<td>13.26 ± 6.12 (53)</td>
</tr>
<tr>
<td>T3</td>
<td>178 ± 44.4 (29)</td>
<td>131 ± 32.4 (6)</td>
<td>7.45 ± 9.38 (10)</td>
<td>12.60 ± 13.52 (35)</td>
<td>0.204 ± 0.345 (35)</td>
<td>14.17 ± 5.24 (35)</td>
</tr>
<tr>
<td>T4</td>
<td>175 ± 50.8 (30)</td>
<td>133 ± 51.8 (5)</td>
<td>7.71 ± 9.22 (15)</td>
<td>12.87 ± 13.98 (35)</td>
<td>0.152 ± 0.188 (35)</td>
<td>14.80 ± 5.08 (35)</td>
</tr>
<tr>
<td>T5</td>
<td>165 ± 43.4 (21)</td>
<td>128.35 ± 27.08 (2)</td>
<td>9.34 ± 11.26 (23)</td>
<td>13.64 ± 11.96 (23)</td>
<td>0.158 ± 0.180 (23)</td>
<td>12.82 ± 5.08 (23)</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD. Number of controls or patients, as applicable, is given in parentheses. F0 indicates fundamental frequency; SDF0, standard deviation of F0; SNR, signal-to-noise ratio; and MPT, maximum phonation time. See the “Study Design” section for definitions of the data collection points (T1-T6).
EMG DATA

Electromyographic data were recorded at each treatment period (ie, T1, T3, and T5). The mean score on the 3-point IMA scale at T1 (n=84) was 2.875±0.328, decreasing to 2.723±0.513 at T3 (n=56) and to 2.653±0.619 at T5 (n=36). This downward trend suggests that decreased IMA and lower-amplitude EMG signals are obtained with repeated BT injections.

Reasons that not all patients completed measurements at all 6 data collection points included (1) late entry into the study, (2) unwillingness to return for evaluation at a point that a BT injection would not be administered (T2, T4, and T6), (3) doing well from the last BT injection and not believing it was necessary to return for another injection before the study ended, and (4) being lost to follow-up. For 26 patients lost to follow-up, a questionnaire was mailed to determine their reasons for not returning for BT therapy or evaluation. Of these, 6 patients subsequently returned for further therapy or reported that their symptoms were manageable and that they would return for further treatment if necessary; 8 cited geographic reasons for discontinuing therapy; 4 cited financial reasons for being unable to continue with therapy; and 7 did not return the questionnaires and were unable to contact them. Only 1 patient stated that BT treatment was not helpful.

COMMENT

Although BT therapy for SD has previously been shown to benefit patients in the short term regarding their acoustic and aerodynamic characteristics, the results of the present study demonstrate that the benefit of BT therapy is maintained in the long term and after repeated injections. In a recent retrospective analysis of their long-term experience with BT treatment of SD, Blitzer et al documented subjective improvements in the symptoms of most patients. However, no objective data have been previously documented for patients who receive long-term or ongoing treatment of SD.

Given that adductor SD is essentially a disorder of phonatory airflow secondary to overclosure of the vocal folds, the efficacy of BT in treating SD primarily results from the improvement in translaryngeal airflow after treatment. Most studies of airflow in patients with SD report lower-than-normal airflow rates. Hirano et al reported airflow rates within the reference range in patients with SD. Normal airflow rates also vary based on the source of information. The Aerophone II device manual reports that normal mean airflow in adults is 140 mL/s. Zwirner et al found controls to have mean airflow of 187 mL/s. It is clear in this study that patients with SD have lower-than-normal airflow and that airflow typically increases to higher than normal after therapy with BT. This increase in airflow can be maintained with repeated injections of BT.

The lowest airflow rate occurred at the T1 baseline measurement. Subsequent pretreatment measurements (ie, T3 and T5) show higher airflow rates than at base-

line, which might be due to patients returning for injections before severe deterioration of their voice.

The ideal study would measure airflow in many patients who received the same dose of BT through serial injections over time. However, variation in dosage among patients was occasionally necessary because the optimal balance between degree and duration of symptom relief and the incidence of adverse effects was patient specific. Feedback from patients regarding their experience throughout the interval between injections was incorporated into the decision regarding successive BT doses. Rather than having an ideal quantitative end point for aerodynamic values, a qualitative end point of “optimal voice” with minimal adverse effects was pursued through treatment with BT injections, and the resultant or quantitative airflow values were evaluated to see how they corresponded to a voice that had reduced or resolved symptoms.

Objective acoustic measures are other important tools used widely in the clinical management of voice disorders. The variables evaluated in this study are related to the salient perceptual characteristics of the voice, namely, vocal pitch, loudness, and quality. The F0 measurements, before and after treatment, did not differ significantly compared with control measurements, suggesting that vocal pitch itself is not significantly altered in SD. In a double-blind controlled study of BT treatment in 13 patients with adductor SD, Truong et al also noted that F0 did not differ between BT- and placebo-treated patients. However, they noted that the range of vocal F0 decreased in patients treated with BT compared with placebo. This might suggest that BT diminishes spasmodic movements of the vocal folds even though the overall F0 remains unchanged.

Although F0 in patients with SD is comparable to that of controls, the SDF0 differs significantly between patients with SD and controls. The SDF0 is a reflection of laryngeal stability and has been noted to be significantly higher in patients with SD than controls in previous studies. Both of these studies also showed that BT therapy resulted in a significant decrease in SDF0, suggesting increased laryngeal stability. In our study, SDF0 was also significantly higher in patients with SD compared with the control group. However, the expected trend of decreases in SDF0 after treatment were seen only for the first 2 rounds of measurements, ie, through T4. The final measurements actually showed a marginal increase in SDF0 from T5 to T6. These differences were not statistically significant (P>.05) and thus might be due to chance. One limitation of this analysis is that the sample size decreased at each successive data collection point. Thus, not all patients received measurements of SDF0, as reflected in Table 2. The initial trend of decreases in SDF0, however, suggests increased laryngeal stability after BT therapy.

Jitter and shimmer are measures of vocal perturbation that can be used to detect vocal abnormalities. The idea of using jitter and shimmer to detect or monitor vocal abnormalities is based on the hypothesis (for which there is growing evidence) that healthy vocal folds form a well-balanced system that produces nearly periodic oscillations. Vocal abnormalities might perturb this mechanical balance, producing oscillations that change from period to period in frequency and amplitude. Measure-
ments of jitter and shimmer thus provide an index of the perturbation present within the vocal system. Higher values of jitter and shimmer have been correlated with rough or harsh-sounding voices. Patients with SD clearly have significantly higher jitter and shimmer values compared with controls. This observation has been corroborated in previous studies. Although there is a trend toward decreased jitter and shimmer values after BT therapy, these measurements remain higher than normal.

Signal-to-noise ratio represents the ratio of the energy in the acoustic signal to the noise components in the vocal symptoms and serves as an objective assessment of voice loudness. Typically, a value of 15 or greater is considered normal for SNR. Patients with SD develop an increase in the amount of noise in the acoustic spectrum and thus typically have lower SNR values. No significant change in SNR was noted in this study after BT therapy, although SNR values did trend up at the T2 and T4 postinjection evaluations compared with the T1 and T3 preinjection values. Previous studies have also shown modest increases in SNR values after BT therapy.

Maximum phonation time is a function of airflow across the glottis during phonation. With disorders such as SD that result in low airflow rates, the MPT is expected to be lower than normal. Our pretreatment data are consistent with this expectation. Normative data for MPT obtained in this study agree with those obtained from the literature: 22.2 seconds for men and 18.4 seconds for women. A previous study by Truong et al showed that phonation times did not improve in patients with adductor SD treated with BT. This was believed to be because BT treatment results in chemodenervation of the adductor muscles of the vocal folds, which can cause decreased vocal fold approximation and thus no improvement or even a decrease in phonation time. In the present study, average MPT decreased significantly in the 3 posttreatment groups compared with the 3 pretreatment groups. These results are consistent with the hypothesis of Truong et al and likely reflect increased air escape due to decreased laryngeal resistance after BT therapy.

In addition to quantitative acoustic and aerodynamic data, we qualitatively looked at EMG signals to gauge whether any change resulted with repeated BT injections into the laryngeal muscles. Our observations of lower-amplitude EMG signals with repeated BT injections suggest that the reinnervation process after treatment takes a long time. In addition, because patients are likely to return for additional injections before their symptoms are at their worst, there is likely to be a small chemodenervation effect remaining from the previous injection. This residual effect manifests itself in lower-amplitude EMG signals. Davidson and Ludlow noted that although the physiological effects of BT are reversible, the reinnervation process continues past 12 months after injection.

CONCLUSIONS

This study demonstrates that BT is not only a safe and effective therapy for SD but that its benefit is maintained even with repeated use over the long term. We objectively documented that BT therapy results in an increase in translaryngeal airflow and that this increase is not compromised even with prolonged use. In addition, BT use results in improvements in vocal perturbation measures such as jitter and shimmer, which correlate with perceptual improvements in voice as being less harsh and strangled.

In addition to the objective measures discussed herein, the quality of life, economic impact, and perceptual analysis of voice recordings from this group of patients with SD treated with BT are presented in separate reports (unpublished data, submitted for publication) but parallel the improvements described herein. Treatment with BT continues to provide effective relief of symptoms and voice perturbations in patients who undergo long-term cumulative therapy and might even have a positive and permanent effect on the overall severity of the disorder.

Accepted for publication September 5, 2000.

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REFERENCES