Short- and Long-term Effects of Neuromodulators for Unexplained Chronic Cough

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Abstract

Objective. To evaluate the short- and long-term effects of tricyclic antidepressants (TCAs) and gabapentin in the treatment of unexplained chronic cough (UCC).

Study Design. Prospective cohort.

Setting. Tertiary care hospital.

Subjects and Methods. Patients seen between July 2016 and March 2017 were included following a formal workup and clinical evaluation indicative of UCC. Patients were placed on either a TCA (amitriptyline or nortriptyline) or gabapentin. Leicester Cough Questionnaire (LCQ) and percentage improvement scores were obtained prior to treatment initiation and at 2 and 6 months of neuromodulator treatment. A linear mixed model assessed the change in LCQ score between the 2 treatment time points and baseline scores.

Results. Twenty-eight patients completed a total of 37 neuromodulator trials. Gabapentin demonstrated statistically significant improvement in LCQ scores at 2 months (2.48 points, \( P < .01 \)) and 6 months (5.40 points, \( P = .01 \)) of treatment as compared with baseline. Patients taking TCAs demonstrated statistically significant improvement of LCQ scores at 2 months of treatment (3.46 points, \( P < .01 \)). However, the majority of patients discontinued treatment, most commonly secondary to the development of tachyphylaxis after 2 months, precluding analysis at 6 months.

Conclusion. While both neuromodulator classes demonstrated short-term benefit, the majority of patients discontinued treatment prior to 6 months, with patients taking TCAs discontinuing more frequently than patients on gabapentin. Future investigations are warranted evaluating tachyphylaxis and the utility of dual treatment therapies designed to address peripheral and central sensory pathways involved in UCC.
The outcomes of either neuromodulator. The purpose of this study was to examine the short- and long-term efficacy of tricyclic antidepressants and gabapentin with validated cough measurements.

**Methods**

Following Cleveland Clinic Institutional Review Board approval, a prospective study was conducted on UCC from July 2016 and March 2017 with patients who were prescribed gabapentin, amitriptyline, or nortriptyline with the intention of completing 6 months of neuromodulator treatment. Participants were initially evaluated in a laryngology clinic or a multidisciplinary cough clinic, consisting of otolaryngology, pulmonology, and speech language pathology evaluation. Patient were assessed per ACCP algorithms (see Supplemental Table S1, available in the online version of the article). Patients were included if their history suggested cough hypersensitivity and they were refractory to empiric treatment for common causes of cough. All other patients, including those who failed to follow up or those whose cough resolved independently, were excluded. Baseline demographics were recorded, including sex, age, duration of cough, comorbidities related to chronic cough, and concurrent speech therapy. Each patient completed a list of questions pertaining to common symptoms and triggers. Figure 1 details the protocol used for neuromodulator selection, drug titration, and follow-up.

**Outcome Measures**

The Leicester Cough Questionnaire (LCQ) was the primary method of measuring treatment success. The LCQ is a validated measurement of cough severity that provides a score between 3 and 21 based on the physical, psychological, and social burden of a patient’s cough. Lower LCQ scores indicate a cough severely affecting quality of life, while a higher score indicates a more favorable health status. The minimal clinically important difference in LCQ score change is 1.3 points, while moderate and large clinically important differences (MoCID and LCID) are 1.7 and 2.7 points, respectively. LCQ forms were completed prior to treatment initiation (baseline) and at 2 and 6 months of treatment. With each LCQ measurement, a percentage improvement score was also recorded, as it is a common method of measuring subjective cough improvement. When patients discontinued neuromodulator treatment before 6 months, an explanation was sought, such as no therapeutic benefit, intolerable side effects, or the development of tachyphylaxis. We define tachyphylaxis as diminishing benefit from a previously effective neuromodulator. We offered an alternative neuromodulator to patients who quit prior to 6 months, obtaining 2-month LCQ scores from these additional trials if available.

**Statistical Analysis**

Associations among baseline characteristics, comorbidities, symptoms, and triggers with LCQ scores were investigated with Wilcoxon rank sum tests. LCQ scores tracked over time for the various treatment groups were modeled with a linear mixed model based on an assumption of an autoregressive first-order correlation structure. This model accounts for the repeated measures over time and allows for

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**Figure 1.** Patient factors determine neuromodulator selection with gradual titration based on response (lowest dose achieving at least 80% perceived cough control) and side effects. Problematic side effects are immediately reported to make treatment adjustments. SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; UCC, unexplained chronic cough.
the inclusion of all patient trials regardless of whether patients completed both the 2- and 6-month LCQs or just the 2-month LCQ. Within this modeling framework, contrast statements investigated the primary comparisons of interest, such as LCQ changes from baseline to 2 months and from baseline to 6 months for the gabapentin and tricyclic antidepressant cohorts. A similar analysis was conducted keeping amitriptyline and nortriptyline separate to ensure that included only initial patient trials. How percentage improvement scores correlated with changes in LCQ scores was assessed with a Pearson correlation analysis.

## Results

### Patient Population and Demographics

During enrollment, 59 patients with chronic cough were evaluated. Thirty-four demonstrated sufficient evidence through clinical history, diagnostic testing, or previously failed empiric treatment to support a diagnosis of UCC. Two patients with spontaneously resolving coughs and 4 patients who failed to complete 2 months of any neuromodulator treatment were excluded. Therefore, the study cohort consisted of 28 patients, who were predominantly women (57%), who had a mean age of 61 years (range, 34-77 years), and whose mean duration of cough was 7.93 years (range, 2 months to 21 years). Half the cohort reported developing the cough following a resolved upper respiratory illness. Ten patients were previous smokers. Twelve patients agreed to undergo concurrent speech pathology–led cough suppression therapy. Table 1 provides a list of chronic cough–related conditions for which the cohort was previously diagnosed and refractory to treatment. The most common comorbidities reported were gastroesophageal reflux disease, followed by upper airway cough syndrome. Table 2 summarizes the diagnostic workup and prior treatment for all patients. There was no evidence of any association between LCQ change at 2 months and any recorded demographics, comorbidities, or behavioral therapy (all $P > .05$).

### Symptoms and Triggers

Table 3 contains frequently reported cough triggers and symptoms. Patients most commonly complained of paroxysmal spasms of coughing (75%), followed by throat irritation and throat clearing (both 71%). The most frequently reported cough triggers were talking and position change (both 79%). Wilcoxon rank sum testing revealed that patients who complained of paroxysmal spasms or dysphonia or had a cough triggered by talking demonstrated significantly better LCQ scores after 2 months of treatment (all $P < .05$).

### Neuromodulators and LCQ Improvement

Mean individual and group average LCQ scores for both neuromodulator classes are presented in Figure 2. Twenty-one patients constituted the gabapentin group, with 19 being in their first neuromodulator trial and 2 completing their trial after discontinuing a tricyclic antidepressant. Nineteen 2-month LCQ scores were obtained from these 21 trials of gabapentin (Table 4). The median change in LCQ for gabapentin through 2 months of treatment demonstrated a significant increase ($P < .01$) of 2.48 points (600 mg, median; 300 mg, mode), with 11 trials (58%) achieving the MoCID (3 trials) or LCID (8 trials) for the LCQ. Analysis of LCQs from the 17 patients who started the study on gabapentin yielded similar results (2.48-point increase, $P = .01$). Of these 17 patients, 10 (59%) completed 6 months of treatment, recording a 5.40 increase in LCQ points from baseline ($P < .01$; 900 mg, median/mode), with 9 (90%) patients achieving the MoCID (2 patients) or LCID (7 patients) for LCQ.

Nine patients were initially prescribed a tricyclic antidepressant, while 7 tried the drug class after discontinuing gabapentin before 6 months (Table 4). Fifteen 2-month LCQs were obtained from these 16 trials. The median change in LCQ for tricyclic antidepressants at 2 months was a significant ($P < .01$) 3.46-point increase (30 mg, median/mode), with 9 trials (60%) achieving the MoCID (1 trial) or LCID (8 trials) for the LCQ. Additionally, a secondary analysis of the 9 patients who began the study with a tricyclic antidepressant demonstrated a significant change (4.27-point increase, $P < .01$). Unfortunately, there was a notable drop-off in the number of patients completing 6 months of treatment, preventing a meaningful analysis of the 6-month scores and leaving only 3 available scores ($-0.27$, +6.41, and +7.07 points). Upon separate examination of amitryptiline...
and nortriptyline (n = 6), the observed effects were similar (amitriptyline, 4.27-point increase; nortriptyline, 2.99-point increase), supporting the combination of these tricyclics into 1 group. Despite the improvements with either neuromodulator class, no patient reported complete cough cessation at 2 or 6 months.

**Percentage Improvement**

Percentage improvement scores were compared with change in LCQ score at 2 and 6 months. There was a significant correlation between the measurements of improvement at 2 months (Figure 3; coefficient, 0.76; 95% CI, 0.53-0.89; \( P < .001 \)). Another significant correlation was observed at 6 months, although with a much wider confidence interval due to the smaller sample size (0.82; 95% CI, 0.38-0.95; \( P = .004 \)).

**Overall Outcomes**

Of the 13 patients who successfully completed 6 months of treatment with the first neuromodulator prescribed, 4 quit shortly after the data acquisition at 6 months, reducing this total to 9 (Table 5). The majority of treatment failures

### Table 2. Diagnostic Workup Summary of Study Cohort.

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Positive for</th>
<th>No Workup</th>
<th>Either Workup or</th>
<th>Explanation for Patients with</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior Workup</td>
<td>but Empiric Treatment</td>
<td>Empiric Treatment</td>
<td>Negative Testing</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>19 (68)</td>
<td>9 (32)</td>
<td>28 (100)</td>
<td>1 patient included following a history of cough trigger and a significant response to nortriptyline</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>27 (96)</td>
<td>0 (0)</td>
<td>27 (96)</td>
<td>I patient included who did not receive exhaled nitric oxide or empiric treatment with steroids but received other pulmonary testing, which was negative; also demonstrated multiple triggers on examination</td>
</tr>
<tr>
<td>Pulmonary exhaled nitric oxide</td>
<td>18 (64)</td>
<td>9 (32)</td>
<td>27 (96)</td>
<td></td>
</tr>
</tbody>
</table>

| Sinonasal | 28 (100) | N/A | 28 (100) | |
| Allergies | 16 (57) | 12 (43) | 28 (100) | |

*The table depicts the number of patients who received formal testing in the organ system specified, did not have formal diagnostic testing but received empiric treatment, or did not have formal testing or complete empiric treatment. The reason for inclusion of patients in the last category is given on the far right. As upper airway cough syndrome, rhinitis, and sinusitis are all diagnosed through clinical examination, all patients effectively had workups for sinonasal pathology during their initial visits. The diagnostic testing performed for each organ system was based on the formal recommendations by the American College of Chest Physicians.*

### Table 3. Cough Symptoms and Triggers.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Yes (%)</th>
<th>Triggers</th>
<th>Yes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal spasms</td>
<td>21 (75)</td>
<td>Talking/singing/laughing</td>
<td>22 (79)</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>20 (71)</td>
<td>Position change</td>
<td>22 (79)</td>
</tr>
<tr>
<td>Throat clearing</td>
<td>20 (71)</td>
<td>Odors, fumes, scents, or aerosols</td>
<td>15 (54)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>16 (57)</td>
<td>Deep breath</td>
<td>14 (50)</td>
</tr>
<tr>
<td>Globus sensation</td>
<td>15 (54)</td>
<td>Eating</td>
<td>14 (50)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>16 (57)</td>
<td>Exercising</td>
<td>13 (46)</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>9 (32)</td>
<td>Cold air</td>
<td>12 (43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Changes in temperature</td>
<td>11 (39)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxiety</td>
<td>10 (36)</td>
</tr>
</tbody>
</table>

*Percentages are based on 28 patients. Questions were adapted from Chung’s 2014 review article on cough hypersensitivity.*

\( n = 9 \) and nortriptyline (n = 6), the observed effects were similar (amitriptyline, 4.27-point increase; nortriptyline, 2.99-point increase), supporting the combination of these tricyclics into 1 group. Despite the improvements with either neuromodulator class, no patient reported complete cough cessation at 2 or 6 months.

Percentage improvement scores were compared with change in LCQ score at 2 and 6 months. There was a significant correlation between the measurements of improvement at 2 months (Figure 3; coefficient, 0.76; 95% CI, 0.53-0.89; \( P < .001 \)). Another significant correlation was observed at 6 months, although with a much wider confidence interval due to the smaller sample size (0.82; 95% CI, 0.38-0.95; \( P = .004 \)).

**Overall Outcomes**

Of the 13 patients who successfully completed 6 months of treatment with the first neuromodulator prescribed, 4 quit shortly after the data acquisition at 6 months, reducing this total to 9 (Table 5). The majority of treatment failures...
during the first trial were due to a diminishing therapeutic effect of the neuromodulator over time (labeled “tachyphylaxis”). For all neuromodulator trials, no perceived benefit was the most common cause of drug discontinuation (Supplemental Table S2, available in the online version of the article). Side effects were the least common reason for drug discontinuation (Supplemental Table S3, available in the online version of the article).

**Discussion**

The origins of UCC are not fully elucidated but are possibly due to repetitive stimulation by noxious stimulants (viral antigens, allergens, adjacent disease processes) causing phenotypic changes in the type or quantity of receptors on afferent airway neurons and leading to increased activation of the cough reflex. While this explains benign cough triggers, it does not fully explain the paroxysmal coughing bouts observed in the absence of stimuli or the refractory response to maximal empiric treatment of patients with UCC. These other observations point to an additional process, referred to as central sensitization, where the pre– and post–synaptic receptor changes, synaptic remodeling, and neuroinflammation that occur within the sensory circuits of the spinal cord, brainstem, somatosensory cortex, and noradrenergic descending pain modulatory pathways result in a state of neuronal overexcitability that remains after removal of an inciting stimulus. Recent functional magnetic resonance imaging studies of patients with chronic cough

**Table 4. Neuromodulator Trials.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients, n</th>
<th>LCQ Scores, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st Trial</td>
<td>2nd Trial</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>8</td>
</tr>
</tbody>
</table>

Abbreviation: LCQ, Leicester Cough Questionnaire.

As some patients discontinued treatment prior to completing a 2-month LCQ score, the number of LCQ scores is less than the sum of all trials for each neuromodulator.

bOnly patients in the first trial of neuromodulator were able to complete 6 months of treatment within length of study.

**Table 5. Outcomes of the First Neuromodulator Trial.**

<table>
<thead>
<tr>
<th>Neuromodulator, n (%)</th>
<th>First trials</th>
<th>Trial successes b</th>
<th>Trial failures</th>
<th>Reason for failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6</td>
<td>1 (17)</td>
<td>5</td>
<td>No benefit</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1 (33)</td>
<td>2</td>
<td>Tachyphylaxis</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>7 (3)</td>
<td>12</td>
<td>Side effects</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>9 (32)</td>
<td>19</td>
<td>Other</td>
</tr>
</tbody>
</table>

Abbreviation: LCQ, Leicester Cough Questionnaire.

The ultimate outcomes of the first neuromodulator that each patient attempted are listed here.

bSuccess is defined as a patient achieving a 6-month LCQ score at least 1.3 points higher than baseline and not quitting the medication at 6 months. For a summary table of outcomes for all neuromodulator trials (not just first), see Supplemental Table S2 (available in the online version of the article).
provide evidence that the processes described in models of neuropathic pain are likely occurring in UCC.17

The neuromodulators are believed to treat the hypersensitivity and central sensitization observed in patients with UCC, as they do for patients with neuropathic pain. While gabapentin is known to classically exert its effect within the central nervous system through inhibition of voltage-dependent calcium channels, more recent investigations demonstrated its ability to increase noradrenergic signaling within the locus coeruleus (brainstem nuclei located upstream of descending pain modulatory pathways).19-21 Tricyclic antidepressants, which are fundamentally serotonin-norepinephrine reuptake inhibitors, also work in descending pain pathways.19 Gabapentin is currently recommended by the ACCP for use in UCC.3 While a randomized placebo-controlled trial of amitriptyline in UCC was performed in 2006, issues with the reporting of the randomization and blinding protocol swayed the ACCP from using the data to make a formal recommendation.2,22 We successfully completed a prospective analysis examining the short- and long-term improvements observed among patients taking a tricyclic antidepressant or gabapentin in the treatment of UCC using the previously validated LCQ as our primary measure.12 With our LCQ scores, we observed a significant improvement in cough symptoms among patients taking a tricyclic antidepressant. As the majority of these changes were above the LCID for the LCQ (8 of 9 patients), our data support the expectation that patients who benefit from tricyclic antidepressants should experience a robust response to treatment within a short-term period. Gabapentin also demonstrated efficacy through 2 months, consistent with the results of a previous randomized trial.23 However, only gabapentin maintained efficacy at 6 months, as nearly all patients on a tricyclic antidepressant discontinued by this time, with a lack of benefit the most willing to undergo a nonpharmacologic intervention. Therefore, baseline LCQ scores between patients who did and did not do speech therapy were similar, which is why we are unable to provide an explanation for this result.

**Limitations and Future Directions**

There are several limitations to our work. While we made every effort to enroll as many patients with UCC as possible, our cohort consisted of only 28 patients. While the sample appears small, it is relatively the same size as those in other recent prospective cough studies.30-32 Additionally, we unexpectedly benefited from the additional neuromodulator trials that some of our study participants completed, which provided additional 2-month LCQ scores for analysis. Inclusion of multiple treatment trials was deemed permissible from our findings in a separate retrospective analysis performed on previously treated patients with UCC, where approximately 40% of patients who benefited from neuromodulator treatment did so with their second or third neuromodulator attempt. This benefit often came following failure with a different neuromodulator class, supporting the notion that completely different responses to neuromodulators can be observed within the same patient (unpublished data). As not including subsequent or multiple neuromodulator trials would be ignoring a clinically relevant finding in this patient population, we were obligated to include these additional trials in our primary analysis. Of note, due to
the length of the study, only a small subset of patients contributed data for multiple treatment trials. To control for this variation, we performed sensitivity analyses including only the results of the patient’s first neuromodulator trial. While our data are largely consistent through these additional analyses, we do acknowledge the added layer of complexity that comes with including these additional neuromodulator trials, which we again believe points to the difficulty in studying this patient population.

As our study was nonrandomized, with neuromodulator selection based on decision making employed by the senior author in routine clinical practice (Figure 1), we do acknowledge the possible influence of selection bias on our reported outcomes. This precluded us from performing an intergroup analysis between gabapentin and tricyclic antidepressant groups. Despite these limitations, we believe that our study, a prospective analysis on the 2 primary neuromodulator classes used to treat UCC, provides valuable insight for clinicians. Our study demonstrates that the majority of patients with UCC who experience benefit with a neuromodulator have moderate to large clinically important improvements in cough control (as demonstrated by LCQ scores) in the short term. While robust responses to treatment are seen at 6 months, they are sparsely observed, as the majority of patients either develop tachyphylaxis to treatment or become intolerant of side effects. This study comes as gains in our understanding of the pathophysiology underlying UCC provides new drug targets, such as the P2X purinoceptor 3, which has a chiefly peripheral site of action. While the inhibitor was effective at reducing coughing, it did not entirely resolve symptoms, likely from not addressing the central hypersensitivity seen among these patients. This is essentially the opposite of our findings with gabapentin and tricyclic antidepressants, which are believed to work centrally but not peripherally, explaining why few of our patients experienced complete resolution of their cough. Clearly, future therapeutic interventions are warranted that address peripheral and central sensory changes, either with new drugs or dual treatments (eg, gabapentin + P2X purinoceptor 3 inhibitor).

**Conclusion**

While tricyclic antidepressants demonstrated short-term efficacy, the majority of patients did not complete 6 months of treatment. Tachyphylaxis was a clinically important finding observed in both drug classes. Percentage improvement scores appear effective at capturing subjective improvement with chronic cough treatment. Investigations of treatment therapies are warranted that address peripheral and central sensory pathways involved in UCC.

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**Author Contributions**

Andrew Jay Bowen, study design, data acquisition, statistical analysis of the data, manuscript preparation and revision, final manuscript approval; Amy S. Nowacki, statistical analysis of the data, study concept and design, manuscript preparation and revision, final manuscript approval; Kevin Contrera, study design, statistical analysis of the data, manuscript preparation and revision, final manuscript approval; Douglas Trask, study concept and design, manuscript preparation and revision, final manuscript approval; James Kaltenbach, study concept and design, manuscript preparation and revision, final manuscript approval; Claudio F. Milstein, data acquisition, manuscript preparation and revision, final manuscript approval; Michelle Adessa, data acquisition, manuscript preparation and revision, final manuscript approval; Michael S. Benninger, study design, manuscript preparation and revision, data interpretation, final manuscript approval; Rachel Taliercio, data acquisition, manuscript preparation and revision, final manuscript approval; Paul C. Bryson, study concept and design, data acquisition, manuscript preparation and revision, final manuscript approval;.

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**Supplemental Material**

Additional supporting information is available in the online version of the article.

**References**


