Tachyphylaxis and Dependence in Pharmacotherapy for Unexplained Chronic Cough

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Abstract

Objective. Unexplained chronic cough (UCC) is a perplexing condition treated with neuromodulators. Although previous literature describes the effectiveness of neuromodulators, there is little on the development of tachyphylaxis or dependence to neuromodulators over time. Our objective is to capture the experience of a large cohort of patients with UCC over an extended period, looking for these 2 phenomena.

Study Design. Case series with chart review.

Setting. Tertiary care hospital.

Subjects and Methods. We performed a retrospective review of patients diagnosed with UCC from 2010 to 2014. Patient outcomes were measured through percentage improvement scores. Treatment failures were attributed to no benefit, intolerable side effects, or tachyphylaxis. Tachyphylaxis was defined as the need for higher doses of medication following diminishing therapeutic benefit, while dependence was defined as a failure to stop therapy following attempted de-escalation or resurgence following drug cessation.

Results. Sixty-eight patients were included in the study. Tachyphylaxis was observed among 35% of patients while dependence was observed among 27% of successfully treated patients, together effecting >50% of the cohort. Sixty-eight percent of patients ultimately experienced successful treatment with neuromodulators, demonstrating strikingly distinct responses to different neuromodulator drug classes.

Conclusion. Tachyphylaxis and dependence occur frequently during UCC treatment and have a major impact on treatment outcomes. Patients sometimes demonstrate distinct responses to different neuromodulator classes. The majority of patients will experience successful treatment for their cough, although several trials may be required.

Keywords

cough, chronic cough, unexplained chronic cough, tachyphylaxis, dependence, cough hypersensitivity syndrome, gabapentin, amitriptyline, nortriptyline

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Unexplained chronic cough (UCC) describes a chronic cough that is refractory to medical treatment or without any identifiable cause. The pathophysiology of this condition is believed to parallel the current theory behind neuropathic pain: plastic changes at the level of the peripheral and central nervous system leading to alldynia, in this case of the cough reflex. The current pharmacotherapy for this “hypersensitivity syndrome” of the airway is also similar, with tricyclic antidepressants (mostly amitriptyline) and gabapentin commonly prescribed. Although multiple studies support the use of neuromodulators in UCC, the condition remains difficult to treat. In line with our clinical experience, Bastian and Bastian’s recent case series reported a 40% frequency of neuromodulator failure requiring a second trial. We have also observed patients fail previously effective neuromodulator t

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treatment following a diminishing response to therapy, or “tachyphylaxis”—a phenomenon alluded to in a long-term retrospective analysis of patients with UCC who were treated with amitriptyline. For our treatment-responsive patients, we also frequently observe an inability to discontinue treatment secondary to cough resurgence. Such a “dependence” to treatment was referenced in the 2012 landmark randomized controlled trial for gabapentin when Leicester Cough Questionnaire responses returned to pretreatment values following drug discontinuation.

As tachyphylaxis and dependence could have significant implications on treatment success and patient expectations, there is a need to thoroughly describe them. Through a retrospective analysis of all patients treated from the start of our practice, we aim to investigate the occurrence of tachyphylaxis and dependence in this population.

**Methods**

Following Cleveland Clinic Institutional Review Board approval, a retrospective chart review was conducted on all patients with chronic cough who visited the senior author’s otolaryngology clinic between September 2010 through December 2014. Patients who were diagnosed with UCC by the senior author, in accordance with guidelines recommended by the American College of Chest Physicians (see Supplemental Table S1, available in the online version of the article), were included in the study. Aside from a UCC diagnosis, we chose to focus only on patients who agreed to undergo neuromodulator treatment with a tricyclic antidepressant (amitriptyline, nortriptyline, or desipramine), gabapentin, or tramadol. Finally, we included only patients who had at least 1 follow-up encounter (telephone or office visit), reporting a duration of neuromodulator treatment of at least 1 month. Patients who did not meet these criteria were considered lost to follow-up.

The practice pattern of the senior author during this period is detailed. Dosages were titrated for 4 to 8 weeks until either the maximum dosage (Figure 1) was reached or a patient experienced at least an 80% improvement in cough symptoms. While an attempt to reach an 80% improvement in cough symptoms was made for all patients, some were unable to reach this percentage improvement without developing side effects. The senior author typically treated these patients at lower doses if they reported some benefit from a neuromodulator, although most were directed to try another neuromodulator unless percentage improvement was >50%. For those patients with a partial improvement (<80% subjective response), the senior author and the patient would often make a shared medical decision regarding changing neuromodulator. Patients who failed their neuromodulator treatment (detailed later) were given the opportunity to try another neuromodulator trial. Patients reporting successful treatment with their cough stayed on their neuromodulator for 6 months, with instructions to follow up monthly (telephone or in office). Typically, a discussion on dosage de-escalation or treatment discontinuation was initiated after 6 months.

To analyze the retrospective cohort, percentage improvement scores were used to classify each patient’s neuromodulator trial as a “treatment success” (if complete/near complete or partial response) or as a trial failure (no response considered a trial failure; Figure 1). Patients could fail a drug trial secondary to any of the following: no response (<50% improvement in cough symptoms), side effects, or tachyphylaxis. For patients who failed a trial and declined to undergo a subsequent trial, cases were labeled “treatment failures.” Tachyphylaxis was recorded when evidence suggested that a patient’s previously effective neuromodulator was no longer controlling his or her cough (manifested as decreasing percentage improvement scores).
This was separate from the patient’s initial dose escalation. This could result in either a trial failure or a higher dose (observed only for “total success” cases). Any findings in the chart of an attempted down titration or drug discontinuation that resulted in cough resurgence and the need to remain on the drug was considered a manifestation of dependence (thus, by definition, observed only in “treatment success” cases). The development, type, and consequence of side effects with each corresponding medication were also recorded.

Associations among successful response and patient demographics, comorbidities, prior treatments, and concurrent treatments were examined with Fisher’s exact tests or logistic regression. Analyses were conducted with JMP Pro 13.0 (SAS Institute Inc, Cary, North Carolina).

## Results

From September 2010 to December 2014, approximately 176 patients presented with a chronic cough: 84 had a cough from a previously untreated cause, while 92 demonstrated sufficient evidence of UCC. As there was insufficient data for 24 patients, 68 were included, who were primarily females (65%), with a mean age of 59 years (range, 18-88 years). The median duration of cough prior to presentation was 36 months (range, 3-600 months). Twenty-two percent of patients reported a previous trial of neuromodulator prior to presentation. The median length of follow-up following administration of neuromodulator was 21 months (range, 1-72 months). While 31% of the cohort had a history of smoking, 1 patient was currently smoking at initial presentation and was included in the study following complete resolution of the cough with gabapentin.

Table 1 shows the workup and history of empiric treatment for each patient. While the majority of patients had either a complete workup or history of failed empiric treatment for prior identified causes of their cough, some had neither. An explanation for their inclusion is detailed in the table. For a breakdown of prior identified causes of cough and treatment history for the cohort, see Supplemental Table S2 (available in the online version of the article).

The majority of patients during the study period were initially prescribed amitriptyline for their cough (Table 2): 29 experienced success with the first neuromodulator trialed, and the remaining 39 were offered additional neuromodulators. For every additional medication trial, the odds of finding success decreased by approximately 53% ($P < .001$). However, 19 of these patients ultimately found treatment success, resulting in a success rate of 67% for all patients (48 of 71).

Comparing overall treatment success rates, we found that patients who underwent concomitant behavior cough suppression therapy demonstrated a statistically significant lower rate of success versus those who did not (59% vs 92%, $P < .01$). No other notable trends among prior identified cough diagnoses, smoking history, duration of cough, or age of presentation were noted ($P > .05$).

For 35 (>50%) of our patients, we observed at least 1 incident of tachyphylaxis or dependence. Tachyphylaxis was observed 35 times among 24 patients, making for a 35% incidence rate per patient (Table 3). Nine patients demonstrated tachyphylaxis with the medication with which they achieved treatment success, as evidenced by escalating doses around the last follow-up. Successful patients also demonstrated the development of dependence on 13 occasions, for a 27% incidence rate.

Of the 68 patients, 40 experienced side effects (Table 4). Although the highest side effect rate was with amitriptyline, this led to drug discontinuation 26% of the time when compared with gabapentin and nortriptyline, where side effects resulted in drug discontinuation >40% of the time. Sedation was the most reported side effect for amitriptyline, gabapentin, and nortriptyline (described in Supplemental Table S3, available in the online version of the article).

The causes of failures are summarized in Table 5. Half of failed trials were secondary to no benefit. Twenty-eight percent of drug failures were due to the development of tachyphylaxis, with nearly a third of these cases following a upper respiratory infection. Amitriptyline had the highest rate of discontinuation secondary to tachyphylaxis, in contrast to gabapentin and nortriptyline, where it...
was the cause once. Twenty percent of drug failures were due to side effects, with sedation the most common complaint.

**Discussion**

We performed one of the largest retrospective reviews of patients with UCC to date to examine the rate of tachyphylaxis and dependence to neuromodulator treatment. To our knowledge, only 1 previous study examining neuromodulator treatment actively assessed for tachyphylaxis. More recently, Ryan and Cohen called for more investigation into the development of tolerance with neuromodulators when they observed a decrease in the number of patients experiencing benefit with amitriptyline after 2 years. Our study found a 35% incidence rate of tachyphylaxis among patients, which was responsible for 28% of all failed drug trials in this population, very similar to the results of our recent prospective study (28% incidence rate, 25% all failed trials [unpublished data]). We believe that this patient group was often masked within side effects in prior studies, as many patients developed side effects when their dosage was increased following a diminished therapeutic benefit. This could explain why our percentage of patients quitting therapy secondary to side effects was so low when compared with that from Ryan and Cohen’s study, where it was responsible for half of all drug discontinuations.

Prior investigations in neuropathic pain animal models identified the locus coeruleus (LC) and the noradrenergic neurons that originate in this nucleus as the site of therapeutic action for gabapentin and amitriptyline. Gabapentin works to promote the release of sequestered intracellular glutamate by glutamate transporter 1 (GLT-1; the opposite of its normal function) from LC nuclei into the extracellular matrix, where it activates noradrenergic descending pain-modulatory neurons. Through alpha-2 adrenergic receptors (site of action of the tricyclic antidepressants) located between these descending modulatory fibers and the dorsal horn of the spinal cord, the antihypersensitivity effect of these drugs is mediated as aberrant sensory transmission passing through the dorsal horn is suppressed. However, over time, downregulation of GLT-1 on LC nuclei leads to reduced noradrenergic signaling and pain modulation despite receiving the same dose of gabapentin. Although these mechanisms were observed in an animal model of a different pathologic process, such a phenomenon would explain the tachyphylaxis observed in both neuromodulator groups. As UCC and neuropathic pain are considered analogous disease processes, we believe at the very least that a similar process occurred in our patient population.

While the efficacy of gabapentin decreased over time in an animal model of neuropathic pain, it was restored with the administration of valproate, which increased the expression of GLT-1 in the LC. As tachyphylaxis is responsible for a clinically significant amount of trial failures, rescue pharmacotherapy strategies such as valproate should be investigated. Additionally, approximately 30% of tachyphylaxis-induced drug failures occurred after a upper respiratory infection or an “exacerbation of allergies.” This may be another opportunity to intervene before drug failure, as clinicians could increase

<table>
<thead>
<tr>
<th>Table 2. Medication Response.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Amithriptyline</td>
</tr>
<tr>
<td>Desipramine</td>
</tr>
<tr>
<td>Gabapentin</td>
</tr>
<tr>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Tramadol</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

*Values are presented as n (%). Percentages represent patients who received successful treatment of their cough at the trial. Patients may have had multiple trials of medication. Other refers to patients who were placed on multiple neuromodulators simultaneously (eg, gabapentin + amitriptyline).
neuromodulator dose, recommend a corticosteroid burst/taper, or even prescribe a short course of opioids during an illness. Clearly, more work is needed to address tachyphylaxis before it leads to neuromodulator failure in this challenging patient group.

We are also one of the first to report on the development of drug dependence, which affected nearly 30% of successfully treated patients. When these patients attempted to stop or titrate down on medication, the cough returned, only to be remedied by the same neuromodulator. It appears that while gabapentin and tricyclic antidepressants are effective at reducing aberrant stimulation of the cough reflex, they do not address the pre- and postsynaptic receptor changes, synaptic remodeling, and neuroinflammatory state that led to the hyper-sensitive state. This explains why many of our successfully treated patients remain neuromodulator dependent for years. The current recommendations for discontinuing neuromodulator therapy suggest initiating a discussion about dose de-escalation around 6 months. Although we do support early drug discontinuation, we do think that patients should be

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Table 3. Rates of Tachyphylaxis and Dependence per Drug.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Trials with Medication, n</th>
<th>Tachyphylaxis</th>
<th>Dependence, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>53</td>
<td>18 (34)</td>
<td>11.0</td>
</tr>
<tr>
<td>Desipramine</td>
<td>15</td>
<td>4 (27)</td>
<td>2.0</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>32</td>
<td>4 (13)</td>
<td>7.5</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>11</td>
<td>2 (18)</td>
<td>6.8</td>
</tr>
<tr>
<td>Tramadol</td>
<td>13</td>
<td>3 (23)</td>
<td>11.0</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>3 (25)</td>
<td>11.0</td>
</tr>
<tr>
<td>Total</td>
<td>136</td>
<td>35 (26)*</td>
<td>13 (27)</td>
</tr>
</tbody>
</table>

*Percentage represents number of times that tachyphylaxis was observed in all medication trials. In total, 24 patients experienced 35 tachyphylaxis events, translating to 35% incidence of tachyphylaxis per neuromodulator trial.

Table 4. Medication Adverse Effects.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients, n (%)</th>
<th>Amitriptyline(n = 47)</th>
<th>Desipramine(n = 14)</th>
<th>Gabapentin(n = 32)</th>
<th>Nortriptyline(n = 11)</th>
<th>Tramadol(n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Had side effect</td>
<td>27 (57)</td>
<td>4 (29)</td>
<td>13 (41)</td>
<td>4 (36)</td>
<td>6 (60)</td>
</tr>
<tr>
<td></td>
<td>Quit drug due to side effect</td>
<td>7 (26)</td>
<td>1 (25)</td>
<td>6 (46)</td>
<td>2 (50)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Median dose, mg</td>
<td>25</td>
<td>38</td>
<td>600</td>
<td>20</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

*Sample sizes cited per drug indicate patients who tried a medication at least once.

Table 5. Causes of Medication Failure.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Failed Trials, n (%)</th>
<th>Due to Tachyphylaxis</th>
<th>Due to No Benefit</th>
<th>Due to Side Effects</th>
<th>Median Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Total: 34</td>
<td>14 (41)</td>
<td>13 (38)</td>
<td>7 (21)</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Due to Tachyphylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>12</td>
<td>4 (33)</td>
<td>7 (58)</td>
<td>1 (8)</td>
<td>25</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>20</td>
<td>1 (5)</td>
<td>13 (65)</td>
<td>6 (30)</td>
<td>600</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>5</td>
<td>1 (20)</td>
<td>2 (40)</td>
<td>2 (40)</td>
<td>10</td>
</tr>
<tr>
<td>Tramadol</td>
<td>9</td>
<td>2 (22)</td>
<td>4 (44)</td>
<td>3 (33)</td>
<td>50</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>3 (38)</td>
<td>5 (62)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>25 (28)</td>
<td>44 (50)</td>
<td>19 (22)</td>
<td></td>
</tr>
</tbody>
</table>

*Percentages across each row are drug specific except for the bottom, where they represent the percentage of all failed trials.
Informed of the possibility of developing dependence and requiring treatment that could last for years or indefinitely.

Our study represents one of the largest retrospective cohort studies of patients with UCC, representing >4 years of clinical treatment of UCC. As is our routine clinical practice, percentage improvement scores were used to capture patient progress and guide dosage titration (titrate to 80% subjective cough improvement rather than to a predetermined level). While this is not a validated measure of cough improvement, it is easy to understand and to administer to patients, which is particularly useful when the telephone is the primary method for follow up. Additionally, in our recent prospective study of patients with UCC, we found a statistically significant positive correlation between percentage improvement and Leicester Cough Questionnaire scores, a validated measuring tool (unpublished data).

Based on 50% cough improvement as the distinction between benefit (at least partial) and no benefit, 71% of our patients benefited from neuromodulator therapy for chronic cough, with therapeutic dosages similar to prior investigations. Maximum therapeutic response typically occurred at a median of 3 months, although the mode was actually 1 month. We therefore believe that a prompt response to neuromodulator treatment should be expected when the drug is going to work. Sixty percent of the patients with treatment success found success during the first medication trial, while success rates in subsequent trials remained <33%. This finding and our logistic regression assessing the effect of total medications prescribed on the final outcome suggest that the greatest chance of success comes during the first trial. Additional trials are not futile, however, as 40% of patients who ultimately experienced treatment success did so during a subsequent trial. Therefore, clinicians should encourage additional neuromodulators when needed, recognizing that successful treatment can take up to 5 medications. It is also important to acknowledge that neuromodulators do not provide meaningful clinical improvement to all patients, as was the case for the medication trials considered “failures” when the response was <50%.

When we focus solely on the results of the first medication trial, we find that patients experienced the most success with gabapentin and nortriptyline, with a low side effect frequency versus amitriptyline. However, in instances where they experienced side effects, patients were more apt to quit treatment than they were with amitriptyline. Additionally, our 2 most concerning side effects occurred with gabapentin (suicidal ideation and possible Parkinson’s exacerbation). These are rare side effects that, to our knowledge, have not been described in the cough literature. The frequency of side effects appears to be independent of the dose, as the median dose with side effects was the same or lower than the therapeutic median dose. Also notable was that, despite nearly 60% of our patients reporting a side effect (40 of 68), it was intolerable only 35% of the time.

Our finding of poorer outcomes among patients undergoing or previously having undergone cough behavioral suppression therapy is contradictory to the overwhelming amount of evidence demonstrating behavioral cough suppression therapy to be one of the best interventions for chronic cough. From our experience offering behavioral cough suppression therapy, only the most debilitated coughers with a history of failed interventions are the most willing to undergo this nonpharmacologic intervention. Thus, the discrepancy between our findings and the reported literature comes from the treatment acting as a surrogate of cough severity. As our clinic only recently incorporated a standardized set of questions to assess cough severity, we are unable to verify this assessment.

There are several limitations to this study. While we do have one of the largest retrospective cohorts of patients with UCC, we were forced to exclude a quarter of the initial population due to lost follow-up. We believe the inherent nature of this challenging patient population is responsible for the rate of exclusion. As a tertiary care center, over half of patients who present with a chronic cough complaint in this population. Indeed, 1 long-term study found that 60% of previously treated patients with UCC possessed an equivalent or worse cough 7 to 10 years after treatment.26 The possibility that tachyphylaxis and dependence rates are higher than our 35% and 30% reported rates is alarming, reinforcing the need for further exploration of these phenomena.

Finally, we acknowledge the extremely variable follow-up times present within this cohort. We do not deny that, consequently, our rates of tachyphylaxis and dependence may be underestimated. Indeed, 1 long-term study found that 60% of previously treated patients with UCC possessed an equivalent or worse cough 7 to 10 years after treatment. The possibility that tachyphylaxis and dependence rates are higher than our 35% and 30% reported rates is alarming, reinforcing the need for further exploration of these phenomena.

**Conclusion**

Tachyphylaxis and dependence are frequently observed phenomena among patients with UCC. Clinicians should be wary of the development of tachyphylaxis following initial successful response within the first year of treatment. Patients should be educated about medication side effects as well as the potential requirement of long-term therapy. The majority of patients who pursue treatment for UCC experience benefit
with neuromodulators. Clinicians should consider tricyclic antidepressants or gabapentin as a reasonable choice for treatment initiation. Patients should be informed that successful treatment typically occurs shortly after drug initiation with some dosage titration. Although the odds of a successful outcome appear to decrease with consecutive drug trials, a substantial number of patients find success during later trials.

Author Contributions
Andrew J. Bowen, study design, data acquisition, statistical analysis of the data, manuscript preparation and revision, final manuscript approval; Tiffany L. Huang, study design, data acquisition, statistical analysis of the data, manuscript preparation, final manuscript approval; Amy S. Nowacki, study concept and design, 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; Rachel Taliercio, data acquisition, manuscript preparation and revision, final manuscript approval; Michael S. Benninger, study design, manuscript preparation, data interpretation, final manuscript approval; Claudio F. Milstein, 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.

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

References