

Topical Capsaicin for the Treatment of Sensory Neuropathic Cough

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Abstract

Objective. To evaluate a novel treatment for sensory neuropathic cough (SNC): topical capsaicin.

Study Design. Retrospective review.

Setting. Tertiary care laryngology clinic.

Methods. A retrospective review was performed on 201 consecutive patients treated for SNC with capsaicin 0.02% to 0.04% applied topically to the upper aerodigestive tract, typically after failure of standard medications. Patients were asked to use the spray 4 times daily for 2 weeks prior to assessment of benefit. Items assessed included the percentage reduction of coughing, type of benefit noted, and side effects.

Results. Of the 201 patients who used the spray, 36.3% noted no benefit, whereas 63.7% (n = 128) had benefit in terms of cough reduction: 30.8% (n = 62) reported ≥75% reduction; 17.4% (n = 35), 50%-74% reduction; 7.0% (n = 14), 25%-49% reduction; and 8.5% (n = 17), 1%-24% reduction. Of all patients, 78.3% reported no side effects or complications. Of the remaining 21.7%, 1 patient noted a nosebleed after a single administration, and 1 patient noted transient wheezing after administration. The others reported unpleasant local effects, including throat/ear discomfort, voice change, sneezing, reflexive vomiting, and headache.

Conclusion. In our group of 201 patients with SNC, most of which had failed to respond to standard treatments, 63.7% had some response to capsaicin spray, with 30.8% reporting ≥75% reduction. Minimal side effects of treatment were reported. Thus, we suggest that this therapy can be another treatment option for patients with SNC.

Keywords

cough, sensory neuropathic cough, capsaicin

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Cough is one of the most common symptoms for which medical attention is sought, accounting for an estimated 3.6% of all visits to office-based physicians in

the United States. Chronic cough also represents the most common reason for referral to subspecialists.^{1,2} The financial burden on the health care system for coughing is therefore enormous, with costs estimated to exceed several billion dollars annually.¹ Cough is commonly self-limited and lasts <4 weeks, particularly when associated with infection. Longer-lasting cough is classified as subacute (≤8 weeks) or chronic (>8 weeks).² Chronic cough that drags on for months to years affects patients not only physically but also psychologically and socially.³

Generally, cough serves to protect or clear the airways from foreign materials, excessive secretions, or infectious particles or by-products. Doctors typically consider several possible causes: chronic bronchitis, asthma, postnasal drip, lung cancer, gastroesophageal reflux disease, or a side effect of ACE inhibitors (angiotensin-converting enzyme) used to treat hypertension.^{2,4}

A subset of patients with chronic cough does not have the common conditions listed here as determined by diagnostic testing and/or a lack of response to empiric treatments. These patients are believed to have damaged nerve endings with a lowered threshold for firing, most commonly in the distribution of the vagus and glossopharyngeal nerves. Sensory neuropathic cough (SNC) is therefore conceptualized as a cousin to neuralgia, except that the aberrant sensation is not pain but instead a dysesthesia that initiates coughing.

The diagnosis of SNC is based on previously published criteria: cough duration at least 8 weeks with recurrent, abrupt sensory disturbances (eg, a “tickle” or “dry patch”) that occur immediately prior to each episode.⁵ While many cough episodes are spontaneous, there may be identified “triggers” analogous to those seen in persons with neuralgia, such as talking, laughing, and strong odors. Episodes can occur hundreds of times per day, and the cough is generally nonproductive.

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Physical responses during coughing spans a spectrum, and during more severe episodes, patients may experience stress incontinence, vomiting, and laryngospasm. For some, sleep is disturbed for the patient or bed partner. Severe episodes that occur in public can be humiliating, leading to reclusiveness, and even the ability to hold a job can be threatened.

While some patients can identify an explanation for onset of their SNC, such as an upper respiratory infection or neck surgery, a large proportion develop symptoms of SNC without an apparent cause.⁶ Viral or iatrogenic etiologies of neuralgia suggest but do not prove nerve injury as the pathophysiology of SNC. Studies showing that chronic cough can be decreased by inhaling topical anesthetic agents or induced more easily than in healthy subjects by application of capsaicin are supportive of this thought process.^{3,4,7} Other studies have shown that the universal tendency to cough after inhaling capsaicin is amplified in those with cough sensitivity.⁸⁻¹⁰

The senior author developed a treatment protocol >20 years ago for patients who match the robust criteria for SNC.^{5,6} His treatment options have, for many years, included amitriptyline, desipramine, and gabapentin.⁶ For refractory cases, he began using topical capsaicin in 2005,¹¹ as well as oxcarbazepine, citalopram, venlafaxine, and mirtazapine. Patients are asked to periodically report the percentage by which their coughing symptoms had reduced. In the study published by Bastian and Bastian in 2015, patients who responded to the medication had, on average, a 77% reduction in coughing with amitriptyline, 73% reduction with desipramine, and 69% reduction with gabapentin.⁶

Unfortunately, there is a subset whose cough is refractory to the aforementioned medications or for whom ≥ 1 medications provided limited benefit or caused unacceptable side effects. The senior author began offering capsaicin spray in 2005 and explained the origin of the idea, codified its application, and explained potential benefits in 2014.¹¹ On the basis of his experience since then, he found that capsaicin can benefit patients in 3 ways.

- It may reduce the severity and frequency of coughing attacks. This is thought to arise from capsaicin's potential to "defunctionalize" nociceptors by depleting the mucosal neurotransmitter substance P. Patients are told that the spray application may trigger a coughing attack and are asked to try to tolerate this reaction to see if they will eventually have a reduction in coughing severity and frequency.
- It may act as a counterirritant to abort or truncate bad coughing attacks. Some patients have found that with the spray always immediately at hand, they can spray their throats immediately after experiencing an urgent sensation of a tickle or dry patch that usually presages a particularly bad attack. This can often stop the cough altogether or at least shorten its duration significantly (in the patient's opinion).
- It may serve as a "cough scheduler" by inducing a severe attack of coughing at a convenient time, because after the induced attack, coughing may not

happen spontaneously for 1 or 2 hours. Some patients pursue this strategy just before entering church or the theater, at intermission, or before a speech.

Our objective here is to report the experience of a large cohort of unselected patients who have utilized capsaicin as described here.¹¹

Methods

This retrospective unselected case series chart review was determined to meet regulatory exemption criteria by Aspire IRB. All patients seen with chronic cough completed an extensive questionnaire that screened for usage of an ACE inhibitor and smoking status. A comprehensive head and neck examination followed. Elimination of pulmonary issues was performed via a chest x-ray at a minimum, if not workup by pulmonology with pulmonary function testing, computed tomography scans, and bronchoscopy prior to presentation. The robust clinical criteria for SNC were as follows: (1) cough duration at least 8 weeks; (2) recurrent, abrupt sensory disturbances (eg, tickle or dry patch) that occur immediately prior to each episode; (3) trigger phenomena associated with an increased likelihood of coughing; and (4) characteristics of a dry, sudden-onset, uncontrollable cough. If patients matched these criteria, they were considered candidates for empiric treatment of SNC, with 1 option being capsaicin topical spray. Prior to beginning therapy, they were also asked to rate the severity of their symptoms and motivation to seek treatment on a 7-point Likert scale, with 7 on the severity subscale being "ruining my life" and 1 being "minor annoyance" and with 7 on the motivation subscale being "extremely motivated" and 1 being "not motivated."

Patients with SNC in this study were identified from a prospectively maintained database of those who had received capsaicin from our clinic, which was supplied in 30-mL aliquots with a spray bottle attachment in a concentration ranging from 0.02% to 0.05% (primarily 0.03%) based on availability and patient tolerance. Patients who had received capsaicin were educated on the method and timing of application, as previously described,¹¹ and the 3 potential benefits: cough reducer, scheduler, and aborter. They were instructed to avoid eating or drinking 15 minutes before and after the application of capsaicin since some food materials can inactivate it. They then inhaled, held their breath, and applied the capsaicin to the posterior pharyngeal wall using the supplied aerosolizing tip. Afterward, they exhaled and swallowed. This was performed 4 times a day for at least 2 weeks before benefits were assessed. Patients whose cough was triggered by each application were asked to continue with the spray for 2 weeks. They were then followed via phone at 2 weeks and asked about their improvement with this intervention as compared with their symptoms prior to beginning capsaicin, despite treatment for acid reflux, allergies, and asthma. Patients who used capsaicin as a reducer and experienced enough of a reduction in their symptoms were encouraged to wean down on the number of times that they used the medication. Those who used it as an aborter or as a scheduler were

Table 1. Demographics for Patients With Diagnosis of Sensory Neuropathic Cough and Follow-up.

| | |
|---------------------|------------|
| Patients, No. (%) | 253 |
| Male | 61 (24.1) |
| Female | 192 (75.9) |
| Age of diagnosis, y | |
| Mean | 57.7 |
| Median | 59.6 |
| Range | 16-84 |
| Mean follow-up, mo | 41.2 |

instructed to stop using it as scheduled and instead when needed.

The following were tabulated: the age at diagnosis, sex, number of years that the patient had been coughing prior to diagnosis of SNC, triggers, the location of the sensory disturbance causing cough, patient-rated severity, motivation to seek treatment, length of follow-up, which of the 3 benefits experienced (if any), and the percentage reduction of their symptoms.

Results

In total, 388 patients with SNC were identified who had received at least 1 bottle of capsaicin, and 135 were excluded due to missing follow-up information. Demographics of the 253 evaluable patients are presented in **Table 1**. The majority of the population was female (75.9%, $n = 192$). The mean and median age at diagnosis was 57.7 and 59.6 years, respectively, with a range from 16 to 84. Of the 228 patients who provided information on the duration of cough prior to diagnosis, the mean and median duration was 10.0 and 6.0 years, respectively, with a range from 1 month to 63 years. Of the 211 patients who rated the severity of the cough, the mean rating on a 7-point scale was 5.8, with a median of 6.0 and a range of 3.0 to 7.0. For the 176 who rated their motivation to submit to treatment, also on a 7-point Likert scale, the mean was 6.9 with a median of 7.0 and a range from 4 to 7. Average follow-up was 41.2 months.

Of the 253 patients, 220 had data on previous interventions: 100% ($n = 220$) had tried at least 1 other therapy for their cough, and 92.3% ($n = 203$) underwent at least 1 test prior to presentation to our clinic. Of those who had undergone testing, the average and median number of studies was 4. Prior to presentation to our clinic, 94.5% ($n = 208$) took acid reflux medication; 77.3% ($n = 170$) took allergy medication; 84.1% ($n = 185$) used an asthma inhaler; 48.2% ($n = 106$) had taken antibiotics; and 23.6% ($n = 52$) had used steroids for this cough. Prior to presentation to our clinic, 83.2% ($n = 183$) underwent imaging; 72.7% ($n = 160$), pulmonary function tests; 65.4% ($n = 144$), allergy testing; and 48.2% ($n = 106$), esophagoscopy (**Table 2**).

Most of the 253 patients (93.7%, $n = 237$) received 0.03% capsaicin spray based on availability and/or tolerance. For the others, 2.8% ($n = 7$) used 0.02% capsaicin spray; 2.8% used

0.02% and 0.03%; and 1 patient each used either 0.02%, 0.03%, and 0.04% or 0.03% and 0.05%.

Of the 253 included patients, 35 did not tolerate usage of the capsaicin spray or did not use as directed and so discontinued it before an effect could be seen. Only 11 of these patients cited a reason: 2 indicated that they did not tolerate it because of the burning sensation that it created; 1 stated that it was “too painful”; 4 reported reflexive vomiting; 2 referenced ear pain; and 2 had a laryngospasm. Of the other 218 patients, 17 had an effect but did not quantifiably report it and thus were excluded, leaving 201 who had used the capsaicin appropriately and had a response. Of these, 61 patients noted minimal to no effect (30.3%), and 2 felt as though it made their cough worse (1.0%). Ten patients cited an improvement, but this was very short-term (5.0%). An overall 128 patients (63.7%) reported a lasting effect in terms of cough reduction: 30.8% ($n = 62$) had $\geq 75\%$ reduction; 17.4% ($n = 35$), 50%-74% reduction; 7.0% ($n = 14$), 25%-49% reduction; and 8.5% ($n = 17$), 1%-24% reduction—all as compared with the period prior to treatment with capsaicin, despite treatment for acid reflux, allergy, and/or asthma (**Figure 1**).

Of the 128 patients who reported improvement, the majority (73.4%, $n = 94$) used the capsaicin as a cough reducer, 6.3% ($n = 8$) as a cough scheduler, 6.3% ($n = 8$) as a cough aborter, and 11.7% ($n = 15$) in a combination of ways. In addition, 2.3% ($n = 3$) did not indicate how they used it. Most patients who cited good control of their cough noted that capsaicin worked for them as a reducer: of the 96 patients who had $\geq 50\%$ cough reduction, there were 72 reducers (75%), 5 schedulers (5.2%), 6 aborters (6.3%), 5 reducers and schedulers (5.2%), 6 reducers and aborters (6.3%), and 2 schedulers and aborters (2.1%).

Minimal complications were noted in this group. One patient had a spontaneous nosebleed after 1 actuation, and 1 patient noted transient wheezing after administration. Otherwise, patients reported only local effects, including throat/ear discomfort, brief voice change, sneezing, reflexive vomiting, and headache. The other 78.3% indicated no side effects.

Discussion

Chronic cough is a difficult problem to treat, particularly in patients without an apparent cause, such as “usual suspect” allergy/postnasal drip, asthma, and acid reflux. Multiple studies have in recent years demonstrated the successful use of antidepressant or antiseizure medications to treat chronic cough, such as amitriptyline, gabapentin, and pregabalin.^{5,12-14} Jeyakumar et al presented a randomized controlled trial showing the effectiveness of amitriptyline vs codeine/guaifenesin for chronic cough resulting from suspected postviral vagal neuropathy.¹² Ryan et al presented a randomized controlled trial showing that gabapentin can be used to treat refractory chronic cough.¹³ Vertigan et al demonstrated that combined speech pathology treatment and pregabalin reduced symptoms and improved quality of life as compared with speech pathology treatment alone in patients with chronic refractory cough.¹⁴

Table 2. Percentage of Population With Data on Previous Interventions.

| Therapy ^a | No. (%) | Test ^b | No. (%) |
|------------------------|------------|--------------------------|------------|
| Acid reflux medication | 208 (94.5) | Imaging | 183 (83.2) |
| Allergy medication | 170 (77.3) | Pulmonary function tests | 160 (72.7) |
| Asthma inhaler | 185 (84.1) | Allergy testing | 144 (65.4) |
| Antibiotics | 106 (48.2) | Esophagoscopy | 106 (48.2) |
| Steroids | 52 (23.6) | | |

^aAt least 1 therapy (220 patients, 100%).

^bAt least 1 test (203 patients, 92.3%).

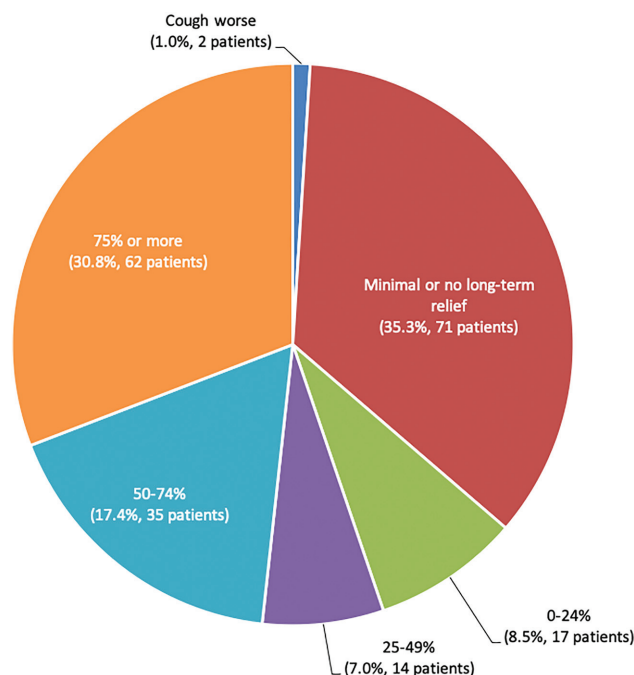


Figure 1. Percentage reduction of symptoms in patients whose outcomes were evaluated (n = 201).

Unfortunately, for a small subset with SNC diagnosed via robust criteria, these classes of medications are ineffective. Additionally, for patients already on antidepressant medications for other reasons, drug interactions may prohibit usage of SNC medications. Capsaicin is one of the few remaining options for these patients.

Capsaicin is a hydrophobic compound produced by chili peppers from the plant genus *Capsicum*.¹⁵ This compound serves as an agonist that binds to the TRPV1 receptor (transient receptor potential vanilloid type 1), a well-characterized ion channel in the neurons that line the oral and nasal cavities. This receptor localizes to peripheral terminals of primary afferent neurons that sense pain and heat. As briefly discussed, when capsaicin is applied to healthy subjects, it results in an enhanced cough response by activating this receptor and promoting the release of neuropeptides, leading to a coughing fit.⁴

Due to its ability to trigger cough even in persons who do not have SNC, use of capsaicin to treat SNC seems counterintuitive. However, usage of ingested capsules of capsaicin may

be followed by brief desensitization.⁴ This is thought to occur via either depletion of the neurotransmitter substance P¹⁶ or a process called “dysfunctionalization” of thermal, mechanical, chemical, and other sensory nerve endings.¹⁷ Furthermore, topical capsaicin has been used to treat other neuropathic conditions, such as neuropathic pain, nonallergic rhinitis, intestinal sensitivity, and headaches.^{4,18,19} However, while there are several published studies on the usage of capsaicin to trigger cough, we were unable to find prior reports on topical application of capsaicin for treatment of chronic cough.

While capsaicin has traditionally been described as a cough inducer, our study shows that it can be useful for the management of SNC, with 63.7% of patients having some response to the medication and approximately 30% citing $\geq 75\%$ reduction in their symptoms. Although the subset that experiences such significant relief is small and rates of permanent cure are yet to be determined, it could be considered an adjunct medication to other therapies.

Moreover, apart from the characteristic burning sensation that it creates, capsaicin has no known systemic side effects. In our population, 1 patient had a spontaneous nosebleed. Little is known about this episode and whether it may have occurred in response to induced coughing. One other patient developed transient wheezing after usage, requiring no treatment. Otherwise, side effects that did not stop patients from using the spray included reflexive vomiting, throat discomfort, headache, transient voice changes, and sneezing and were the only issues for 21.7% who used the medication regularly. For those who discontinued the medication prior to the benefits being assessed, referred ear pain and laryngospasm were the only other side effects. The rest tolerated the medication.

A primary limitation of this study is its retrospective nature and lack of comparison with a placebo arm. This means that capsaicin use correlates to benefit but cannot be proven to be the cause of improvement. Additionally, this study relies on patient-reported “overall reduction of cough,” and reporting bias may have occurred. Despite these limitations, this study at the least brings this large patient experience to the attention of others who may wish to validate the efficacy of capsaicin more robustly. In the meantime, given capsaicin’s low-risk profile, it can be considered another treatment option. This option may be especially interesting for those who do not experience good relief of their symptoms with current standard treatments.

Conclusion

SNC, by robust clinical criteria, can dramatically decrease a patient's quality of life and ability to work. While several medications are effective in this group, some patients do not respond to them, cannot tolerate side effects, and/or are prohibited due to drug interactions. Capsaicin has the benefit of ease of use via topical application and no known drug interactions. In our study, 63.7% of 201 patients had some benefit from capsaicin spray, with 30.8% having $\geq 75\%$ reduction in their cough. Thus, we suggest that, pending further study, it might be offered as an option to patients with SNC who do not respond to other therapies or for those who prefer nonpharmacologic treatments for their cough.

Author Contributions

Rebecca C. Hoesli, substantial contribution to acquisition, analysis, and interpretation of data; revising manuscript critically for important intellectual content, final approval, and agreement to be accountable; **Melissa L. Wingo**, substantial contribution to acquisition of data, creation of draft, final approval, and agreement to be accountable; **Benjamin Wajsberg**, substantial contribution to acquisition and interpretation of data, drafting the work, final approval, and agreement to be accountable; **Robert W. Bastian**, conception of work, revising it critically for important intellectual content, final approval, and agreement to be accountable.

Disclosures

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