HHS Public Access

Author manuscript

Laryngoscope. Author manuscript; available in PMC 2018 May 01.

Published in final edited form as:

Laryngoscope. 2017 May ; 127(5): 1007–1008. doi:10.1002/lary.26393.

Are Neuromodulating Medications Effective for the Treatment of Chronic Neurogenic Cough?

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BACKGROUND

Chronic cough is vexing for patients and is an extremely common chief complaint in ambulatory settings.[1,2] A cough persisting longer than 8 weeks is considered chronic, and many patients seek evaluation by an otolaryngologist. After considering a broad differential, including reflux, chronic rhinitis/sinusitis, primary pulmonary diagnosis, and medication side effects, the diagnosis of chronic neurogenic cough can be considered.

Both peripheral neuropathy and central sensitization/potentiation of the cough reflex[3] have been implicated in the pathophysiology of chronic neurogenic cough. Thus pharmacologic neuromodulators have been used in patients with chronic neurogenic cough to reduce cough severity[1–5] and to improve cough-related quality of life.[3–5]

LITERATURE REVIEW

Neuromodulating medications, such as gabapentin, amitriptyline, pregabalin, and baclofen, have been used to treat chronic neurogenic cough.

Gabapentin

A randomized, double-blinded, placebo-controlled trial by Ryan et al. evaluated the efficacy of gabapentin for improvement in cough severity and cough-related quality of life.[3] Inclusion and exclusion criteria and dosing are listed in Table I. Twenty-six patients completed the trial in both the placebo and gabapentin arms. Compared to placebo, patients in the gabapentin arm reported significantly greater improvements in cough-specific quality of life (clinically significant difference measured with Leicester Cough Questionnaire [LCQ]), cough severity (measured with visual analog scale [VAS]), cough frequency (measured with Leicester Cough Monitor [LCM] using external microphone), and overall quality of life (measured with Short Form-36).

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The authors have no funding, financial relationships, or conflicts of interest to disclose.

Amitriptyline

A randomized controlled trial (RCT) by Jeyakumar et al. looked at the effect of amitriptyline compared to codeine/guaifenesin (trial specifics are in Table I). Of 15 patients randomized to receive amitriptyline, 13 (87%) reported ≥ 50% reduction in their cough, compared to only one of 13 patients in the codeine/guaifenesin group.[4] Amitriptyline was also associated with improved cough-related quality of life (measured by Cough-Specific Quality- of-Life Questionnaire).

Pregabalin

Vertigan et al. conducted a randomized, double-blinded, placebo-controlled trial comparing the effects on chronic cough of pregabalin with speech therapy versus speech therapy and a placebo (trial specifics in Table I).[5] Eighteen patients completed speech therapy and pregabalin, whereas 17 had speech therapy and a placebo. Both arms had improved cough-related quality of life (LCQ), cough severity (VAS), and cough frequency (LCM) at the completion of treatment (14 weeks); however, patients on pregabalin had a larger improvement in LCQ scores (clinically significant) and VAS.[5]

Long-term and Side Effects

Long-term success of neuromodulator therapy for chronic cough remains unclear. A prospective series reported durable benefit following amitriptyline[2]; however, in the gabapentin RCT reviewed above, the benefit of gabapentin was no longer present at 4 weeks after completion. At the 4-week follow-up (after weaning the pregabalin), both arms maintained improvements from baseline, including clinically significant improvement in LCQ and cough severity. However, the differences between pregabalin with speech therapy and placebo with speech therapy groups were not sustained.[5] Ryan and Cohen retrospectively reviewed medium and long-term outcomes in patients treated with amitriptyline for chronic idiopathic cough.[1] At 2.6 months, 89% of patients were still taking medications, with 67% of patients reporting a ≥ 50% cough reduction. At 2 to 3 years (with excellent response rate on the survey), 21 of 38 patients maintained ≥ 50% cough reduction; of those, 11 were still taking amitriptyline.

A systematic review of neuromodulators in chronic idiopathic cough summarized findings from two RCTs, two prospective cohort studies, and four retrospective case series,[2] describing data on gabapentin (3), amitriptyline (3), baclofen (1), and pregabalin (1). No studies directly compared individual neuromodulating medications. Side effects were common, although no serious complications were noted, and adverse effects were resolved with cessation of the medication. The rate of reported adverse effects varied by study, ranging from 0% to 31% of patients, and included blurry vision, confusion, dizziness, dry mouth, headache, memory loss, nausea or vomiting, and sedation or drowsiness.[2] In long-term follow-up of amitriptyline use for idiopathic cough, Ryan and Cohen reported that by 2 to 3 years following treatment, 12 of 38 (32%) patients had stopped amitriptyline due to side effects including sedation, dry mouth, anxiety, difficulty sleeping, and weight gain.[1] Formal meta-analysis of existing studies is precluded due to the small number and size of the studies and heterogeneity of data in the literature.

BEST PRACTICE

The use of neuromodulators appears to be helpful in patients with chronic idiopathic/neurogenic cough. Small RCTs support short-term improvement in cough-related quality of life and cough severity for pregabalin with speech therapy, amitriptyline, and gabapentin. There is also limited lower-level evidence supporting the use of baclofen. Adverse effects are common, necessitating appropriate counseling when initiating treatment; however, no serious complications were reported. Data on long-term effects are mixed. Further studies, ideally including both patient-reported outcome measures and objective measures of cough, are necessary to draw conclusions on superior agent(s), dosing regimen, optimal duration of therapy, the individual versus combined benefits of neuromodulating agents and speech therapy, and long-term outcomes.

LEVEL OF EVIDENCE

Current literature includes three level 1 evidence studies (3 RCTs) and several level 2 and 3 studies supporting the use of neuromodulating medications in chronic neurogenic cough.

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TABLE I

Summary of Reviewed Randomized Controlled Trials.

Author	Treatment	Comparison	Inclusion Criteria	Exclusion Criteria	Outcomes
Ryan et al.[3]	Gabapentin titration: 300 mg by mouth daily; increase over 7 days to 1,800 mg by mouth daily; maximum dose for 10 weeks	Placebo	8 weeks chronic cough and failed treatment for asthma, GERD, and allergic rhinitis	Productive cough, tobacco use, active respiratory disease, ACE inhibitor use, impaired LFTs, pregnant/breastfeeding	LCQ,† VAS,† cough/hour,† SF-36,† FeNO, C5 dose†
Jeyakumar et al.[4]	Amitriptyline 10 mg by mouth daily for 10 days	Codeine/guaifenesin	6 months of dry cough, refractory to PPI, negative chest X-ray	Asthma, ACE inhibitor use, tobacco use	Reduction in cough frequency/severity†; CQLQ†
Vertigan et al.[5]	Speech therapy* and pregabalin titration: 75 mg by mouth daily; increase over 7 days to 300 mg by mouth daily; maximum dose for 11 weeks	Speech therapy* and placebo	Chronic idiopathic cough or refractory cough failing treatment for asthma, GERD, and allergic rhinitis	Productive cough, tobacco use, active respiratory disease, ACE inhibitor use, impaired LFTs, pregnant/breastfeeding	LCQ,† VAS,† cough/hour, C5 dose, VHI, CAPE-V, DSI

*Four sessions over 12 weeks.

†Statistically significant difference between treatment and comparison groups.

ACE = angiotensin-converting enzyme; cough/hour = cough frequency per hour as measured by the Leicester Cough Monitor; C5 dose = capsaicin dose needed to induced 5 coughs, a measure of central cough reflex sensitivity; CAPE-V = Consensus Auditory-Perceptual Evaluation of Voice, a clinician assessment of severity of voice disorder; CQLQ = Cough-specific Quality-of-Life Questionnaire, a cough-related quality-of-life questionnaire; DSI = Dyspnea Symptom Index, a dyspnea questionnaire; FeNO fractional exhaled nitric oxide and hypertonic saline test for bronchial hyper-responsiveness; GERD = gastroesophageal reflux disease; LCQ = Leicester Cough Questionnaire, a cough-related quality-of-life instrument; LFT = liver function tests; PPI = proton pump inhibitors; SF-36 = Short Form 36, a overall quality-of-life questionnaire; VAS = visual analog scale, a scale to measure cough severity; VHI = Voice Handicap Index, a measure of voice-related quality of life.