

REVIEW

Using Gabapentin to Treat Chronic Cough: A Review of Literature

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Abstract

Chronic cough is a multifactorial symptom, and a legitimate medical concern, that often requires further investigation if resolution is not attained with initial therapeutic options. Gabapentin, an anticonvulsant used for a myriad of disease states, is suggested to have a positive effect on chronic cough. Pertinent literature was searched for, and critically appraised in order to determine the potential value of gabapentin in the treatment of chronic cough. Findings from salient literature demonstrate a decrease in both frequency and severity of chronic cough as primary endpoints. However, discontinuation of gabapentin precipitated a return of symptoms towards baseline values, which may suggest that sustained use is required to maintain such benefits. It is felt that, in light of recent literature, the use of gabapentin as an off-label treatment for chronic cough, refractory to typical treatment regimens, may be a viable option for select patients.

Of the many reasons patients visit their family physician, cough is the most frequently reported symptom with approximately 33 million ambulatory care visits made between 2001-2002 in the US.¹ Patients with a chronic cough, defined arbitrarily as a cough lasting longer than 8 weeks², may require additional appointments to further investigate the cause.³ The highest incidence of chronic cough has been reported in the middle-aged female population and is thought to be due, in part, to an increased likelihood of reporting the condition.⁴

Chronic cough is a diagnosis made by exclusion, and may have many etiologies in the adult population.² Often these underlying causes, most commonly gastroesophageal reflux disease, asthma, and/or upper airway cough syndrome (UACS) secondary to rhinosinus diseases (formerly post-nasal drip syndrome)⁵, have logical and well explained treatment options.² Chronic cough that is refractory to such treatments may be explained by the involvement of more complex physiological processes such as sensory neuropathic cough, laryngeal sensory neuropathy and post-viral vagal neuropathy.⁶ For this subset of patients it is clear that a significant burden exists that can affect their overall quality of life.^{7,8}

A review of the American College of Chest Physicians (ACCP) 2006 guidelines revealed few treatment options for the management of chronic cough.⁹ Since its publication, however, several uncontrolled studies have demonstrated a benefit with the off-label use of the antiepileptic medication, gabapentin, in the symptomatic control of chronic cough.¹⁰⁻¹² The suggested mechanism by which gabapentin exerts

benefit entails binding to the $\alpha 2\delta$ -1 subunit of neuronal calcium channels.^{13,14} This is postulated to desensitize hypersensitive neurons, which may be the cause for excessive cough reflex.^{15,16} In this report, we exemplify the potential role of therapy with gabapentin through a review of the literature.

Clinical Question

In an otherwise healthy middle aged person with chronic cough, for whom common cough suppressants were ineffective and/or undesired, is gabapentin effective in reducing functional impairment and the severity and frequency of cough?

Search Strategy

To answer this question, searches of the following databases were carried out on October 1st, 2013: PubMed, Embase, and the Cochrane Library. Search terms for PubMed and the Cochrane Library included "gabapentin", "chronic cough", and "coughing". Emtree keywords included "gabapentin" and "chronic cough". Searches of primary literature were restricted to English. We prioritized randomized-controlled trials (RCTs), but were also interested in related uncontrolled trials (e.g. case series) that addressed the use of gabapentin for the treatment of chronic cough. We excluded citations wherein the majority of patients were treated with agents other than gabapentin (e.g. amitriptyline). Our search identified one RCT, two case series, and one retrospective cohort analysis that met our inclusion criteria (Figure 1). A Web of Science search and hand review of our main citations did not reveal additional articles of interest.

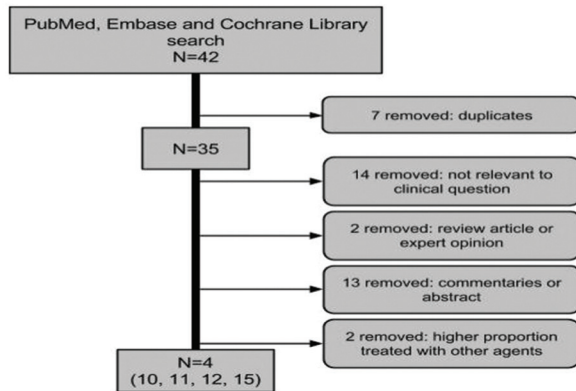


Figure 1. Study selection progression

Results

Our search strategy yielded three uncontrolled trials ($n=69$)¹⁰⁻¹² and one RCT ($n=62$)¹⁷ where patients all had refractory, idiopathic chronic cough. The findings of the three uncontrolled, observational studies indicated a potential role for gabapentin in the treatment of refractory chronic cough. Among the uncontrolled trials, between 57% and 83% of patients showed improvement in cough severity and/or frequency with gabapentin over 4 weeks or more.¹⁰⁻¹² From the three uncontrolled trials, Van Kerkhove et al. reported improvement in cough score for 20 of 35 patients, with a mean improvement in cough severity of 2.8/10 points.¹⁰ Lee et al. reported improvement in 19 of 28 patients¹¹, and Mintz noted substantial improvement or cough resolution in 5 of 6 patients.¹² The positive findings across these uncontrolled trials prompted the conduct of the more definitive RCT.

In a randomized controlled trial, Ryan et al. compared gabapentin to placebo in 62 patients, selected from a respiratory outpatient clinic in Australia, with refractory chronic cough and negative investigations for GERD, asthma, and UACS. Patients were randomized to gabapentin (maximum tolerable dose 1800 mg/day), or matching placebo, for 12 weeks. The primary outcome was a Leicester Cough Questionnaire (LCQ) change from baseline at 8 weeks, with change in cough frequency (coughs/h), and cough severity (Visual Analog Scale (VAS)) as secondary outcomes. The LCQ is a validated, reproducible, cough-specific, and self-reported quality of life questionnaire. A total of 19 questions are spread across three domains: physical, psychological, and social. Each domain is scored from 1-7 on a Likert scale to yield a final potential range in LCQ scores of 3 to 21. A higher score indicates a higher

quality of life.¹⁸ An analysis of the LCQ done by Raj et al. determined that a difference of >1.3 from baseline score indicated clinical significance for patients.¹⁹

The results of the RCT by Ryan et al. were obtained using an intention-to-treat analysis. Completion rates were 81% and 87% in the gabapentin and placebo group, respectively. Over 90% of those patients in the gabapentin group who completed the trial did so at the maximum dose of 1800 mg per day. Only two patients in the gabapentin group dropped out due to adverse effects. After an eight-week treatment, 74.1% of patients with refractory chronic cough in the gabapentin group achieved a LCQ score increase of >1.3 as compared to 46.2% of patients in the placebo group, resulting in an absolute benefit increase of 27.9% ($p=0.038$). These results indicate that for every four patients treated with gabapentin, one will achieve a clinical improvement in their cough as compared to placebo. Patients in the gabapentin group also reported a greater mean reduction in cough frequency (-22.5 coughs/h) as compared to patients in the placebo group (-4.3 coughs/h) after 8 weeks of treatment ($p=0.028$). A post-hoc analysis revealed patients in the gabapentin group had a reduction in VAS score for cough severity of -11.1 mm, while those on placebo had an increase of 0.8mm ($p=0.029$). The relevance of these VAS data, though clinically important, should be interpreted with care given the timing of its analysis. Four weeks after the interventions were discontinued, a return towards pre-treatment values in LCQ scores, VAS scores and cough frequency was observed.

Discussion

The utility of gabapentin as a cough suppressant, while remaining relatively innocuous in long-term treatment, has been demonstrated in a scarce, yet evolving body of evidence. No information was available in the 2006 ACCP guidelines on use of gabapentin in chronic cough; however, pertinent studies that assessed gabapentin for the symptomatic relief of chronic cough were carried out in the years immediately before and/or following the publication of the guidelines, which explains the absence of information regarding gabapentin.⁹

The results of the study by Ryan et al. show potential for gabapentin as a novel treatment for chronic cough, with clinically significant improvements in both primary and secondary outcomes. Post-discontinuation, the observed return to baseline for LCQ, VAS, and cough frequency suggests gabapentin may need to be taken chronically in order to see sustained improvement. Given the acute duration of treatment, and small

number of patients enrolled in this study, the observed differences between side effects experienced may not be reflective of their true proportion in a larger population with chronic use.

A recent Cochrane review, evaluating the use of gabapentin for the management of chronic neuropathy in 3,571 patients, reported that for every 32 patients using gabapentin (average duration of 2-14 weeks), one patient would discontinue therapy due to adverse reactions (relative risk (RR): 1.36; 95% CI: 1.09-1.71). The review also noted that for every 6 patients using gabapentin chronically, one patient would experience at least one adverse reaction compared to placebo (RR: 1.28; 95% CI: 1.20-1.37). Serious adverse events, such as drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens-Johnson Syndrome (SJS), have been reported in patients taking gabapentin; however, this particular review found no significant difference between the event rates reported with gabapentin as compared to placebo.²⁰

Overall, the results of the RCT improve upon the paucity of evidence available on gabapentin use in chronic cough.¹⁰⁻¹² A Jadad score of 5 was assigned to the RCT by Ryan et al.; however, methodological limitations were still apparent. Patients in this RCT were recruited from a specialized cough clinic which may introduce the potential for prevalence bias, as it may not capture the population of patients managed by other care providers. However, it is important to appreciate that sampling from a specialized setting, due to a low prevalence of chronic cough in the general population, resolves any limitations in the recruiting process. Furthermore, Ryan et al. did not report the handling of missing data (e.g. last-value-carried-forward) and despite similar dropout rates in both groups (19% vs. 13%), potential for bias is still present.²¹

Results from the RCT suggest that patients are more likely to experience a reduction in frequency and severity of cough with gabapentin compared to no treatment at all. Conversely, the Cochrane review suggests that there is also increased risk of continued functional impairment due to more common adverse reactions such as somnolence, dizziness, and/or peripheral edema. The long-term benefits in reduction of frequency and severity of cough may be of benefit, warranting the offer of a trial to test the efficacy of gabapentin against its potential intolerances.

Conclusion

Based on the best available evidence for the use of gabapentin in the treatment of idiopathic chronic cough, gabapentin may be a viable chronic treatment option.

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