Review Article

Recent additions in the treatment of cough

Nicole M. Ryan[1,2], Peter G. Gibson[1,2]

[1]Priority Centre for Asthma and Respiratory Diseases, School of Medicine and Public Health, The University of Newcastle, NSW 2308, Australia; [2]VIVA, Level 2 West Wing, Hunter Medical Research Institute, New Lambton Heights, NSW 2305, Australia

Correspondence to: Nicole M. Ryan. Clinical Toxicology, Level 5 New Med Building, Calvary Mater Hospital, Edith Street, Waratah NSW 2298, Australia. Email: Nicole.Ryan@newcastle.edu.au.

Background: Worldwide, cough is regarded as a challenging clinical problem due to its frequency and often limited therapeutic options. Chronic cough that remains refractory to usual medical treatment causes significant quality of life impairment in people with this problem.

Methods: We have examined current evidence on recent additions in the treatment of cough, specifically treatment of refractory chronic cough with speech pathology and gabapentin. Relevant randomised control trials, reviews and case reports were identified through a PubMed and SCOPUS search of English-language literature referring to these concepts over the last eight years.

Summary: Of the one hundred and two articles comprising this review the majority investigated the role of the transient receptor potential (TRP) receptors TRP Vanilloid 1 (TRPV1) and TRPA1 in cough and the potential of TRP antagonists as effective anti-tussives. However, these have only been tested in the laboratory and therefore their clinical effectiveness is unknown. Behavioural treatments such as speech pathology have gained momentum and this was evident in the increasing number of articles investigating its positive effect on cough. Investigation on the effectiveness of neuromodulating medications in the treatment of cough have been supported primarily through case series reports and prospective reviews however; their use (particularly gabapentin) has been significantly advanced through recently conducted randomised controlled trials.

Conclusions: Recent additions in the treatment of chronic cough have been significant as they consider cough to have a unifying diagnosis of cough hypersensitivity with or without the presence of a neuropathic basis. Primarily, effective treatments for chronic cough target these areas and include behavioural treatment such as speech pathology and pharmaceutical treatment with neuromodulating medications such as gabapentin.

Keywords: Chronic cough; speech pathology; gabapentin; neuropathic cough; cough hypersensitivity

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Background

Cough is the most commonly reported symptom during primary care consultations and chronic cough is the most common reason for patients seeking specialist respiratory assessment. Refractory cough accounts for up to 40% of these cases and remains challenging for the clinician as there are limited effective treatment options. There is also a profound effect on the patient as a prolonged cough has significant impact on their quality of life. Fortunately, recent advances have been made in the treatment of refractory and idiopathic chronic cough and even more fortuitous is that these include both advances in pharmacological and non-pharmacological treatments for patients.

These new treatments have originated from a number of different sources including otolaryngology where there is recognition of the upper airway involvement in cough; proximity of the larynx/pharynx to the oesophagus and the upper and lower respiratory tract; and hypersensitivity of the larynx from upper and lower airway inputs such as respiratory tract infections and laryngopharyngeal reflux.

Up to 40% of people with refractory chronic cough suffer significant voice problems (1) and around 56% may also have paradoxical vocal cord movement (PVCM) that is, adduction of the vocal cords during inspiration and sometimes expiration (2). Speech pathologists and physiotherapists have previously recognised and demonstrated the effectiveness of treating laryngeal symptoms and breathing disorders through tailored interventions for individuals with persistent cough (3-6).

Traditionally, chronic cough has been suggested to be due to three conditions, asthma, post nasal drip, and gastroesophageal reflux disease. A different paradigm has now been proposed in which cough is viewed as the primary condition characterised by afferent neuronal hypersensitivity and different aspects of this syndrome are manifest in the different phenotypes of cough. There are several advantages to viewing "cough hypersensitivity" (7) as the unifying diagnosis; communication with patients is aided, aetiology is not restricted and therapeutic avenues are opened.

Sensory laryngeal neuropathic cough shares similarities to other hypersensitivity neuropathic syndromes such as chronic pain. Central neural mechanisms are thought to be involved since refractory chronic cough patients have abnormal laryngeal sensations (laryngeal paraesthesia), increased sensation to non-tussive stimuli (allotussia), and a heightened response to tussive stimuli (hypertussia) (8) that responds to centrally acting medications such as gabapentin (9). The pathophysiological basis of this hypersensitivity in the larynx involves upregulation of the transient receptor potential (TRP) nociceptors. Capsaicin hypersensitivity can be mediated through TRP Vanilloid 1 (TRPV1), and airway epithelium immunostained with anti-TRPV1 antibody has shown that patients with chronic cough of diverse causes have a five-fold elevation of TRPV1 containing nerves (10). Novel compounds are in development to block these receptors and hold promise for chronic cough and upper airway hypersensitivity. As these compounds await clinical testing this review will primarily focus on speech pathology management and gabapentin treatments for chronic cough.

Methods

Search process

We have examined current evidence on recent additions in the treatment of cough, specifically treatment of refractory chronic cough with speech pathology and gabapentin. Relevant randomised control trials, reviews and case reports were identified through a PubMed and SCOPUS search of English-language literature referring to these concepts over the last eight years. One hundred and twenty six articles containing the keywords of 'chronic cough' with 'treatment', and/or 'speech pathology/therapy', 'gabapentin', 'pregabalin', 'TRP antagonists' were identified. Articles identified as not including treatment of the cough specifically or referring to a paediatric population were removed resulting in one hundred and two relevant articles.

Summary

Of the 102 articles, 12 relevant review articles dedicated to the treatment of chronic cough with either mainstay diagnostic therapy combined with speech therapy (11), empiric therapy (12,13), speech pathology/behavioural techniques (14-17) or with pregabalin or gabapentin were identified (18-22). A further 20 articles focused on the investigation of the TRP channels (TRPV1 and TRPA1) (23-42) as potential treatment targets for respiratory disease with cough. Ten investigated the treatment of cough with speech pathology alone (3-5,43-49). Five articles investigated the role of gabapentin (9,50-53) in the treatment of cough, one article focused on pregabalin treatment of cough (54) and a further two articles included both pregabalin and gabapentin treatment trials (55,56). Amitriptyline a tricyclic antidepressant was also investigated in the treatment of chronic cough in two recent reports (57,58). Four studies investigated a multifaceted treatment scenario such as with cause-directed therapy with speech pathology or neuromodulating treatment (59-62). Remaining articles investigated other treatments for cough such as with opiates (63,64), itraconazole (65), corticosteroids (66,67), proton pump inhibitors (68-71), antihistamines (72), and even camphor (73). This reference list is not exhaustive as the primary focus of this review is to provide a summary of recently investigated clinical treatments for chronic cough specifically the treatment of refractory chronic cough with speech pathology and gabapentin.

Results

Non-pharmacological/behavioural approaches to cough

Non-pharmacological approaches such as speech pathology

Table 1 Comparison of mean (SD) pre- and post-intervention breathing, cough and upper airway symptom scores and degree of change for participants in the treatment and placebo groups

Symptom	Group	Pre	Post	Difference	95% CI	P value
Breathing	Treatment†	7.9 (4.1)	5.0 (4.2)	2.9 (3.6)	1.8 to 3.9	<0.001*
	Placebo†	6.6 (4.7)	5.5 (3.5)	1.1 (3.4)	0.1 to 2.0	0.004*
	Difference‡			2.2 (3.7)	0.4 to 3.2	<0.001*
Cough	Treatment†	8.8 (2.8)	4.9 (3.0)	3.9 (3.2)	3.0 to 4.9	<0.001*
	Placebo†	7.5 (3.6)	6.3 (3.5)	1.2 (3.4)	0.3 to 2.2	<0.001*
	Difference‡			2.8 (3.6)	1.3 to 4.0	0.003*
Upper airway	Treatment†	9.2 (6.6)	6.5 (6.3)	2.7 (4.7)	1.4 to 4.1	<0.001*
	Placebo†	7.4 (4.9)	7.4 (5.5)	0.1 (4.1)	–1.1 to 1.2	0.946
	Difference‡			1.5 (4.8)	0.9 to 4.4	0.002*

†, calculated using Wilcoxon signed rank test; ‡, calculated using Mann-Whitney U test; *, statistically significant difference between pre and post measures and difference between the two comparison groups of treatment and placebo are statistically significant also.

focus on reducing laryngeal hypersensitivity. As far back as 1987 Gay *et al.* (74) utilised a treatment program involving speech therapy, relaxation and psychotherapy in subjects with psychogenic habit cough.

A year later Blager, Gay and Wood (75) reported a similar treatment program and applied techniques such as diaphragmatic breathing, laryngeal tension reduction and psychotherapy.

Recognition of this treatment for cough really began after Vertigan published the largest ever randomised controlled trial on speech pathology management of refractory chronic cough in 2006 (47). The aim of this trial was to determine the efficacy of a speech pathology intervention programme for chronic cough. Patients were randomly allocated to receive either the speech pathology programme (termed SPEICH-C) which comprised four components on (I) education about the nature of chronic cough; (II) strategies to control the cough; (III) psycho-educational counselling; and (IV) vocal hygiene education to reduce laryngeal irritation, or to a placebo intervention that involved lifestyle changes. Both of these interventions involved the patient spending four clinic sessions with a qualified speech pathologist.

The magnitude of improvement was significantly greater in the treatment group than in the placebo group for all symptom scores (*Table 1*, breathing, cough and upper airway symptoms only shown here). A lack of significant difference in the pre-intervention symptom scores between these groups indicated that improvements observed in the treatment group were due to the intervention.

This study showed that speech pathology treatment based on the approaches used in vocal cord dysfunction/PVCM and hyperfunctional voice disorders is also effective in chronic cough. Although this study really informed investigators of the potential of this treatment for chronic cough the mechanism behind the symptom improvement had not been determined nor were the effects of the treatment on laryngeal dysfunction known.

Ryan *et al.* therefore investigated the relationship between cough reflex sensitivity and laryngeal dysfunction, which was assessed as PVCM and extrathoracic airway hyperresponsiveness (EAHR), in patients with chronic cough. Adults with chronic cough and healthy controls were assessed with validated subjective and objective cough outcomes and fiberoptic laryngoscopy to identify PVCM.

PVCM was found to be present in 56% of participants with chronic cough, accompanied by cough reflex hypersensitivity, and impaired quality of life (measured with the Leicester Cough Questionnaire, LCQ).

Inspiratory airflows were reduced in the Cough with PVCM subjects, and there was significant EAHR.

This study identified that laryngeal dysfunction commonly occurs in chronic cough where it causes laryngeal symptoms, quality of life impairment and PVCM. It is accompanied by hyperresponsiveness of the extrathoracic airway to inhaled stimuli that lead to reduced inspiratory airflow. PVCM and EAHR were also found to be associated with cough reflex hypersensitivity and after implementing a cough diagnostic and treatment algorithm (76) with speech pathology treatment (47), the degree of improvement in cough reflex sensitivity correlated with the improvement in EAHR (61).

These findings provided an explanation for the

Table 2 Mean change in cough outcome measures from pre-treatment (baseline) to full-dose treatment for participants on placebo compared to participants on gabapentin

Outcome	Placebo mean change from baseline to treatment period^	Gabapentin mean change from baseline to treatment period^	Difference between treatment groups (Gabapentin *vs*. Placebo) during the treatment period* Coefficient (95% CI)	P-value
LCQ[#]	+1.1	+2.5	1.80 (0.56, 3.04)	0.004
Cough frequency, (coughs/h)[§]	–4.3	–22.5	–27.31 (–51.75, –2.88)	0.028
Cough severity, VAS, mm[#]	–0.8	–11.1	–12.23 (–23.22, –1.25)	0.029
CRS, C5 (μM)[§]	+5.1	+15.1	3.12 (–13.59, 19.82)	0.720

^, Baseline period, visit 1 (before treatment), treatment period, visits 2 and 3 (on treatment), treatment cessation period, visits 4 and 5 (off treatment); [#], mean; [§], GEM; *, baseline differences adjusted for; C5, concentration of capsaicin required to induce five coughs; LCQ, leicester cough questionnaire; Cough VAS, cough visual analogue score.

proven success of speech pathology treatment as part of the treatment programme for chronic cough, however, the mechanism behind the improvement had not been determined. It could be due to active cough suppression, reduced cough sensitivity or increased cough threshold from reduced laryngeal irritation.

In a subsequent study by Ryan *et al.* (4) objective measures such as cough reflex sensitivity testing and cough frequency were used to determine whether the treatment response was due to reduced underlying cough sensitivity or to more deliberate control exerted by individual patients. The number of treatments required to effect a response was also assessed. Following speech pathology treatment there was a significant improvement in cough related quality of life, LCQ, objective cough frequency, and cough reflex sensitivity. This study treated patients with cough that was refractory to usual medical care with or without the presence of PVCM and investigated the mechanism of action. Generally, a patient needed 3 to 4 speech pathology treatment sessions and the response was maintained after the intervention ceased. The mechanism behind the improvement was due to reduced laryngeal irritation that results in decreased cough sensitivity.

Speech pathology treatment for chronic cough is now standard practice in Australia with the Australian cough guidelines summary statement (59) being released in 2010. Most of the speech pathology treatment for chronic cough literature in the last five years has come from Vertigan *et al.* (4,5,45,49,59,61) however, other contributions come from Morrison & Schindler (60), Murry & Sapienza (3), and Gaziano & Serrano (44) from the field of otolaryngology. While Chamberlain *et al.* (43) and Pacheco *et al.* (46) investigated speech pathology and cough suppression therapy from a pulmonary point of view.

Pharmacological approaches to cough

Recent pharmacological approaches to treating chronic cough have originated from the field of otolaryngology with case reports that investigate the treatment of neuropathic cough or, laryngeal sensory neuropathy with cough as the primary symptom and their treatment with neuromodulating medications such as gabapentin (50,52), pregabalin (54) and amitriptyline (57).

Gabapentin

To investigate the effectiveness of gabapentin treatment on refractory chronic cough a double-blind randomised controlled trial comparing gabapentin to a matching placebo has been recently completed (9). Objective and subjective measures of cough were taken before, during and after treatment in adult non-smoking refractory cough participants who were randomly assigned to treatment with gabapentin 1,800 mg/day maximum tolerable dose or to a matching placebo dose over a period of ten weeks. Investigators and participants remained blinded to the treatment until completion of the study. There were no inherent differences between the two participant groups prior to treatment and when the treatment was undertaken it was found that patients on gabapentin responded positively when taking the medication unlike those patients on placebo. Gabapentin significantly improved cough specific quality of life, and reduced cough severity and cough frequency (*Table 2*). The onset of action of gabapentin was within four weeks and the effect was maintained during maximal dosing at eight weeks. However, the improvement in cough specific quality of life LCQ was not sustained after treatment withdrawal and the LCQ score returned to

baseline. A similar trend was seen in cough visual analogue score (VAS). These results indicate that gabapentin may be an effective therapy for refractory chronic cough and the reduction in efficacy of gabapentin after withdrawal further supports its antitussive effect. The treatment was generally well tolerated apart from a low frequency of expected side effects that were managed by dose reduction (9).

Peripheral cough reflex sensitivity to capsaicin did not change significantly suggesting that gabapentin did not act by reducing peripheral sensitisation. The authors draw on similarities between refractory cough and other conditions with central sensitisation (77), such as neuropathic pain. Paraesthesia (abnormal sensation in the absence of a stimulus), hyperalgesia (pain triggered by a lower level exposure to a known painful stimulus), and allodynia (pain triggered by a non-painful stimulus) are all features of neuropathic pain. These are similar to the clinical features of refractory chronic cough such as an abnormal throat sensation or "tickle" representing laryngeal paraesthesia, increased cough sensitivity in response to known tussigens (hypertussia), and cough triggered in response to nontussive stimuli such as talking or cold air (allotussia) (8). Gabapentin is effective for neuropathic pain with central sensitisation (20) and in this study, participants presenting with symptoms of central sensitisation were found to have an enhanced response to the gabapentin treatment (9).

This study supports the finding of previous case studies but improves on those by including validated objective and subjective cough measures in the comparison of gabapentin to placebo in refractory chronic cough patients. Further, it has stimulated discussion (78) and investigation (53) into considering chronic cough as a neuropathic disorder and treating it as such.

TRP antagonists

Findings suggest that the pathophysiology of sensory laryngeal hypersensitivity is related to airway mucosal TRP receptors in the sensory nerves, not only to the TRPV1 but also to the TRPA1 receptors (79). In the airways, the physiological effect of TRPV1 activation is demonstrated by the response to inhalation of capsaicin (80). There is a fivefold increase in the number of nerve profiles that express TRPV1 in airway biopsies from subjects with chronic cough compared with normal controls (10). TRPV1 and TRPA1 antagonists modify C-fibre function and reduce peripheral sensitization.

McLeod *et al.* (36) examined the molecular pharmacology and *in vivo* effects of the TRPV1 receptor antagonist, N-(4-Tertiarybutylphenyl)-4(3-cholorphyridin-2-yl)-tetrahydro-pyrazine (2H)—carboxamide (BCTC) on the guinea pig TRPV1 cation channel. High dose BCTC (3.0 mg/kg, i.p.) produced a maximum inhibition of capsaicin-induced cough of 65%. V112220 (a pyridazinylpiperazine analog of BCTC) has also been shown to effectively decrease coughs evoked by capsaicin aerosol exposure in the guinea pig by 70% (81).

The TRPA1 antagonists GRC17536 (82) and HC-030031 (83) have shown to be effective in neuropathic pain and GRC17536 was shown in a vivo model of asthma to have an effect on airway inflammation, bronchoconstriction and cough. Pharmacology and toxicology studies confirm a good safety profile and it currently awaits clinical testing.

Whether therapeutic intervention of TRPV1 results in an improved quality of life in patients suffering from refractory cough remains to be tested in the clinic (84). Since antitussives available to control cough are often not effective (85) more potent antitussives are needed. TRPV1 antagonists may represent a potential class of antitussives that could be useful in the control of chronic persistent cough (84).

Conclusions

Implications for practice

Cough remains a major unmet clinical need in respiratory medicine (40) however, recent additions in its treatment have arisen and include behavioural approaches such as speech pathology and cough suppression therapy to pharmacological approaches such as neuromodulating medications like gabapentin. Recognising the similarities between chronic cough symptoms and chronic pain symptoms has led to a reinterpretation of cough triggers with a focus on behavioural and pharmacological treatments that can target central sensitisation processes (8,9). Speech pathology treatment for chronic cough has recently been included as standard treatment in the Australian cough guidelines and further RCT studies into this treatment will result in its inclusion in other national cough guidelines. The addition of gabapentin to cough practice guidelines should also be considered as it results in a significant improvement in cough and is well tolerated (9).

Implications for research

This review highlights the need for more randomised

controlled trials to replicate recent findings with gabapentin treatment of cough. Other neuromodulating medications such as pregabalin and their role in the treatment of cough should also be investigated. TRP antagonists need to be investigated in a clinical forum as they have shown significant promise in the laboratory. Central mechanisms are important in chronic cough and the use of magnetic imaging in clinical studies would confirm this. The concept of laryngeal hypersensitivity and its association with cough needs to be validated and measurement tools for this concept expanded on and investigated. Further RCT studies into speech pathology treatment and effectiveness of its specific components would also be useful.

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