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Review

Gabapentin in chronic cough

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ABSTRACT

Background: Chronic 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.
Methods: Recent developments in the treatment of cough include the use of speech pathology and pharmacotherapy with 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.
Results: The effectiveness of neuromodulating medications such as gabapentin and pregabalin in the treatment of cough has been supported primarily through case series, case reports, prospective reviews and a double blind randomised controlled trial. Gabapentin results in a reduction in cough frequency and cough severity. It improves cough related quality of life. The effect is greatest in patients with features of central reflex sensitisation such as laryngeal paraesthesia, hypertussia and allotussia. These symptoms can be measured using the Newcastle Laryngeal Hypersensitivity Questionnaire. Side effects of gabapentin include somnolence and dizziness.
Conclusion: 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. Effective treatments for refractory chronic cough that target these areas include behavioural treatment such as speech pathology and pharmaceutical treatment with neuromodulating medications such as gabapentin.

1. Introduction

Chronic cough is a common and troublesome problem that impairs quality of life. Chronic cough frequently requires medical assessment and intervention, however when this fails to resolve the cough, then the problem is termed refractory chronic cough, unexplained chronic cough, or idiopathic cough [1-5]. Refractory chronic cough occurs in up to between 0% and 50% of patients presenting to specialty cough clinics, and in up to 10% of unselected cases. It remains a challenge for the clinician, as there are limited effective treatment options. The patient with refractory cough experiences a prolonged cough that can have a very significant impact on their quality of life.

Cough reflex hypersensitivity is a key concept that has aided the understanding and management of chronic cough. The afferent limb of the cough reflex comprises peripheral receptor activation and neural transmission via the vagus nerve to the cough centre in the brainstem. Peripheral neural activation and peripheral reflex hypersensitivity (peripheral sensitisation) in the areas innervated by the vagus nerve underpin the anatomic-diagnostic protocol (ADP), which forms the basis of successful management of chronic cough [6,7]. By definition, refractory chronic cough occurs when the ADP has been applied and the cough persists. Several new concepts have emerged to aid in the understanding of refractory chronic cough [8–10]. These include laryngeal hypersensitivity, central reflex hypersensitivity, and cough hypersensitivity syndrome. Laryngeal hypersensitivity, with or without vocal cord dysfunction [11], is now a recognised cause of cough persistence [12–14]. When this is treated, then cough improves [15], as does peripheral cough reflex sensitivity [16]. The cough reflex is subject to cortical control, and central reflex sensitisation can develop as a part of refractory cough. Recognition of this forms the basis of using centrally acting neuromodulators, such as gabapentin, for chronic cough. These concepts have also been combined to view refractory chronic cough as a sensory laryngeal neuropathy [8,17,18]. Sensory laryngeal

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neuropathic cough shares similarities to other hypersensitivity neuropathic syndromes such as chronic pain and chronic itch [19]. Reformulation of chronic cough as a neuropathic disorder may yield benefits for the assessment and management of refractory cough, similar to the advances that have occurred in other chronic sensory disorders such as pain and itch.

1.1. Central sensitivity in refractory cough

Central sensitisation involves changes in the central nervous system characterised by increased excitability in central sensory pathways [20].

There are similarities between refractory cough and other conditions with central sensitisation [21], 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 features can be elicited by clinical history and confirmed by quantitative sensory testing. Similar clinical features can also be identified in refractory chronic cough such as an abnormal throat sensation or "throat tickle" representing laryngeal paraesthesia, increased cough sensitivity in response to known tussigens representing hypertussia, and cough triggered in response to nontussive stimuli such as talking or cold air which is termed allotussia [8]. Gabapentin is effective for neuropathic pain with central sensitisation [21].

Evidence for the involvement of central neural mechanisms in chronic cough can be elicted from a history of abnormal laryngeal sensations (laryngeal paraesthesia), cough hypersensitivity to nontussive stimuli (termed allotussia), a heightened response to tussive stimuli (hypertussia), and a response to centrally acting medications such as gabapentin [22], pregabalin [23], morphine [24], and amitryptyline [18,25].

1.2. Assessing laryngeal hypersensitivity

Although laryngeal hypersensitivity is an important concept in the understanding and management of refractory chronic cough, measurement has been elusive. A number of tests are available to objectively measure laryngeal hypersensitivity however these tests are expensive and are rarely available outside of specialist cough clinics. Furthermore, many patients with chronic cough report significant laryngeal irritation [8] and for some this is their most annoying symptom. In fact approximately one third of patients with refractory chronic cough report that they cough deliberately in response to cough triggers [12]. The Newcastle Laryngeal Hypersensitivity Questionnaire (NLHQ) [26] was developed in attempt to quantify the patient experience of laryngeal irritation in attempt to quantify this practice gap. The questionnaire scores items are using a seven point likert scale ranging from *1 All of the time* to *7 None of the time*. Questions are grouped into three distinct domains of laryngeal hypersensitivity: Obstruction (sensations of throat obstruction), Irritation (abnormal sensation of throat irritation) and Pain/Thermal (altered sensory experience of pain and/or temperature sensation in the laryngeal area) (Table 1).

The questionnaire is useful for discriminating between patients with laryngeal hypersensitivity (mean scores= 14.4 (SD 3.3) and healthy controls (mean scores=19.2 (SD 0.7) and can therefore characterise patients with these conditions. The cut off for normal laryngeal function is 17.1. The NLHQ can also detect a change in laryngeal hypersensitivity following successful speech pathology treatment. The minimally important change was calculated as 1.7 and the average change in the LHQ with therapy was 2.3. The NLHQ is a cost effective and non-invasive method of measuring the patient experience of laryngeal sensitivity that can easily be adapted for most clinical settings. It is therefore a useful outcome measure in both clinical practice and in research. We recommend that the NLHQ could be a very useful outcome measure of the effectiveness of neuromodulatory therapies and behavioural intervention that target cough and possibly other upper airway disorders.

Table 1
Items contained in the NLHQ.

Factor	Item
Obstruction	
	Abnormal sensation in throat
	Sensation of something stuck in throat
	Blocked throat
	Tight throat
	Irritation in throat
	Sensation of pressing on throat
	Sensation of constriction (as though needing to inspire large quantities of air
	Food catches
Irritation	
	Sensation of phlegm and mucous in throat
	Tickle in throat
	Itch in throat
Pain/Thermal	
	Pain in throat
	Pushing in chest
	Hot burning sensation in throat

2. Gabapentin in chronic cough

2.1. Gabapentin pharmacology

Gabapentin [1-(aminomethyl) cyclohexaneacetic acid] is a structural analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The molecular formula is C9H17NO2, and it has a molecular weight of 171.237 g/mol [27] .

Gabapentin binds to the α2δ subunit of the voltage-dependent calcium channel, regulating the action of calcium channels and subsequent neurotransmitter release. The drug was originally developed for use as an anti-epileptic, but gabapentin has found greater use in neuropathic pain syndromes. The use of gabapentin in refractory cough is relatively recent. Gabapentin prevents mechanical and thermal allodynia and hyperalgesia in neuropathic pain models. The specific mechanisms of action of gabapentin in the treatment of neuropathic pain and neuropathic cough are not clear. Gabapentin is absorbed orally by diffusion and by the carrier-mediated, L-amino acid transport system. Bioavailability varies due to saturation of the transport system, and is not affected by food ingestion. Bioavailability ranges from 60% for a 300 mg dose to 40% for a 600 mg dose and 35% at steady state with doses of 1600 mg three times daily. The bioavailability of gabapentin is decreased by antacids(by 20%) when they are taken simultaneously or up to 2 h after gabapentin administration. Gabapentin has a high volume of distribution and does not bind to human plasma proteins. The drug crosses the blood–brain barrier, resulting in CSF concentrations equal to 20% of plasma concentrations, and brain tissue concentrations that are 80% of corresponding plasma levels. Gabapentin is not metabolized and is excreted unchanged in urine. The elimination half-life of gabapentin is between 5 and 9 h. No significant pharmacokinetic interactions have been reported.

The side-effects of gabapentin frequently limit its use, especially at higher doses. The most frequently reported side effects are somnolence and dizziness. They usually diminish with time.