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Antitussive efficacy of the current treatment protocol for refractory chronic cough: our real-world experience in a retrospective cohort study

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Mengru Zhang, Alyn H. Morice, Fengli Si, Li Zhang, Qiang Chen, Shengyuan Wang, Yiqing Zhu, Xianghuai Xu, Li Yu and Zhongmin Qiu

Abstract

Background: The management of refractory chronic cough (RCC) is a great challenge. Neuromodulators have long been used for RCC with imperfect efficacy.

Objectives: We summarized the outcomes of the current treatments used at our specialist cough clinic, which provides a guideline-led service and real-world experience for the future management of RCC.

Design: This is a single-centre retrospective observational cohort study.

Methods: Consecutive RCC patients (the first clinic visit between January 2016 and May 2021) were included into this observational cohort study. Medical records in the Chronic Cough Clinical Research Database were fully reviewed using uniform criteria. The included subjects were followed-up for at least 6 months after the final clinic visit via instant messages with the link to self-scaled cough-associated questionnaires.

Results: Overall, 369 RCC patients were analysed with a median age of 46.6 years and a cough duration of 24.0 months. A total of 10 different treatments were offered. However, 96.2% of patients had been prescribed at least one neuromodulator. One-third of patients had alternative treatments prescribed given the poor response to the initial therapy and 71.3% favourably responded to at least one of the treatments. Gabapentin, deanxit, and baclofen had comparable therapeutic efficacy (56.0%, 56.0%, and 62.5% respectively; $p = 0.88$) and overall incidences of adverse effects (28.3%, 22.0%, and 32.3% respectively; $p = 0.76$). However, 19.1 (7.7–41.8) months after the last clinic visit, 65.0% reported improvement (24.9%) or control of their cough (40.1%); 3.8% reported a spontaneous remission and 31.2% still had a severe cough. Both HARQ ($n = 97$; $p < 0.001$) and LCQ ($n = 58$; $p < 0.001$) demonstrated marked improvement.

Conclusion: Trying different neuromodulators is a pragmatic strategy for RCC, which helped around two-thirds of patients. Relapse is common on withdrawal or reduction of dosage. Novel medication for RCC is an urgent clinical need.

Plain language summary

This is the first report that fully represented a guideline-led treatment protocol for refractory chronic cough (RCC) based on a large series of patients, which evaluated the short- and long-term effects of the currently available treatments for RCC. We found that the therapeutic trial of different neuromodulators is a pragmatic strategy, which helped around two-thirds of patients. Gabapentin, deanxit (flupentixol/melitracen), and baclofen had similar therapeutic outcomes. This study may offer real-world experience for the future management of RCC.

Keywords: antitussive agents, cough, neuromodulators, treatment

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Correspondence to:
Zhongmin Qiu
Department of Pulmonary and Critical Care Medicine, School of Medicine, Tongji Hospital, Tongji University, No. 389 Xincun Road, Shanghai 200065, China.
qiuzhongmin@tongji.edu.cn

Alyn H. Morice
Centre for Clinical Science, Respiratory Medicine, Hull York Medical School, University of Hull, Castle Hill Hospital, Castle Road, East Yorkshire, Cottingham HU16 5JQ, UK.
a.h.morice@hull.ac.uk

Mengru Zhang
Department of Pulmonary and Critical Care Medicine, School of Medicine, Tongji Hospital, Tongji University, Shanghai, China

Centre for Clinical Science, Respiratory Medicine, Hull York Medical School, University of Hull, Castle Hill Hospital, Cottingham, UK

Fengli Si
Li Zhang
Qiang Chen
Shengyuan Wang
Yiqing Zhu
Xianghuai Xu
Li Yu
Zhongmin Qiu
Department of Pulmonary and Critical Care Medicine, School of Medicine, Tongji Hospital, Tongji University, Shanghai, China

Introduction

Cough is a physiological protective reflex to combat airway aspiration. However, in some pathological conditions, this reflex can be excessive and become troublesome. Broadly, in adults, a cough lasting for more than 8 weeks is termed chronic cough (CC), which has been widely reported as a common complaint in respiratory clinics. In a recent national cross-study conducted in China, CC was found in 3.6% of adults.[1] Currently, in approximately 12–42% of CC patients, the guideline-recommended aetiology-targeted treatments have been of little help, or no underlying aetiology was found after thorough investigations.[2] As an important subphenotype of CC, this persistent and intractable coughing has been defined as refractory chronic cough (RCC) or unexplained chronic cough (UCC).[3–5] In these patients who share the common feature of cough hypersensitivity, consequent worsening quality of life (QoL) is associated with somatic socio-economic pressure.[2]

The term cough hypersensitivity syndrome (CHS) has been considered as the intrinsic nature of cough, which indicates that irritant nerves are the main culprits to drive cough.[6] Thus, targeting neural pathways may achieve non-specific antitussive effects by inhibiting central cough hypersensitivity. Recently, a newly developed drug named gefapixant, an antagonist of P2X3 receptors has shown its antitussive efficacy on RCC and UCC in two global randomized placebo-controlled trials (COUGH-1 and COUGH-2).[7] However, in most countries, gefapixant has not yet been approved for clinical use. Neuromodulators have been recommended for RCC for over 10 years.[5] Among them, gabapentin, baclofen, amitriptyline, pregabalin, and codeine are commonly used and are recommended by Chinese cough guideline because of their known action on neural pathways.[8] Recently, our research group also preliminarily demonstrated the antitussive efficacy of deanxit (a combination of flupentixol and melitracen) in RCC.[9] Herein, we summarized the outcomes of the current treatments used at our specialist cough clinic to provide a guideline-led real-world experience for the future management of RCC.

Methods

Patients

Consecutive adult patients diagnosed with RCC in the specialist cough clinic (Tongji Hospital, Shanghai, China) between January 2016 and May 2021 (the first clinic visit) were included into this observational cohort study. RCC diagnosis was made only after the common causes of CC being ruled out by negative laboratory examinations or failure to etiologically targeted treatments, as suggested by Chinese guidelines for cough management.[8] The patients (1) had to be aged $\geqslant$ 18 years with a cough duration $\geqslant$ 1 year and a Visual Analogue Scale (VAS) score $\geqslant$ 40 mm and (2) had a history or were currently on double-dose proton-pump inhibitor (PPI) or neuromodulators for cough. Cases with incomplete or missing data, comorbid chronic respiratory disease, and on angiotensin-converting enzyme inhibitors were excluded.

This study was conducted in accordance with the principles of the Declaration of Helsinki. The ethical protocol was approved by the Ethics Committee in Tongji Hospital, Shanghai, China, which covered both the retrospective aspect and the follow-up part of the study (K-2020-018). Verbal consent was gained from all patients at follow-ups.

Study procedure

Medical records in the CC Clinical Research Database (a database for collecting and assessing data, such as patient-reported outcomes, medication use, and laboratory tests from patients attending CC specialist clinics, either in person or by telephone) were fully reviewed. Patients were screened using inclusion and exclusion criteria. Baseline demographic data, clinical manifestations, and assessment results were retrospectively collected. Cough condition was assessed every 2–4 weeks by VAS score, cough symptom score (CSS),[10] Hull airway reflux questionnaire (HARQ),[11] and Leicester cough questionnaire (LCQ).[12] Laboratory investigations mainly included lung function testing, fractional exhaled nitric oxide (FeNO), multi-channel intraluminal impedance-pH monitoring (MII-pH), and cough sensitivity to inhaled capsaicin represented with the minimum concentration of capsaicin

stimulating ⩾ two (C2) or ⩾ five coughs (C5). Neuromodulators were prescribed equal to our previous studies[9,13,14] and the administration was shown in Table 1. The included subjects were followed-up at least 6 months after the final clinic visit via instant messages with the link of self-scaled cough-associated questionnaires, including HARQ and LCQ. The follow-up interview was repeated a week later if the initial invitation was missed. Patients who did not respond to the second attempt were called by an investigator and asked about their willingness to complete the interview on the phone. The Capsaicin challenge test was also reperformed if consent was given. Cough was considered controlled when cough resolved completely; improved when the CSS decreased by ⩾ 50%; persisted when CSS decreased by < 50% or cough worsened.[15] Treatment success rate was calculated as the percentage of patients whose cough was controlled or improved due to treatments and did not recur within 3 days of ceasing medication. Spontaneous cough remission was defined as a cough that disappeared without any treatment aimed against it after discontinuation of treatment due to lack of efficacy or poor compliance and did not reoccur by the last follow-up visit.

Statistical analysis

The normally distributed descriptive data were expressed as mean ± standard deviations (SDs) and skewed distributed data were expressed as median with a 25–75% interquartile range (IQR). C2 and C5 were log-transformed and shown as geometric mean ± SD. The difference between groups was assessed using the Student's *t*-test, Mann–Whitney U test, chi-squared test, and Kruskal–Wallis test, where applicable. Statistical calculation was performed using SPSS version 21.0 (SPSS, Inc. Chicago, IL, USA) and GraphPad Prism 8.0 (GraphPad Software, Inc. San Diego, CA) for the personal computer. A *p*-value of less than 0.05 was considered statistically significant.

Results

Retrospective review outcomes (routine follow-up during treatment)

Between January 2016 and May 2021, a total of 1304 patients were seen with CC, of whom 466 patients were diagnosed with RCC. Of these, 392 patients with uniform criteria were included. In addition, 23 patients did not respond to the repeated follow-up. Thus, 369 patients (199 females, 53.9%) were analysed with a median age of 46.6 (34.3–60.0) years and a median cough duration of 24.0 (12.0–72.0) months. Other general clinical characteristics and main investigation results are listed in Table 2. Among these patients, 34.7% (128 cases) of coughs were presumed to be caused by reflux responding to neuromodulators as an add-on therapy to anti-reflux treatments or double-dose PPIs and were diagnosed as refractory gastroesophageal reflux-associated cough (GERC). Detailed intensified therapeutic protocol used for these patients was provided in Table 3, which included 10 different treatments. However, 96.2% of patients had been prescribed at least one of the following eight neuromodulators: gabapentin, deanxit, baclofen, pregabalin, paroxetine, codeine, duloxetine, and meperidine hydrochloride.

A total of 123 cases (33.3%) had further adjustments of therapy given the poor response or poor tolerance (16/123 patients) to the initial treatment and 71.3% (263 patients) favourably responded to at least one of the listed options in Table 3. The leading three neuromodulators, gabapentin, deanxit, and baclofen, had a similar therapeutic efficacy when used as initial treatment for the neuromodulator-naïve patients (56.0%, 56.0% and 62.5% respectively; $p = 0.88$) (Table 4). The overall incidences of their side effects were also comparable (Table 5). Only 10 patients on gabapentin (12/322, 3.7%), 3 patients on baclofen (3/65, 4.6%), and 3 patients on deanxit (3/114, 2.6%) reported an intolerable side effect, which disappeared after discontinuation or swapping medication. No matter which of these three agents was used, the therapeutic efficacy was observed within 5 days after treatment initiation, but cough may reoccur in approximately a fifth of patients mainly without obvious triggers within a median of approximately 2 weeks after cessation or reduction of dosage (Table 6).

Long-term follow-up outcomes

At the time of the last follow-up, which was conducted a median of 19.1 (7.7–41.8) months after the last clinic visit, 65.0% of patients reported improvement (24.9%) or control of their

Table 1. Details of neuromodulators prescription.

Treatments	Usage	Dosage	Maximal dosage
Gabapentin	Gradually increase and decrease the dose; take as needed if cough recurs after complete cessation	Day 1–3: 0.1 g, TID; day 4–6: 0.2 g, TID; day 7~: 0.3 g, TID; first week after cough has completely gone for a month: 0.2 g, TID; second week: 0.1 g, TID; afterward: 0.1 g, QD, for 2 weeks, then discontinue if cough does not worsen, otherwise, go back to effective dose	0.3 g, TID (this can increase to 0.6 g, TID for overweight patients)
Deanxit	Gradually decrease the dose; take as needed if cough recurs after complete cessation	One tablet, morning and midday; a month after cough has completely gone for a month: one tablet, morning or midday, then discontinue if cough does not worsen, otherwise, go back to the effective dose	One tablet, BID
Baclofen	Gradually increase and decrease the dose; take as needed if cough recurs after complete cessation	Day 1–3: 10 mg, TID; day 4–6: 10 mg, morning and evening, 20 mg, midday; day 7–9: 10 mg, morning, 20 mg, midday and evening; day 10~: 20 mg, TID; first week after cough has completely gone for a month: 10 mg, TID; second week: 10 mg, morning and evening; afterward: 10 mg, QD, for 2 weeks, then discontinue if cough does not worsen, otherwise, go back to effective dose	20 mg, TID
Pregabalin	Gradually increase and decrease the dose; take as needed if cough recurs after complete cessation	Day 1–3: 75 mg, morning and evening; day 4–6: 150 mg, morning and 75 mg, evening; day 7–9: 150 mg, morning and evening; day 10–12: 225 mg, morning and 150 mg, evening; day 13~: 225 mg, morning and evening; first week after cough has completely gone for a month: 150 mg, morning and evening; second week: 75 mg, morning and evening; afterward: 75 mg, QD, for 2 weeks, then discontinue if cough does not worsen, otherwise go back to effective dose	225 mg, morning and evening
Paroxetine	Gradually increase and decrease the dose; take as needed if cough recurs after complete cessation	Day 1–7: 20 mg, QD; day 8–14: 10 mg, morning and 20 mg, evening; day 15~: 20 mg, BID; first week after cough has completely gone for a month: 10 mg, morning and 20 mg, evening; afterward: 20 mg, QD, for 2 weeks, then discontinue if cough does not worsen, otherwise, go back to effective dose	20 mg, BID
Codeine	Take as needed if cough recurs after complete cessation	15 mg, BID	15 mg, BID
Duloxetine	Gradually increase and decrease the dose; take as needed if cough recurs after complete cessation	Day 1: 20 mg, QD; day 2: 20 mg, BID; day 3~: 20 mg, TID; first week after cough has completely gone for a month: 20 mg, BID; afterward: 20 mg, QD, for 2 weeks, then discontinue if cough does not worsen, otherwise, go back to effective dose	20 mg, TID
Meperidine hydrochloride	Gradually increase and decrease the dose; take as needed if cough recurs after complete cessation	Day 1–7: 10 mg, QD; day 8~: 10 mg, BID; 2 weeks after cough has completely gone for a month: 10 mg, QD, then discontinue if cough does not worsen, otherwise, go back to effective dose	10 mg, BID

BID, twice daily; QD, once a day; TID, three times daily.

coughing (40.1%); 3.8% reported a spontaneous remission and 31.2% still had a severe cough or were even worse. In total, 63/369 patients (17.1%) were still taking one neuromodulator (12/63 patients still coughed badly): 29 patients were on gabapentin, 27 on deanxit, 4 on baclofen, 2 on pregabalin, and 1 on codeine. Overall, the median treatment duration of gabapentin, deanxit, and

Table 2. Clinical characteristics of RCC patients ($n = 369$).

Clinical characteristics and findings	All
Age (years)	46.6 (34.3–60.0)[a]
Sex (male/female)	170/199
BMI (kg/m^2)	23.8 ± 3.4[b]
Cough duration (months)	24.0 (12.0–72.0)[a]
VAS score	60.0 (50.0–70.0)[a]
CSS	
Daytime	3.0 (3.0–4.0)[a]
Night-time	1.0 (1.0–2.0)[a]
Accompanying symptoms	
Nasal, *n* (%)[c]	133 (36.0)
Stomach, *n* (%)[d]	212 (57.5)
Larynx, *n* (%)[e]	354 (95.9)
Chest tightness, *n* (%)	167 (45.3)
FEV_1/predicted (%)	101.0 ± 14.0[b]
FVC/predicted (%)	102.9 ± 14.9[b]
FEV_1/FVC (%)	82.2 ± 7.6[b]
MMEF/predicted (%)	78.2 ± 25.6[b]
FeNO ⩾ 25 ppb, *n* (%)	50 (13.6)
PD20-FEV1 < 7.8 mol, *n* (%)	21 (5.7)
Blood total IgE ⩾ 100 IU/ml, *n* (%)	34 (9.2)
Positive allergen skin prick test, *n* (%)	20 (5.4)
Blood eosinophils counting, (10^9/litre)[e]	0.1 (0.1–0.2)[a]
Blood eosinophils, %	1.4 (0.9–2.4)[a]
Induced sputum cytology	
Percent eosinophils > 2.5%, *n* (%)	33 (8.9)
AET > 6%, *n* (%)	37 (10.0)
Total reflux episodes in 24 h > 80, *n* (%)	79 (21.4)
SAP ⩾ 95%, *n* (%)	36 (9.8)
DeMeester score ⩾ 12.70, *n* (%)	57 (14.6)
Gastroscopy showing reflux oesophagitis, *n* (%)	34 (9.2)
Positive saliva pepsin test, *n* (%)	9 (2.4)
HARQ score	22.5 (17.0–31.3)[a]
Total LCQ score	13.4 (11.0–14.8)[a]
Physical domain	4.5 (3.9–5.1)[a]
Psycho domain	3.9 (3.1–4.6)[a]
Social domain	4.5 (3.5–5.3)[a]
Cough threshold	
C2 (μmol/litre)	0.6 ± 0.2[f]
C5 (μmol/litre)	0.8 ± 0.3[f]

AET, acid exposure time; BMI, body mass index; C2 or C5: the minimum concentration of capsaicin stimulating ⩾ 2 or ⩾ 5 coughs; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HARQ, Hull airway reflux questionnaire; LCQ, Leicester cough questionnaire; MMEF, maximal mid-expiratory flow; PD20-FEV1, the cumulative provocative dose of histamine causing a 20% fall in FEV_1; RCC, refractory chronic cough; SAP, the symptom association probability; VAS, Visual Analogue Scale.
[a]Median with a 25–75% IQR.
[b]Mean ± SD.
[c]Nasal symptoms include runny nose, sneezing, postnasal drip, and so on.
[d]Gastric symptoms include reflux, heartburn, belching, nausea, vomiting, dyspepsia, and so on.
[e]Larynx symptoms include hoarseness, throat clearing, and itchy or obstructed throat.
[f]Geometric mean ± SD.

baclofen was 2.0 (1.0–4.0), 2.0 (0.8–3.3) months, and 1 (0.6–1.8) months, respectively ($p = 0.01$). For responsive patients, the median treatment duration was 2.7 (1.5, 4.0), 2.3 (1.0, 5.0) months, and 1.0 (1.0, 2.6) months, respectively ($p = 0.04$).

Table 3. Treatment summary of the study cohort (final medication tried in bold).

Frequency	First attempt	Second attempt	Third attempt	Fourth attempt	Fifth attempt
203	**Gabapentin**				
18	**Deanxit**				
14	**Double-dose PPIs**				
9	**Baclofen**				
2	**Pregabalin**				
53	Gabapentin	**Deanxit**			
16	Gabapentin	**Baclofen**			
4	Baclofen	**Gabapentin**			
4	Deanxit	**Gabapentin**			
2	Deanxit	**Baclofen**			
1	Gabapentin	**Paroxetine**			
1	Gabapentin	**Radiofrequency ablation**			
1	Double-dose PPIs	**Gabapentin**			
1	Double-dose PPIs	**Pregabalin**			
1	Double-dose PPIs	**Radiofrequency ablation**			
12	Gabapentin	Baclofen	**Deanxit**		
10	Gabapentin	Deanxit	**Baclofen**		
2	Gabapentin	Deanxit	**Paroxetine**		
2	Gabapentin	Deanxit	**Pregabalin**		
1	Gabapentin	Baclofen	**Codeine**		
2	Baclofen	Gabapentin	**Deanxit**		
1	Baclofen	Gabapentin	**Pregabalin**		
1	Deanxit	Gabapentin	**Baclofen**		
3	Gabapentin	Baclofen	Deanxit	**Paroxetine**	
1	Gabapentin	Baclofen	Deanxit	**Duloxetine**	
1	Gabapentin	Baclofen	Deanxit	**Radiofrequency ablation**	
1	Gabapentin	Codeine	Deanxit	**Pregabalin**	
1	Gabapentin	Meperidine hydrochloride	Baclofen	**Deanxit**	
1	Gabapentin	Baclofen	Paroxetine	Pregabalin	**Deanxit**

Deanxit, flupentixol/melitracen.

Table 4. Efficacy of gabapentin, deanxit, and baclofen used as initial treatment for neuromodulator-naïve patients.

Treatments	Cough controlled (*n*)	Cough improved (*n*)	Cough persisted (*n*)	Overall response rate (%)
Gabapentin (*n* = 309)	86	87	136	56.0
Deanxit (*n* = 25)	10	1	11	56.0
Baclofen (*n* = 16)	3	7	6	62.5

Table 5. Side effects of three mainly used neuromodulators.

Side effects	Gabapentin (*n* = 322)	Deanxit (*n* = 114)	Baclofen (*n* = 65)	*p* value
Drowsiness, *n* (%)	63 (19.6)	15 (13.2)	8 (12.3)	
Dizziness, *n* (%)	34 (10.6)	4 (3.5)	9 (13.9)	
Rash, *n* (%)	5 (1.6)	/	/	
Fatigue, *n* (%)	2 (0.6)	4 (3.5)	3 (4.6)	
Gastric discomfort, *n* (%)	2 (0.6)	1 (0.9)	3 (4.6)	
Increased appetite, *n* (%)	2 (0.6)	/	/	
Back pain, *n* (%)	2 (0.6)	/	/	
Memory loss, *n* (%)	1 (0.3)	1 (0.9)	/	
Increased blood pressure, *n* (%)	1 (0.3)	/	/	
Insomnia, *n* (%)	/	7 (6.1)	/	
Constipation, *n* (%)	/	5 (4.4)	/	
Palpitation, *n* (%)	/	2 (1.8)	/	
Dry mouth, *n* (%)	/	2 (1.8)	/	
Frequent urination, *n* (%)	/	1 (0.9)	/	
Blurred vision, *n* (%)	/	/	1 (1.5)	
Total	91 (28.3)	35 (22.0)	21 (32.3)	0.76

Table 6. The maintenance of antitussive efficacy of three mainly used neuromodulators.

Medication	Cough relapses, *n* (%)	Time to relapse after cessation or reduction of dosage (weeks)	Reasons for the non-maintenance of antitussive efficacy (frequency)					
			No reason	Reduction of dosage	Common cold	Fatigue	Cold air	Over-salty diet
Gabapentin	63 (19.6)	3.0 (1.0–12.0)[a]	43	5	4	2	8	1
Deanxit	28 (24.6)	2.0 (1.0–8.0)[a]	19	6	1	1	1	0
Baclofen	17 (26.2)	7.0 (1.0–48.0)[a]	17	0	0	0	0	0

[a]Median with a 25–75% IQR.

However, 97 patients repeated HARQ, and 58 repeated LCQ. Both assessments presented marked improvement [HARQ: from 20.0 (14.0–29.0) to 14.0 (9.0–21.0), $p < 0.001$; LCQ: from 13.4 (10.5–14.8) to 15.2 (13.8–18.9), $p < 0.001$]. In addition, 45 patients attended to the outpatient clinic and reperformed capsaicin challenge test, but the results did not show any significant change compared with that before the initiation of treatments (C2: 0.68 ± 0.34 *versus* 0.69 ± 0.33 μmol/litre, $p = 0.39$; C5: 0.85 ± 0.46 *versus* 0.81 ± 0.38 μmol/litre, $p = 0.98$).

Discussion

This is the first report that fully represented a guideline-led treatment protocol for RCC in a real-world cohort based on a large series of patients. The short- and long-term effects of the current available treatments for RCC were evaluated in this study.

The dysregulation of neuronal pathways arising from the airways has been considered the root culprit to produce excessive cough reflex. Neuromodulators, as their name suggests, reduce afferent neuronal sensitivity rather than address the treatable traits and are recommended as an alternative antitussive strategy for RCC.[16] However, prominent drug-related adverse events, such as sedation, are common. In this study, 96% of patients had been prescribed eight different neuromodulators based on the recommendations of Chinese guideline for cough management and our practical experience. All the neuromodulators, including gabapentin, deanxit, baclofen, pregabalin, paroxetine, duloxetine, codeine, and meperidine hydrochloride, were prescribed under the Institutional Review Board–approved ethical protocol as reported in our previous studies[9,13] and used alone for RCC except for refractory GERC in which they were used as an add-on therapy to acid-suppressive treatment. The first three drugs have demonstrated antitussive efficacy in our previous published work.[9,14,17–19] Herein, we found their treatment outcome, the incidence of adverse events, and the maintenance of antitussive efficacy to be similar. Baclofen has long been used only in patients with non-acid reflux, as it increases the lower oesophageal sphincter (LES) tone and has non-specific antitussive activity. However, we have adopted gabapentin as the first alternative to baclofen since 2019 given its better performance for refractory GERC,[13] until deanxit, an accepted anxiolytic and antidepressant agent, demonstrated its potential antitussive property in our preliminary observational work, which is speculated to be due to the inhibitory effect on the sensitized cough centre.[9] The preliminary promising data from deanxit allowed the process of the well-designed randomized, double-blinded, and placebo-controlled clinical trial to further confirm its antitussive ability, which will be available soon. Pregabalin up to 150 mg twice a day along with speech pathology proved to improve cough symptoms but was limited in clinical practice by its high incidence of adverse effects.[20,21] We only had eight patients (five of them did not respond to gabapentin, deanxit or baclofen) who were prescribed pregabalin and four had a good response. Seven patients were prescribed paroxetine, an antidepressant agent which was reported to cease the cough in a small case series (only five patients).[22] Its antitussive efficacy was recently confirmed in a group of patients with advanced cancer and no side effects were documented.[23] Although the reported efficacy in this study was over 70%, only two patients in our cohort favourably responded to paroxetine. Given the low quality of evidence for the use of paroxetine in cough, a large and well-designed randomized placebo-controlled clinical trial is needed. One case in this cohort took duloxetine as well, which is also an antidepressant medicine, and reported an improvement in his coughing. Currently, no available result could be found that reports the application of duloxetine in cough. Due to the strict rule in the prescription of the opioid class of medications in China, although the low-dose release morphine (the main alkaloid of opium) had shown benefits in reducing cough severity,[24] we only prescribed two patients with codeine (an opiate and prodrug of morphine) and one responded well. Only one patient used meperidine hydrochloride, which is similar to morphine as an opioid analgesic, but this did not work. We also gave 17 patients with double-dose PPI due to the high DeMeester score ($\geqslant 14.70$) and abnormal acid exposure time ($> 6\%$) in MII-pH and 14 of them reported relief in cough. These responsive patients were finally diagnosed with refractory GERC, which does not respond to low-dose PPI therapy but responds to intensified treatment (double-dose PPI).[25] The three patients who well responded to radiofrequency ablation were speculated to be refractory GERC as well. This procedure acts on the muscularis propria layer of LES

at a radiofrequency of 465 kHz and a temperature of 65–85°C. Theoretically, the postoperative fibrotic tissue remodelling can reinforce the LES anti-reflux barrier and reduce the frequency of transient LES relaxation. Injury to the sensory nerves of the oesophageal mucosa by radiofrequency may also play a role in cough relief. Although radiofrequency demonstrated a favourable improvement in reflux-related respiratory symptoms including cough in a prospective study,[26] its efficacy in treating gastroesophageal reflux remains in doubt due to the lack of evidence from randomized controlled trials.[27]

Considering the imperfect efficacy of each drug, even without ruling out the placebo effect, and the fact that around a fifth of patients had cough relapses mostly without obvious triggering factors within a median of 2 weeks after cessation or reduction of dosage, we recommend patients to undergo further therapeutic trials. In this study, although approximately 60% of neuromodulator-naïve patients could have good responses without the need to try further treatment, treatment trials with different neuromodulators can increase the likelihood of a good outcome to over 70% with markedly reduced HARQ scores and improved QoL. However, there were still quite a large proportion of patients who were completely bereft of effective treatments or suffered from relapsed coughing and drug-related side effects. How to manage these patients is still a challenge. In fact, we believe that the efficacy of gabapentin and baclofen would be significantly improved by pre-screening patients with HARQ scores and the pressure/length of the LES, respectively, as we previously reported.[14,17] Further validation work in controlled studies is currently ongoing.

Collectively, the efficacy of neuromodulators for RCC may be as follows: first, they are effective when administered, but coughing tends to reoccur after cessation, due to the underlying aetiology not being eliminated; second, the cough may not reoccur after cessation due to spontaneous remission of the causes underlying refractory cough; third, the hypersensitivity of the cough reflex is successfully suppressed and the cough may not reoccur in response to sub-threshold tussive stimuli after cessation, although our failure to demonstrate the change in capsaicin sensitivity would speak against this argument; fourth, the desensitization to neuromodulators leads to an initial efficacy but then relapse. Thus, neuromodulators are clinically necessary for the treatment of RCC. In addition to relieving cough symptoms and improving QoL, neuromodulation may also offer an increased chance of relieving RCC by reducing the hypersensitivity of the cough reflex. Alternatively, they may accelerate the spontaneous remission of the underlying aetiology, as evidenced by that a small proportion in this study developed a spontaneous relief at long-term follow-up. However, given that it may take months to settle the irritant nerves to normal, it is important to seek a suitable duration of dosing in a well-designed study to minimize the risk of cough recurrence. This may be complicated by poor drug adherence in some patients. Our current practice is to prescribe a 2-week supply of medication with a gradual increase from the initial dose to the maximum tolerated dose to avoid side effects and adjust the dose or switch medication according to the patient's reported treatment outcome. Patients with the subtherapeutic response (less than 50% improvement) continue with the treatment for a further 2 weeks. The effective drug (cough relieved no less than 50%) is used until the cough has completely disappeared for 1 month and then taper the dose; if the cough worsens during the taper, go back to the most effective dose (Table 1). An ineffective drug (cough relieved less than 50%) is stopped and switched to an alternative. Neuromodulators act like a cough switch, which can work fast if effective for the individual. This is generally within 1–5 days after initiation of treatment. The treatment course also does not need to be very long (generally 2–6 months), and the effective drug should be taken as needed after withdrawal due to the common occurrence of cough relapse. More alternate options are still urgently needed for the list of neuromodulators. Gefapixant has been confirmed for its antitussive efficacy and has been approved for clinical use in some countries.[7,28,29] Hopefully, it will be the first licenced agent for CC. However, its higher selectivity for P2X2/3 heterotrimers over P2X3 homotrimers leaves taste disturbance as a common adverse effect. Newer highly selective P2X3 antagonists are in the late stage of clinical development.

Certain methodological issues in this study need to be addressed. First, long-term follow-up data in an observational study are not possible to be fully obtained due to the loss of follow-up, especially in a retrospective study, in which the recall

bias is hard to avoid. Second, we do not have a long-term objective assessment to measure the change in cough and there was no wash-out period before switching to an alternative. Third, this is a single-centre study. However, as one of the few specialist cough clinics in China, most of our patients come from across the country. This makes the samples in this study quite representative. Some demographic characteristics, such as female bias and younger age, also do not differ much from some results reported previously in China.[30] Finally, as the powerful placebo effect was often observed in cough studies, it cannot also be ruled out here. However, this is not a randomized designed clinical trial but an observational report that represents the guideline-led clinical practice and a real-world experience.

Conclusion

In conclusion, currently, the management of RCC is a great challenge. Therapeutic trial of different neuromodulators is a pragmatic strategy, which helps around two-thirds of patients. However, given that the current agents, such as gabapentin and deanxit, have been of little help in nearly a third of patients, novel medication for the treatment of RCC is in an urgent clinical need.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical protocol was approved by the Ethics Committee in Tongji Hospital, Shanghai, China, which covered both the retrospective aspect and the follow-up part of the study (K-2020-018). Verbal consent was gained from all patients at follow-ups.

Consent for publication

Not applicable.

Author contributions

Mengru Zhang: Data curation; Formal analysis; Investigation; Methodology; Software; Writing – original draft; Writing – review & editing.

Alyn H. Morice: Data curation; Methodology; Supervision; Validation; Writing – review & editing.

Fengli Si: Data curation; Methodology; Writing – review & editing.

Li Zhang: Data curation; Methodology; Writing – review & editing.

Qiang Chen: Data curation; Methodology; Writing – review & editing.

Shengyuan Wang: Data curation; Methodology; Writing – review & editing.

Yiqing Zhu: Data curation; Methodology; Writing – review & editing.

Xianghuai Xu: Data curation; Methodology; Writing – review & editing.

Li Yu: Data curation; Methodology; Writing – review & editing.

Zhongmin Qiu: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The datasets analysed during the current study are available from the corresponding author or Mengru Zhang (zhangmr@tongji.edu.cn) on reasonable request.

ORCID iDs

Shengyuan Wang https://orcid.org/0000-0003-1245-2998

Xianghuai Xu https://orcid.org/0000-0002-8713-5332
Li Yu https://orcid.org/0000-0003-4469-4756
Zhongmin Qiu https://orcid.org/0000-0002-6612-7413

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