Review Article

Systematic literature review of treatments used for refractory or unexplained chronic cough in adults

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Abstract:

BACKGROUND: Refractory or unexplained chronic cough (RCC or UCC) is difficult to manage and is usually treated by the off-label use of drugs approved for other indications.

OBJECTIVE: The objectives of this systematic literature review (SLR) were to identify and characterize the current published body of evidence for the efficacy and safety of treatments for RCC or UCC.

METHODS: The SLR was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The SLRs pre-defined population included patients ≥18 years of age who were diagnosed with chronic cough. The review was not restricted to any intervention type or study comparator, nor by timeframe.

RESULTS: A total of 20 eligible publications from 19 unique trials were included. Seventeen of these trials were randomized controlled trials and most (14/17) were placebo-controlled. There was considerable variability between trials in the definition of RCC or UCC, participant exclusion and inclusion criteria, outcome measurement timepoints, and the safety and efficacy outcomes assessed. Several trials identified significant improvements in cough frequency, severity, or health-related quality of life measures while participants were on treatment, although these improvements did not persist in any of the studies that included a post-treatment follow-up timepoint.

CONCLUSIONS: In the absence of an approved therapy, placebo remains the most common comparator in trials of potential RCC or UCC treatments. The between-study comparability of the published evidence is limited by heterogeneity of study design, study populations, and outcomes measures, as well as by concerns regarding study size and risk of bias.

Keywords:

Chronic cough, clinical trials, refractory chronic cough, systematic literature review, unexplained chronic cough

Chronic cough – daily or near-daily cough for at least 8 weeks – is a common condition that affects an estimated 5% of the United States (US) population.[1] Chronic cough negatively impacts quality of life, sleep, work, and other daily activities, and is associated with decreased physical and mental health as well as increased health-care resource use.[1-5]

The diagnosis and treatment of chronic cough are challenging.[6-9] Many cases can be successfully treated using therapies directed at underlying conditions - including gastroesophageal reflux disease, asthma, or upper airway cough syndrome - or by smoking cessation or discontinuation of certain prescription drugs such as ACE inhibitors that can cause cough as a side-effect.[10] However, a subset of people experience refractory chronic cough (RCC) or unexplained (previously "idiopathic")

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chronic cough (UCC).[6,11] As per the Chest guidelines, RCC is a cough that remains uncontrolled despite comprehensive investigation and treatment of comorbid conditions, while UCC is a cough that persists when no cause can be determined despite extensive evaluation of comorbid conditions.[12,13]

At present, there are no US Food and Drug Administration (FDA) or European Medicine Agency (EMA) approved treatments for chronic cough. A systematic literature review (SLR) conducted in 2016 by the American College of Chest Physicians (ACCP) found limited evidence related to the management of UCC, with only one pharmacological intervention (a neuromodulator, gabapentin, with or without speech pathology therapy [SPT]) supported as a potential treatment recommendation after consideration of the risk–benefit profile.[6] Similarly, of the possible treatments for RCC or UCC listed in the European Respiratory Society's 2020 clinical guidelines, all but one (low-dose morphine) were conditionally recommended and/or had a low or very low level of supporting evidence.[8] As a result, people with RCC or UCC often undergo multiple rounds of specialist referrals, diagnostic testing, and treatment attempts.[6,8,11,14] Treatments such as antitussives, protussives, bronchodilators, neuromodulators, and corticosteroids have been used off-label in an attempt to treat RCC or UCC.[15] Gefapixant, a P2 × 3 receptor antagonist, was recently approved in Switzerland and Japan for the treatment of chronic cough.[16] No drugs specifically for the treatment of chronic cough have yet been approved in other countries, but Merck & Co., Inc., is currently seeking approval for gefapixant as a treatment for RCC and UCC from the FDA and EMA.[17]

The primary objective of this SLR was to define the current clinical trial evidence base for the safety and efficacy of interventions investigated in patients with RCC or UCC. We also aimed to characterize the comparators most commonly used in clinical trials of treatments for RCC or UCC.

Methods

Study identification

This SLR was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] The pre-defined population, intervention, comparator, outcome, time, and study design (PICOTS) inclusion and exclusion criteria are described in Table 1. Briefly, eligible studies were clinical trials (randomized controlled trials [RCTs], non-RCTs, and single-arm trials) with participants ≥18 years of age who were diagnosed with RCC or UCC.[12,19] Since "refractory" and "unexplained" are relatively new concepts, first defined in the 2016

Table 1: Study eligibility criteria for inclusion in the systematic literature review

Study aspect	Criteria (for inclusion, unless otherwise stated)
Populations	≥18 years of age
	Clinical evidence of chronic cough (defined as >8 weeks)
	Exclusion criteria
	History of malignancy, respiratory tract infection, chronic bronchitis, or substance abuse
	Currently taking an angiotensin-converting enzyme inhibitor
	Immunocompromised status
	Cough resulting from invasive respiratory tract instrumentation (e.g., ventilator-dependent, tracheostomy, endotracheal intubation)
Interventions*	No restrictions
Comparators	No restrictions
Outcomes	Cough symptoms
	Cough severity
	Cough frequency
	Cough intensity
	Complications related to chronic cough
	Functional status
	Generic or cough-specific PROs including, but not limited to
	EQ-5D
	SF-12 or SF-36
	Cough severity diary
	LCQ
	Cough-specific quality of life questionnaire
	Punum Ladder Scale
	HARQ
	Patient global impression of change
	Global assessment of change in cough
	Physician's global impression of change in cough
	Chronic cough impact questionnaire
	Cough and sputum assessment questionnaire
	Cough VAS
	Adverse cough outcome survey
	Chronic Bronchitis Symptoms Assessment Scale
	AEs
	Any grade
	Discontinuations due to AEs (e.g., sleep disturbance/sleepiness, allergic reaction, constipation, drowsiness, headache, chest pain, dizziness, rash)
Time	No restrictions
Study design	RCTs
	Non-RCTs
	Single-arm trials
	Exclusion criteria
	Prospective and retrospective cohort studies
	Case–control studies
	Cross-sectional studies
	Case reports/case series
	Nonsystematic review
	Editorials/letters to the editor

Contd...

Table 1: Contd...

Study aspect	Criteria (for inclusion, unless otherwise stated)
Other	English language

*Interventions were eligible if given with or without a combined nonpharmacological treatment (e.g., chest physical therapy, cognitive behavioral therapy, speech therapy, behavioral cough suppression therapy, acupuncture, tai chi, yoga, meditation, aromatherapy, humidifiers, and herbal tea) additionally, studies were eligible for inclusion if participants with RCC were receiving concomitant treatment for the underlying cause (e.g., inhaled beta 2-agonists for asthma or proton pump inhibitors for GERD).
RCC: Refractory chronic cough, AEs: Adverse events, PROs: Patient-reported outcome, GERD: Gastroesophageal reflux disease, HARQ: Hull airway reflux questionnaire, LCQ: Leicester cough questionnaire, RCTs: Randomized controlled trials, VAS: Visual Analog Scale

ACCP guidelines,[6] studies published before 2016 were categorized for the purposes of this SLR using the previous terminology of "idiopathic" cough. The outcomes of interest were cough symptoms, including symptom frequency, severity intensity, general or cough-specific patient-reported outcomes (PROs), and adverse events (AEs). Given the lack of approved agents for the treatment of chronic cough, the literature search was not restricted by terms relating to intervention type or study comparator.

The literature search was executed on October 5, 2020, with a predefined search strategy, as described in Supplementary Table 1. The following databases were searched: MEDLINE (via Ovid); Embase (via Ovid); and CENTRAL (via Cochrane Library). Additional searches were conducted of the American Thoracic Society and European Respiratory Society conference proceedings from 2019 to 2020, as well as the US NIH Clinical Trial Registry (clinicaltrials.gov) and European Clinical Trial Register (clinicaltrialsregister.eu). No date restrictions were imposed on the main database or clinical trial registry searches.

Study selection and data extraction

Two reviewers independently screened all titles, abstracts, and proceedings identified in the literature searches. All PICOTS selection criteria except outcomes were applied at this stage. The same reviewers then screened the full text of studies identified as eligible during abstract screening, applying all PICOTS criteria. A third reviewer adjudicated any discrepancies between the two reviewers. The two reviewers independently extracted relevant data from each eligible study. The extracted data comprised detailed information on study characteristics, interventions, participants, and outcomes.

Studies that evaluated interventions approved for use for any medical indication, or doses of gefapixant that are currently approved in Japan and/or under consideration for regulatory approval by the FDA and/or EMA, were considered in the narrative synthesis. Other studies of interventions not approved for use for any medical indication, or doses of gefapixant that are currently not approved and/or under consideration for regulatory approval by the FDA and/or EMA, are summarized in the Supplementary Tables.

Study assessment

The risk of bias in included clinical trials was assessed using the Cochrane Collection Risk of Bias 2 (RoB2) tool.[20] The quality of the included non-RCTs and single-arm trials was assessed using the Newcastle–Ottawa scale.[21] All evaluations were conducted by two independent reviewers. Following the initial reconciliation between each set of assessments, a third reviewer resolved any remaining discrepancies.

Results

Studies included

The PRISMA flow diagram for the study selection process is shown in Figure 1. The literature search of Embase, MEDLINE, and CENTRAL identified 2,151 publications, of which 687 were duplicates. The title and abstract screening excluded a further 1,380 publications. Of the 84 publications that underwent a full-text review, 59 were excluded: 24 for reasons pertaining to population, 17 for intervention, 11 for outcome, 3 for study design, 3 that were conference abstracts published before 2019, and 1 that was a protocol for a trial. All conference abstracts identified through the database searches were excluded during this full-text selection process. An additional 28 publications identified by searching pre-specified conference proceedings and clinical trial registries, plus 2 citations were found through a bibliographic search, were also reviewed and found to be eligible for inclusion in the SLR. The initial list of eligible studies thus comprised 55 publications pertaining to 39 unique trials.

Twelve of the initial 55 publications reported on 5 unique trials that evaluated doses of gefapixant that are not currently under consideration for regulatory approval in any jurisdiction; these trials are summarized in Supplementary Table 2. A further 23 publications represented 15 unique trials of other interventions that do not currently have regulatory approval for use for any medical indication. A summary of these trials is presented in Supplementary Table 3. These 35 publications were deprioritized for inclusion in the narrative synthesis.

The following results are drawn from the remaining 20 published reports on 19 unique trials evaluating interventions approved for use for any medical indication, or doses of gefapixant that are currently approved in Japan and/or under consideration for regulatory approval by the FDA and/or EMA.

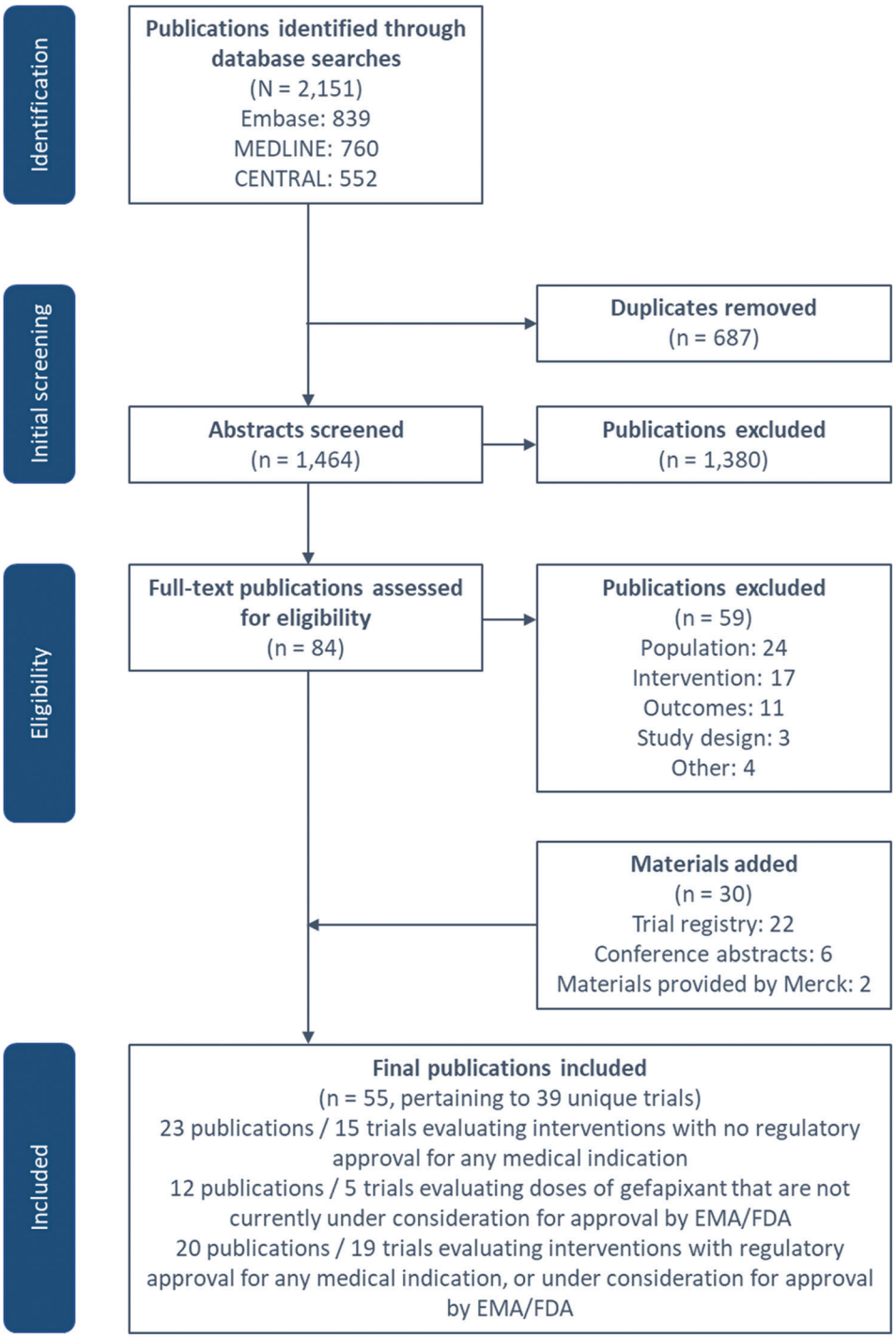

Figure 1: Study selection flow diagram for systematic literature reviews. CENTRAL = Cochrane Central Register of Controlled Trials, EMA = European Medicines Agency, Embase = Excerpta Medica database, FDA = Food and Drug Administration, MEDLINE = Medical Literature Analysis and Retrieval System Online

Trial characteristics

A summary of the included trials and associated publications is presented in Table 2 and key study eligibility criteria are shown in Supplementary Table 4. The evidence base for the narrative synthesis comprised 17 RCTs (5 of corticosteroids with a total of 205 participants,[22-26] 4 of neuromodulators with a total of 363 participants,[27-30] 3 of P2 × 3 antagonists with a total of 2,067 participants,[31-34] 2 of antibiotics with a total of 74 participants,[35,36] and 1 each of a β-adrenergic agonist [30 participants],[37] a mast cell stabilizer [27 participants],[38] and a neuorkinin-1 (NK-1) antagonist [35 participants][39]), plus 2 small single-arm trials (1 each of a neuromodulator [16 participants][40] and an The evidence base for the narrative N-Methyl-D-aspartate antagonist [14 participants](41) for a total of 19 included

Table 2: Summary of trials and publications included in systematic literature review

Trial name and ID (s)	Intervention	*n*	Study design		Study location		Dates	Crossover permitted	Publication (s)	
			Phase	Masking	Country	Multicenter			Citation (s)	Type*
RCTs of P2X3 antagonists										
COUGH-1 (NCT03449134)	Gefapixant versus placebo	730	III	Double	Multiple	Yes	2018–2020	No	McGarvey *et al.*, 2020[32]	Presentation
									Muccino *et al.*, 2020[34]	Abstract
									Dicpinigaitis *et al.*, 2021[31]	Abstract
COUGH-2 (NCT03449147)	Gefapixant versus placebo	1314	III	Double	Multiple	Yes	2018–2020	No	McGarvey *et al.*, 2020[32]	Presentation
									Muccino *et al.*, 2020[34]	Abstract
									Dicpinigaitis *et al.*, 2021[31]	Abstract
MK-7264-033 (NCT03482713)	Gefapixant versus placebo	23	II	Double	Japan	No	2018–2018	No	Merck, 2018[33]	Registry
RCTs of corticosteroids										
Chaudhuri, 2004	Fluticasone versus placebo	10	NR	Double	UK	Yes	NR	Yes	Chaudhuri *et al.*, 2004[22]	Full text
Evald, 1989	Beclomethasone versus placebo	31	NR	Double	Denmark	No	NR	Yes	Evald *et al.*, 1989[23]	Full text
Ribeiro, 2007	Beclomethasone versus placebo	64	NR	Double	Brazil	No	NR	No	Ribeiro *et al.*, 2007[25]	Full text
Pizzichini, 1999	Budesonide versus placebo	50	NR	Double	Canada	No	NR	No	Pizzichini *et al.*, 1999[24]	Full text
Sadeghi, 2018 NCT02479074 EudraCT 2015-001736-38	Prednisolone + montelukast versus montelukast	50	IV	Open	UK	No	2016–2017	No	Sadeghi *et al.*, 2018[26]	Full text
RCTs of β-adrenergic agonists										
Ellul-Micallef, 1983	Terbutaline sulfate versus placebo	30	NR	Double	Kuwait	No	NR	Yes	Ellul-Micallef, 1983[37]	Full text
RCTs of antibiotics										
Hodgson, 2016	Azithromycin versus placebo	44	III	Double	UK	No	2009–2011	No	Hodgson *et al.*, 2016[35]	Full text
Yousaf, 2010	Erythromycin versus placebo	30	NR	Double	UK	No	2007–2009	No	Yousaf *et al.*, 2010[36]	Full text
RCTs of mast cell stabilizers										
Birring, 2017 NCT02412020 EudraCT 2014-004025-40	Sodium cromoglycate versus placebo	27	II	Quadruple	K and Netherlands	Yes	2015–2016	Yes	Birring *et al.*, 2017[38]	Full text
RCTs of neuromodulators										
Dong, 2019	Gabapentin versus baclofen	234	NR	Open	China	No	2013–2017†	No	Dong *et al.*, 2019[27]	Full text
Morice, 2007	Morphine sulfate versus placebo	27	NR	Double	UK	No	2003–2005	Yes	Morice *et al.*, 2007[28]	Full text
Ryan, 2012	Gabapentin versus placebo	62	III	Double	Australia	No	2008–2010†	No	Ryan *et al.*, 2012[29]	Full text
Vertigan, 2016	SPT + pregabalin versus SPT	40	III	Double	Australia	No	2012–2014†	No	Vertigan *et al.*, 2016[30]	Full text
RCTs of NK-1 antagonists										
Schering-Plough, 2007 EudraCT 2006-002164-26	Rolapitant versus placebo	35	II	Double	UK	No	2007–2007	Yes	Schering-Plough, 2007[39]	Registry
Single-arm trials of neuromodulators										
Xu, 2013	Baclofen	16		Open	China	No	2010–2011†	No	Xu *et al.*, 2013[40]	Full text
Single-arm trials of NMDA antagonists										
MEM-COUGH-01 (EudraCT 2011-005151-13)	Memantine	14		Open	UK	No	NR–2013	No	Manchester University, 2011[41]	Registry

*"Presentations" comprise conference abstract and slides, †First and last dates of participant enrollment. EudraCT: European union drug regulating authorities clinical trials database (https://eudract.ema.europa.eu/), NA: Not applicable, NCT: US NIH clinical trial registry (https://clinicaltrials.gov), NK-1: Neurokinin-1, NMDA: N-Methyl-D-aspartate, NR: Not reported, RCT: Randomized controlled trial, SPT: Speech pathology treatment, UK: United Kingdom

trials. Most (84.2%) of the studies included in the SLR enrolled fewer than 65 participants.

The characteristics of study participants, and their baseline cough characteristics, are summarized in Table 3. The 19 trials had different inclusion and exclusion criteria and used different definitions of refractory and UCC/idiopathic chronic cough [Supplementary Table 4].

Treatment characteristics

Full details of the treatments and treatment regimens evaluated in the included studies are presented in Table 3. Placebo was used as a treatment comparator in 14 of the 17 RCTs. No consistent pattern was observed regarding the length of trials, with the time span ranging from 1 to 24 weeks. All 3 P2 × 3 antagonist trials evaluated the efficacy of oral gefapixant versus placebo.[31-34] The 5 corticosteroid studies, all of which ran for 2 weeks, comprised 2 trials of inhaled beclomethasone dipropionate versus placebo and 1 trial each of inhaled fluticasone propionate versus placebo, inhaled budesonide versus placebo, and oral prednisolone plus montelukast versus montelukast, a leukotriene receptor antagonist.[22-26] The 4 neuromodulator RCTs ran for 4–14 weeks and evaluated gabapentin or slow-release morphine sulfate versus placebo, gabapentin versus baclofen, and pregabalin plus SPT versus SPT alone.[27-30] Three of the neuromodulator studies incorporated dose-escalation designs [Table 3 footnotes for details].[27,29,30] Baclofen was also evaluated in an 8-week single-arm study.[40] The antibiotics azithromycin and erythromycin were both evaluated in placebo-controlled trials,[35,36] as were the β-adrenergic agonist terbutaline sulfate,[37] the mast cell stabilizer sodium cromoglicate,[38] and the NK-1 antagonist rolapitant (all administered orally).[39] Finally, oral memantine was evaluated in a single-arm dose-escalation study.[41]

Efficacy outcomes

The efficacy outcomes assessed in the included trials generally related to cough frequency and severity, as well as cough-specific and general health-related PROs. Only 2 trials (gabapentin versus placebo and SPT plus pregabalin versus SPT alone) assessed outcomes at a post-treatment follow-up timepoint.[29,30]

Cough frequency

Thirteen trials reported cough frequency as the outcome. These trials commonly measured this outcome objectively using automated ambulatory devices such as the Leicester Cough Monitor (LCM; 5 trials) or VitaloJak (2 trials), and/or through subjective cough diary methods [2 trials; Table 4].[42,43] Most trials were of short duration (1–16 weeks).[42,44]

Among the P2 × 3 antagonist (gefapixant) trials, the primary outcome of MK-7264-033 (4-week trial at 45 mg) was safety, with efficacy as the secondary outcome; COUGH-1 (12 weeks at 15 or 45 mg) and COUGH-2 (24 weeks at 15 or 45 mg) were designed with efficacy and safety as co-primary endpoints. The latter 2 RCTs reported significant reductions in cough frequency for the 45 mg gefapixant group compared to control, after 12 or 24 weeks of treatment (COUGH-1, $P = 0.041$ for 24-hour cough, no significant difference for waking hours cough; COUGH-2, $P = 0.031$ for 24-hour cough and $P = 0.022$ for waking hours cough).[31,32,34] No significant improvements compared to placebo were observed for the 15 mg gefapixant group in either trial.[31,32,34] No significant improvements in cough frequency were observed in the remaining gefapixant trial.[33]

Two of the corticosteroid RCTs reported cough frequency outcomes. Ribeiro (2007) reported a greater decrease in daily cough frequency in the beclomethasone dipropionate group than in the placebo group after 2 weeks of treatment;[25] in contrast, the observed decreases in daily cough frequency after 4 weeks were similar for participants in all arms of the montelukast versus montelukast plus prednisolone trial.[26] *P* values were not reported.

Among the neuromodulator RCTs, daytime cough frequency after 4 weeks was significantly reduced compared to placebo in the trial of morphine sulfate ($P < 0.01$), as was 24-h cough frequency after 4 and 8 weeks in the trial of gabapentin ($P = 0.028$), although the latter difference was not maintained in the post-treatment period.[28,29] No significant differences in cough frequency were observed between the 2 treatment arms in the trial comparing SPT plus pregabalin to SPT alone (measurement timepoint not specified), although both groups had a significantly reduced cough frequency after treatment compared to baseline.[30]

None of the 3 RCTs of other treatment classes (erythromycin for 12 weeks, sodium cromoglicate for 1 and 2 weeks, and rolapitant for 1 week) that incorporated measures of cough frequency reported a significant difference between the treatment and placebo arms.[36,38,39] A single-arm trial of memantine found no significant change from baseline waking hours cough frequency after 4 weeks of treatment.[41]

Cough severity

Only 9 trials reported cough severity. Most of the studies that assessed cough severity used Visual Analog Scale (VAS) measures [7 trials; Table 5]. However, the placebo-controlled RCTs of azithromycin and rolapitant used the cough symptom score (CSS) as the sole measure of cough severity.[42,43]

Among the corticosteroid trials, a single study reported a significant reduction in VAS score after

Table 3: Treatment and participant characteristics of the studies included in the systematic literature review

Trial name	Treatment				
	Arm	Intervention*	Dose (mg)	Frequency (/day)	Duration (week)
RCTs of P2X3 antagonists					
COUGH-1	1	Gefapixant	15	2	12
	2	Gefapixant	45	2	12
	3	Placebo	NA	NR	12
COUGH-2	1	Gefapixant	15	2	24
	2	Gefapixant	45	2	24
	3	Placebo	NA	NR	24
MK-7264-033	1	Gefapixant	45	2	4
	2	Placebo	NA	NR	4
RCTs of corticosteroids					
Chaudhuri, 2004	1	Fluticasone[§]	0.50	2	2
	2	Placebo[I]	NA	NR	2
Evald, 1989	1	Beclomethasone dipropionate[§]	0.05	2×4 puffs	2
	2	Placebo[I]	NA	NR	2
Ribeiro, 2007	1	Chlorofluorocarbon-beclomethasone dipropionate[§]	0.25	6	2
	2	Placebo[I]	NA	NR	2
Pizzichini, 1999	1	Budesonide[§]	0.40	2	2
	2	Placebo[I]	NA	NR	2
Sadeghi, 2018	1	Montelukast (low FeNO [≤20 ppb])	10	1	2
	2	Montelukast (high FeNO [≥30 ppb])	10	1	2
		Prednisolone + montelukast (high FeNO [≥30 ppb])[K]	5	4	2
RCTs of β-adrenergic agonists					
Ellul-Micallef, 1983	1	Terbutaline sulfate	2.5	3	3
	2	Placebo[I]	NA	NR	NR
RCTs of antibiotics					
Hodgson, 2016	1	Azithromycin[M]	250	3× per week	8
	2	Placebo	NA	NR	NR
Yousaf, 2010	1	Erythromycin	250	1	12
	2	Placebo	NA	NR	12
RCTs of mast cell stabilizers					
Birring, 2017	1	Sodium cromoglicate	40	3	2
	2	Placebo	NA	NR	2
RCTs of neuromodulators					
Dong, 2019	1	Gabapentin[N]	100–300	3	8
	2	Baclofen[N]	10–20	3	8
Morice, 2007	1	Morphine sulfate	5	2	4
	2	Placebo[I]	NA	NR	4
Ryan, 2012	1	Gabapentin[P]	300	1–6	NR
	2	Placebo	NA	NR	NR
Vertigan, 2016	1	Pregabalin[Q] + speech pathology	75–100	1–3	14
	2	Speech pathology	NA	NR	14
RCTs of NK-1 antagonists					
Schering-Plough, 2007	1	Rolapitant	50	1	1
	2	Placebo	NA	NR	1
Single-arm trials of neuromodulators					
Xu, 2013	1	Baclofen	20	3	8
Single-arm trials of NMDA antagonists					
MEM-COUGH-1	1	Memantine	10–40	1	4

Contd...

Table 3: Contd...

Trial name	Participant characteristics							Cough characteristics			
	n	Mean age (years)	Chronic cough		Smoking status			Mean duration (years)	Baseline values (mean)		
			U/I[†], *n* (%)	R[‡], *n* (%)	Current, *n* (%)	Former, *n* (%)	Never, *n* (%)		Frequency (coughs/h over 24 h)	Severity VAS (mm)	FEV_1/FVC ratio (%)
RCTs of P2X3 antagonists											
COUGH-1	244	Mean NR: 39% ≥65	42.0	58.0	NR	NR	NR	11.8	27.0	68.4	NR
	243							11.2	28.4		
	243							11.8	37.9		
COUGH-2	440	Mean NR: 33% ≥65	37.0	63.0	NR	NR	NR	11.9	26.8	67.9	NR
	439							11.0	26.8		
	435							10.7	27.4		
MK-7264-033	11	54.5	NR	NR	NR	NR	NR	NR	NR	NR	NR
	12	57.2									
RCTs of corticosteroids											
Chaudhuri, 2004	NR	57.7	10 (100)	NR	0	4 (40.0)	6 (60.0)	13.9	NR	44.0	101.0 (FEV_1)
Evald, 1989	NR	35.0[¶]	NR	NR	22 (71.0)	0	9 (29.0)	NR**	NR[††]	NR	85.0 (FEV_1)[‡‡]
Ribeiro, 2007	44	46.0	44 (100)	NR	0J	NR	NR	20 weeks[¶]	NR	NR	96.0
	20	50.0	20 (100)		0K			19 weeks[¶]			96.0
Pizzichini, 1999	21	43.0	NR	21 (100)	0	6 (28.6)	15 (71.4)	9.8	NR	61.4	82.0
	23	47.0		23 (100)	0	6 (26.1)	17 (73.9)	11.8		51.0	80.0
Sadeghi, 2018	20	62.0	NR	NR	0	NR	NR	NR	NR	NR	NR
	15	59.0			0						
	14	65.0			0						NR[L]
RCTs of β-adrenergic agonists											
Ellul-Micallef, 1983	NR	NR	NR	100	0	NR	NR	NR	NR	NR	NR
				100	0						
RCTs of antibiotics											
Hodgson, 2016	22	59.6	22 (100)	NR	0	NR	NR	NR	NR	NR	NR
	22	56.9	22 (100)		0						
Yousaf, 2010	15	63.0	15 (100)	NR	0	NR	NR	12.0	NR	57.0	77.0
	15	61.0	15 (100)		0			11.1		52.0	76.0
RCTs of mast cell stabilizers											
Birring, 2017	NR	62.0	NR	27 (100)	NR	NR	NR	9.9	NR	70.5	NR
RCTs of neuromodulators											
Dong, 2019	117	47.5	NR	117 (100)	0	NR	NR	7.5 months	3.0[O]	NR	81.8
	117	45.2		117 (100)	0			6.5 months	3.0[O]	NR	80.9
Morice, 2007	NR	55.0	27 (100)	NR	NR	NR	NR	NR	NR	NR	NR
Ryan, 2012	32	62.7	NR	32 (100)	0	12 (38.0)	20 (63.0)	36 months	45.3	43.6	89.4 (FEV_1)
	30	60.9		30 (100)	0	14 (47.0)	16 (53.0)	48 months	68.8	44.2	94.7 (FEV_1)
Vertigan, 2016	20	61.0	NR	20 (100)	0	8 (40.0)	12 (60.0)	94 months	24.3	52.0	85.7 (FEV_1)
	20	64.0		20 (100)	0	8 (40.0)	12 (60.0)	151 months	23.8	49.7	84.6 (FEV_1)
RCTs of NK-1 antagonists											
Schering-Plough, 2007	NR	NR	NR	35 (100)	0	NR	NR	NR	NR	NR	NR
Single-arm trials of neuromodulators											
Xu, 2013	16	47.8	NR	16 (100)	0	NR	NR	36 months	3.0[O]	NR	80.3
Single-arm trials of NMDA antagonists											
MEM-COUGH-1	14	57.9	NR	NR	0	3 (21.4)	11 (78.6)	13.7	NR	NR	NR

*Interventions were administered by the oral route unless otherwise stated, **Duration of cough >15 days (*n*=3); >1 month (*n*=6); >3 months (*n*=10), [†]Unexplained/idiopathic, [‡]Refractory, [§]Administered by inhalation, [I]Route of administration not reported, [¶]Median, [††]Cough attacks/day 1–5 (*n*=10); 6–10 (*n*=10); >10 (*n*=11), [‡‡]Study authors did not report whether data represent the mean or median value, [J]Mean (SD) pack years: 4.0 (5.0), [K]20 mg of prednisolone for 2 weeks followed by 10 mg of montelukast for 2 weeks, [L]Mean (SD) forced expiratory volume in 1 s and forced vital capacity were 105% (20%) and 115% (21%) of predicted in the total population, respectively, [M]Azithromycin 500 mg daily for 3 days, followed by 250 mg 3 times a week for 8 weeks, [N]Baclofen 10 mg, 3 times a day for 3 days, followed by extra 10 mg increase every 3 days until a maximal dose of 60 mg/day. Gabapentin 100 mg, 3 times a day, followed by a 300 mg increase daily every 3 days until a maximal dose of 900 mg/day, [O]Cough symptom score for daytime cough, [P]Gabapentin 300 mg/day, then increased to 600 mg/day on 2nd day, then 900 mg/day on 3rd day until a maximal dose of 1800 mg/day for 10 weeks, [Q]Pregabalin 75 mg on day 1–2, followed by increases to 150 mg on day 3–4 and 225 mg on day 5–6, then a decrease to 150 mg on day 7–84. FeNO: Fractional nitric oxide concentration in exhaled breath, FEV/FVC: Forced expiratory volume/forced vital capacity, NA: Not applicable, NR: Not recorded, PPB: Parts per billion, VAS: Visual Analog Scale, NK-1: Neurokinin-1, NMDA: N-Methyl-D-aspartate, NR: Not reported, RCT: Randomized controlled trial, SD: Standard deviation

Table 4: Cough frequency outcomes for intention-to-treat population

Trial	Intervention	*n*	Time (week)	Score (device)	Coughs/h, 24 h	
					Baseline	Follow-up
RCTs of P2X3 antagonists						
COUGH-1	Gefapixant 15 mg	227	12	Geometric mean (95% CI) (VitaloJak)	19.86	9.66
	Gefapixant 45 mg	217			18.24	7.05
	Placebo	222			22.83	10.33
COUGH-2	Gefapixant 15 mg	415	24	Geometric mean (95% CI) (VitaloJak)	19.35	8.10
	Gefapixant 45 mg	409			18.55	6.83
	Placebo	419			19.48	8.34
MK-7264-033	Gefapixant 45 mg	11	4	Mean (SD or 95% CI) (automated)	40.10 (86.7)	NR
	Placebo	12			22.90 (20.5)	
RCTs of corticosteroids						
Evald, 1989	Beclomethasone dipropionate	NR	NR	NR	NR	NR‡
Ribeiro, 2007	Beclomethasone dipropionate	44	2	Mean (SD or 95% CI) (diary score)	NR	
	Placebo	20				
Sadeghi, 2018	Montelukast (low FeNO [≤20 ppb])	15	4	Mean (SD) (LCM)	292.0 (158.0)	150.0 (104.0)
	Montelukast (high FeNO [≥30 ppb])	14			237.0 (223.0)	114.0 (122.0)
	Prednisolone+montelukast (high FeNO [≥30 ppb])	20			566.0 (388.0)	265.0 (267.0)
RCTs of antibiotics						
Yousaf, 2010	Erythromycin	15	12	Geometric mean (SD or 95% CI) (LCM)	353.0	243.0
	Placebo	15			536.0	390.0
RCTs of mast cell stabilizers						
Birring, 2017	Sodium cromoglicate	25	1	Mean (SD or 95% CI) (LCM)	NR	
	Placebo	27				
	Sodium cromoglicate	25	2			
	Placebo	27				
RCTs of neuromodulators						
Morice, 2007	Morphine sulfate	27	4	Mean (SD) (diary score)	NR	
	Placebo	27				
Ryan, 2012	Gabapentin	32	4 and 8‖	Mean (SD or 95% CI) (LCM)**	45.30 (1.90)	NR
	Placebo	30			68.80 (1.90)	
	Gabapentin	32	12 and 16¶		45.30 (1.90)	
	Placebo	30			68.80 (1.90)	
Vertigan, 2016	SPT + pregabalin	20	NR	Geometric mean (SD) (LCM)	14.10 (27.50)	4.90 (20.50)
	SPT	20			19.00 (15.60)	9.10 (16.00)
RCTs of NK-1 antagonists						
Schering-Plough, 2007	Rolapitant	NR	1	Mean (automated)	NR	NR
	Placebo					
Single-arm trials of NMDA antagonists						
MEM-COUGH-01	Memantine	11	4	Geometric mean (95% CI) (automated)	NR	

Contd...

Table 4: Contd...

Trial	Coughs/h, 24 h		Coughs/h, waking h			
	Change	Difference	Baseline	Follow-up	Change	Difference
RCTs of P2X3 antagonists						
COUGH-1	0.48 (0.41–0.55)* ratio	1.58 (−16.12–23.01)†	25.80	NR	0.47 (0.41–0.55)* ratio	2.97 (−15.32–25.21)†
	0.38 (0.38–0.44)* ratio	**−18.45 (−32.92–−0.86)**†	24.05		0.38 (0.33–0.44)* ratio	−17.68 (−32.57–0.50)†
	0.47 (0.41–0.54)* ratio	Reference	30.43		0.46 (0.40–0.53)* ratio	Reference
COUGH-2	0.43 (0.38–0.47)* ratio	−1.14 (−14.27–14.02)†	25.56	NR	0.41 (0.37–0.46)* ratio	−3.03 (−16.14–12.12)†
	0.37 (0.33–0.41)* ratio	**−14.64 (−26.07–−1.43)**†	24.26		0.36 (0.32–0.40)* ratio	**−15.79 (−27.27–−2.50)**†
	0.4 (0.4–0.5)* ratio	Reference	25.83		0.42 (0.38–0.47)* ratio	Reference
MK-7264-033	−0.23 (0.39) LSM	0.79 (−0.34–1.93) LSM	49.00 (103.0)	NR	−0.20 (0.38) LSM	−0.76 (−0.35–1.88) LSM
	−1.02 (0.38) LSM	Reference	27.30 (21.0)		−0.97 (0.37) LSM	Reference
RCTs of corticosteroids						
Evald, 1989	NR	NR			NR	
Ribeiro, 2007			3.00	0.00 (1.00)	NR	1.00 (0.40–1.50)
			3.00	3.00 (1.00)		Reference
Sadeghi, 2018	49.00	NR	NR			
	51.90					
	53.00					
RCTs of antibiotics						
Yousaf, 2010	0.67 (0.29)	1.10 (0.70–1.50)	NR			
	0.73 (0.66)	Reference				
RCTs of mast cell stabilizers						
Birring, 2017			48.00 (79.00)	NR	0.94 (0.74–1.19) LSM	1.30 (0.99–1.71) LSM ratio
			44.00 (35.00)	NR	0.72 (0.57–0.91) LSM	Reference
			NR	NR	0.86 (0.59–1.26) LSM	1.27 (0.78–2.06) LSM ratio
			NR§	NR	0.68 (0.47–0.98) LSM	Reference
RCTs of neuromodulators						
Morice, 2007			NR	3.40 (1.80)	−40.0	NR
				5.00 (1.70)	NR	
Ryan, 2012	−22.50	**−27.31 (−51.75–−2.88)**			NR	
	−4.30	Reference				
	−9.70	−3.10 (−43.31–37.11)				
	−8.90	Reference				
Vertigan, 2016	11.20 (18.30)	2.30			NR	
	8.90 (18.10)	Reference				
RCTs of NK-1 antagonists						
Schering-Plough, 2007	−2.10	NR			NR††	
	−1.10					
Single-arm trials of NMDA antagonists						
MEM-COUGH-01	NR		41.10 (22.90–73.80)	30.90 (15.60–61.20)	NR	NR

*Model-based geometric mean ratio (week 12/baseline), **LCM was attached to each participant for 1 h, †Estimated relative reduction versus placebo was estimated by 100 × (exp [diff⁻¹]), where diff was the difference provided by the analysis of the log-transformed variable, ‡No significant difference during run-in was found between the 2 groups, nor between beclomethasone and placebo during period 1 in any of the 7 variables, §The difference between the sodium cromoglicate and placebo arms was not significant using the ratio of LSM for the change from baseline in the log-transformed 24-h average cough count at day 14, ¶On treatment, ¶Post-treatment, ††Change in nighttime coughing (coughs/h) was –4.70 for the Rolapitant group and –0.30 for the placebo group. Statistically significant differences (P<0.05) between arms of trials are presented in bold. Please see main text for details. Only those trials that reported on cough frequency are included in the table. CI: Confidence interval, FeNO: Fractional nitric oxide concentration in exhaled breath, LCM: Leicester cough monitor, LSM: Least squares mean, NR: Not reported, SD: Standard deviation, SPT: Speech pathology treatment, NK-1: Neurokinin-1, NMDA: N-Methyl-D-aspartate, RCT: Randomized controlled trial

treatment (2 weeks of inhaled beclomethasone dipropionate) compared to placebo ($P < 0.01$).[25] Two other RCTs of corticosteroids (inhaled fluticasone propionate or budesonide) included measures of cough severity but did not observe significant improvements following treatment.[22,24]

Vertigan (2016) observed a significant improvement in cough severity in the combined pregabalin and SPT group compared to those receiving SPT alone ($P = 0.002$), although the difference was not maintained in the follow-up period.[30] Similarly, in an RCT of gabapentin, the significant improvement in cough severity compared

Table 5: Cough severity outcomes for intention-to-treat population

Trial	Intervention	*n*	Time (week)	Score	VAS (mm)				CSS			
					Baseline	Follow-up	Change	Difference	Baseline	Follow-up	Change	Difference
RCTs of corticosteroids												
Chaudhuri, 2004	Fluticasone	10	NR	*n* (95% CI)	NR	NR	5 (−10–21)	NR			NR	
	Placebo	NR		NR			NR					
Ribeiro, 2007	Beclomethasone dipropionate	44	2	Mean (95% CI)	94.00	3.00	NR	1.1 (0.6–1.8)			NR	
	Placebo	20		Mean	93.00	91.00		Reference				
Pizzichini, 1999	Budesonide	21	2	Mean	61.40*	NR	NR	NR	NR			
	Placebo	23			51.00*							
RCTs of antibiotics												
Hodgson, 2016	Azithromycin	21	8	Mean (SD or 95% CI)	NR				6.40 (1.90)	5.40 (2.90)	−1.00 (−2.20–0.10)	NR
	Placebo	21		Mean (SD)					6.00 (1.90)	5.80 (2.30)	Reference	
Yousaf, 2010	Erythromycin	15	3 months	Mean (SD or 95% CI)	57.00 (18.00)	NR	−12.00 (33.00)	10.00 (−11.00–33.00)	NR			
	Placebo	15		Mean (SD)	52.00 (17.00)		2.00 (29.00)	Reference				
RCTs of mast cell stabilizers												
Birring, 2017	Sodium cromoglicate	25	1	Mean (SD)	65.40 (20.80)	60.30 (21.80)	−5.30	NR			NR	
	Placebo	27			71.20 (12.20)	63.30 (19.80)	−8.10					
	Sodium cromoglicate	25	2	Mean (SD or 95% CI)	65.40 (20.80)	57.80 (22.80)	−7.70	−0.40 (−9.37–8.58) LSM				
	Placebo	27		Mean (SD)	71.20 (12.20)	61.20 (23.80)	−10.00	Reference				
RCTs of neuromodulators												
Ryan, 2012	Gabapentin	32	4 and 8 (on-treatment)	Mean (SD or 95% CI)	43.60 (29.60)	NR	−11.10	**−12.23 (−23.22—1.25)**			NR	
	Placebo	30		Mean (SD)	44.20 (21.30)		0.80	Reference				
	Gabapentin†	32		Mean (SD or 95% CI)	4.00 (1.80)		−0.70	0.59 (−0.52–1.70)				
	Placebo†	30		Mean (SD)	4.30 (2.80)		−1.40	Reference				
	Gabapentin	32	12 and 16 (post treatment)	Mean (SD or 95% CI)	43.60 (29.60)		2.00	5.57 (−4.93–16.07)				
	Placebo	30		Mean (SD)	44.20 (21.30)		−4.80	Reference				
	Gabapentin†	32		Mean (SD or 95% CI)	4.00 (1.80)		−0.90	0.021 (−1.29–1.34)				
	Placebo†	30		Mean (SD)	4.30 (2.80)		−1.10	Reference				
Vertigan, 2016	SPT + pregabalin	20	NR	Geometric mean (SD or 95% CI)	52.00 (22.50)	19.30 (22.60)	38.80 (23.40)	**25.10 (10.60–39.60)**	NR			
	SPT	20		Geometric mean (SD)	49.70 (19.70)	29.50 (24.80)	14.50 (20.10)	Reference				

Contd...

Table 5: Contd...

Trial	Intervention	*n*	Time (week)	Score	VAS (mm)				CSS			
					Baseline	Follow-up	Change	Difference	Baseline	Follow-up	Change	Difference
RCTs of NK-1 antagonists												
Schering-Plough, 2007	Rolapitant[‡]	NR	1	Mean	NR				NR	NR	−0.17	NR
	Placebo[‡]										0.02	
	Rolapitant[§]										**−0.27**	
	Placebo[§]										0.10	

*The effect of 2 weeks of treatment with budesonide on cough discomfort, as measured by the VAS, was similar to the placebo effect whether analyzed as the difference between actual values or as the difference between the percentage reduction in cough discomfort, †Measure of urge to cough, ‡Daytime cough, §Nighttime cough. Statistically significant differences (P<0.05) between arms of trials are presented in bold. Please see main text for details. Only those trials that reported on cough severity are included in the table. CI: Confidence interval, CSS: Cough symptom score, LSM: Least squares mean, NK-1: Neurokinin-1, NR: Not reported, SD: Standard deviation, SPT: Speech pathology therapy, VAS: Visual Analog Scale

to the placebo that was observed during the treatment period (P = 0.029) did not persist after the follow-up period.[29] No significant improvement in the urge to cough score was observed at either timepoint.[29]

Neither of the 2 antibiotic RCTs identified any significant differences in cough severity after treatment.[35,36] Two trials of other treatment classes reported cough severity outcomes: treatment with rolapitant was associated with a significant reduction in cough severity compared to placebo in the nighttime, but not the daytime, CSS measure (P = 0.043),[39] but no significant difference in cough severity was observed following treatment with sodium cromoglicate compared to placebo.[38]

Health-related quality of life

Eleven trials reported health-related quality of life (HRQoL) measures. Most of these trials used one or more VAS and/or validated survey instrument to assess overall health- and cough-related outcomes [Table 6]. These included the Leicester Cough Questionnaire (LCQ, 10 trials), which contains 19 questions about physical, psychological, and social health, each scored on a scale of 1–7, with higher scores on the overall scale of 19–133 representing better quality of life.[43,44] The cough quality of life questionnaire (CQLQ, 1 trial) comprises 28 items relating to physical and emotional health, functional ability, and other outcomes, each scored on a scale of 1–4, with higher total scores indicating worse quality of life due to cough.[45,46] The Hull airway reflux questionnaire (HARQ, 1 trial) assesses cough hypersensitivity syndrome using 14 items, each scored on a scale of 1–5, with total scores of >13/70 indicating a higher likelihood of cough hypersensitivity syndrome.[47] Finally, the 36-item short-form health survey version 2 (SF-36 v2, 1 trial) assesses general physical and mental health, with higher scores representing better health.[43,48,49]

Patients were treated with gefapixant or placebo in the COUGH-2 trial. It was reported that participants given the 45 mg dose of gefapixant, but not the 15 mg dose, had significantly improved LCQ scores at 24 weeks compared to placebo (P = 0.042).[31,32,34] In the sole corticosteroid trial to report PROs, Sadeghi (2018) observed significant improvements from baseline in the HARQ and LCQ scores of participants in all treatment arms of their RCT of montelukast versus montelukast plus prednisolone, but did not report on between-arm differences.[26]

HRQoL measures were available for 3 of the neuromodulator RCTs. Treatment with morphine sulfate was associated with significant improvements compared to placebo in the total score (P < 0.02) and all subdomain scores of the LCQ.[28] Significantly improved total LCQ scores compared to placebo were also

Table 6: Health-related quality of life measures for intention-to-treat population

Trial	Intervention	*n*	Time (week)	Type of measure	Baseline mean (SD)	Follow-up mean (SD)	Change from baseline mean (95% CI)	Between-arm difference mean (95% CI)	Proportion with improvement, *n* (%)
RCTs of P2X3 antagonists									
COUGH-1	Gefapixant 15 mg	244	12	LCQ	10.50 (2.90)	NR	NR	NR	NR
	Gefapixant 45 mg	243			10.50 (2.70)				
	Placebo	243			10.00 (3.10)				
COUGH-2	Gefapixant 15 mg	404	24	LCQ	10.40 (3.00)	NR	NR	5.55 OR: 1.33, 95% CI: 0.96–1.84, *P*=0.085	76.10
	Gefapixant 45 mg	399			10.40 (3.00)			**6.58** **OR: 1.41, 95% CI: 1.01–1.96, *P*=0.042**	77.10
	Placebo	406			10.30 (3.00)			Reference	70.60
RCTs of corticosteroids									
Sadeghi, 2018	Montelukast (low FeNO [≤20 ppb])	15	4	HARQ	33.00 (5.00)	20.00 (11.00)	NR	NR	NR
	Montelukast (high FeNO [≥30 ppb])	14			27.00 (11.00)	15.00 (10.00)			
	Prednisolone + montelukast (high FeNO [≥30 ppb])	20			NR	31.00 (14.00)			
	Montelukast (low FeNO [≤20 ppb])	15		LCQ	14.00 (3.00)	16.00 (2.00)			
	Montelukast (high FeNO [≥30 ppb])	14			15.00 (3.00)	NR*			
	Prednisolone + montelukast (high FeNO [≥30 ppb])	20			12.00 (4.00)	15.00 (3.00)			
RCTs of antibiotics									
Hodgson, 2016	Azithromycin	21	8	LCQ	10.20 (3.30)	12.60 (4.90)	2.40 (0.50–4.20)	**1.90 (0.10–3.80)**	11 (52.00)
	Placebo	21			11.50 (3.10)	12.10 (4.20)	0.70 (−0.60–1.90)	Reference	NR
Yousaf, 2010	Erythromycin	15	3 months	LCQ	NR	NR	1.80 (3.80)	0.00 (−2.00–2.00)	NR
	Placebo	15					1.80 (3.80)	Reference	
RCTs of mast cell stabilizers									
Birring, 2017	Sodium cromoglicate	25	1	LCQ	10.90 (3.40)	12.40 (3.90)	1.40	NR	NR
	Placebo	27			11.10 (3.10)	12.30 (3.90)	1.20		
	Sodium cromoglicate	25	2		10.90 (3.40)	12.60 (4.50)	1.60	0.50 (−0.80–1.80) LSM	
	Placebo	27			11.10 (3.10)	12.00 (4.10)	1.00	NR	
RCTs of neuromodulators									
Morice, 2007	Morphine sulfate	NR	NR	LCQ	12.30 (2.50)	15.50 (2.70)	3.20	NR	NR
	Placebo				12.30 (2.50)	13.50 (2.70)	NR		
Ryan, 2012	Gabapentin	32	4 and 8†	LCQ	13.30 (3.10)	NR	2.50	**1.80 (0.56–3.04)**	20 (74.10)‡
	Placebo	30			12.10 (3.90)		1.10	Reference	12 (46.20)§
	Gabapentin	32	12 and 16‖		13.30 (3.10)		1.70	0.85 (−0.75–2.44)	NR
	Placebo	30			12.10 (3.90)		1.40	Reference	NR
	Gabapentin	32	NR	SF-36	521.90 (160.90)	481.80 (197.90)	NR	NR	NR
	Placebo	30			522.80 (196.20)	581.80 (160.20)			

Contd...

Table 6: Contd...

Trial	Intervention	*n*	Time (week)	Type of measure	Baseline mean (SD)	Follow-up mean (SD)	Change from baseline mean (95% CI)	Between-arm difference mean (95% CI)	Proportion with improvement, *n* (%)
RCTs of P2X3 antagonists									
Vertigan, 2016	SPT + pregabalin	20	NR	LCQ	10.20 (3.70)¶	17.10 (3.20)¶	6.60 (4.50)¶	**3.50 (1.10–5.80)**	NR
	SPT	20			12.00 (2.70)¶	15.30 (3.50)¶	3.30 (2.30)¶	Reference	
RCTs of NK-1 antagonists									
Schering-Plough, 2007	Rolapitant	NR	1	VAS	39.0	NR	–6.0	NR	NR
	Placebo				36.0		1.4		
	Rolapitant		2	LCQ	11.5		1.5		
	Placebo				11.5		0.3		
Single-arm trials of NMDA antagonists									
MEM-COUGH-1	Memantine	13	4	CQLQ	64.6 (58.4–70.8)**	62.0 (54.3–69.7)**	NR	NR	NR

*In the montelukast+prednisolone FeNO group, the LCQ score improved from 15 (3) to 18 (2) in the 2nd week, and this improvement was maintained for the 2nd treatment period, †On treatment, ‡Sample size: *n*=27, §Sample size: *n*=26, ¶Post-treatment, ¶Geometric mean (SD), **95% CI. Statistically significant differences (*P*<0.05) between arms of trials are presented in bold. Please see main text for details. Only those trials that incorporated HRQoL measures are included in the table. CI: Confidence interval, CQLQ: Cough quality of life questionnaire, FeNO: Fractional nitric oxide concentration in exhaled breath, HARQ: Hull airway reflux questionnaire, LCQ: Leicester cough questionnaire, LSM: Least squares mean, NK-1: Neurokinin-1, NMDA: N-Methyl-D-aspartate, NR: Not reported, OR: Odds ratio, SD: Standard deviation, SF-36: 36-item short-form survey, VAS: Visual Analog Scale, HRQoL: Health-related quality of life

reported in an RCT of gabapentin ($P = 0.004$), although the on-treatment improvements were not maintained at the post-treatment follow-up timepoint.[29] Finally, Vertigan (2016) observed improved LCQ scores in both treatment arms, with a significantly greater improvement in the pregabalin plus SPT group than in those receiving SPT alone ($P = 0.024$).[30]

In the antibiotic RCTs, Hodgson (2016) reported significantly improved LCQ scores in the azithromycin compared to the placebo arm at 4 weeks ($P = 0.04$) but no significant difference at the end of the trial, while Yousaf (2010) did not observe any significant differences between arms of the trial.[35,36] In the trials of other drug classes treatment with sodium cromoglicate was not associated with any significant improvement in LCQ scores,[38] while the mean CQLQ score decreased from 64.6 to 62.0 after 4 weeks of treatment with memantine, although this change was not significant.[41]

Safety outcomes

Not all trials reported safety outcomes. The available combined rates of all-cause and treatment-related AEs, including treatment discontinuations, are summarized in Table 7, and the available rates of specific AEs of interest are presented in Supplementary Table 5.

In the 3 gefapixant trials, the overall incidence of AEs correlated with the treatment dose, although the incidence of serious AEs (SAEs) was similar between all arms of the 2 trials that reported this outcome separately.[31-34] In all 3 trials, AEs and treatment discontinuations were frequently due to taste-related symptoms (which were pre-defined in these studies as AEs of special interest), notably dysgeusia and ageusia.

None of the included corticosteroid or neuromodulator trials reported combined all-cause or treatment-related AEs, although Pizzichini (1999) did report that there were no treatment discontinuations in either arm of their placebo-controlled RCT investigating budesonide.[24] All 4 of the neuromodulator trials recorded individual AEs of interest, however. The most commonly reported AEs observed by Dong (2019) were nausea and dizziness, with a significantly higher incidence of dizziness in the gabapentin treatment arm than in the baclofen treatment arm ($P = 0.01$).[27] Dizziness and nausea, as well as dry mouth, were also the most common AEs in both arms of a placebo-controlled trial of gabapentin, although *P* values were not reported.[29] Headache was also reported by 6% of participants receiving gabapentin, compared to 0% of the placebo group.[29] Vertigan (2016) observed a higher incidence of dizziness among participants receiving pregabalin in combination with SPT than in those receiving SPT alone (45% vs. 5%, $P < 0.001$).[30] Finally, the most commonly reported AEs in the RCT of morphine

Table 7: Safety outcomes for intention-to-treat population

Trial	Intervention	*n*	All-cause AEs			Treatment-related AEs		
			Any grade, *n* (%)	Serious, *n* (%)	Discontinuations, *n* (%)	Any grade, *n* (%)	Serious, *n* (%)	Discontinuations, *n* (%)
RCTs of P2X3 antagonists								
COUGH-1	Gefapixant 15 mg	244	136 (55.7)	7 (2.9)	12.0	46 (18.9)	NR	3.0
	Gefapixant 45 mg	243	183 (75.3)	7 (2.9)	25.0	152 (62.6)		15.0
	Placebo	243	128 (52.7)	5 (2.1)	12.0	32 (13.2)		3.0
COUGH-2	Gefapixant 15 mg	404	347 (78.7)	13 (2.9)	19.0	138 (31.3)		8.0
	Gefapixant 45 mg	399	383 (87.0)	14 (3.2)	29.0	311 (70.7)		20.0
	Placebo	406	314 (72.5)	16 (3.7)	15.0	88 (20.3)		5.0
MK-7264-033	Gefapixant 45 mg	11	9 (81.8)	NR	1 (9.1)	0	NR	NR
	Placebo	12	2 (16.7)		0	0		
RCTs of corticosteroids								
Pizzichini, 1999	Budesonide	NR	NR	NR	0	NR		
	Placebo							
RCTs of mast cell stabilizers								
Birring, 2017	Sodium cromoglicate	25	NR	0	2 (8.0)	NR		
	Placebo	27		0	2 (7.4)			
RCTs of NK-1 antagonists								
Schering-Plough, 2007	Rolapitant	30	22 (73.3)	0	0	NR		
	Placebo	32	22 (68.8)	0	0			
Single-arm trials of NMDA antagonists								
MEM-COUGH-1	Memantine	14	14 (100)	0	NR	NR		

Only those trials that reported safety outcomes are included in the table. The frequencies of AEs have been categorized and color-coded according to the European medicines agency's ranking of AEs. NK-1: Neurokinin-1, NMDA: N-Methyl-D-aspartate, NR: Not reported, AEs: Adverse events

Very common (≥1/10)
Common (≥1/100–<1/10)
No AEs

sulfate were constipation (40%) and drowsiness (25%); however, the incidence of these and other AEs in the placebo group was not reported.[28]

In trials of other drug classes, Birring (2017) observed similar rates of treatment discontinuation in the treatment and placebo arms of their trial of sodium cromoglicate, although no participants experienced SAEs.[38] The discontinuations were related to angioedema, sinus tachycardia, pharyngeal hypoesthesia, cough, and dyspnea.[38] Among participants in the trial of azithromycin, 4.5% discontinued treatment due to gastrointestinal symptoms.[35] No discontinuations and no SAEs were observed in a placebo-controlled trial of rolapitant,[39] and no SAEs were reported for the single-arm trial of memantine, although 71.4% of participants reported dizziness; headache, nasopharyngitis, and nausea were also common AEs.[41]

Study quality

Concerns regarding potential biases were identified for 11 RCTs, with 6 of these trials considered to carry a high overall risk of bias [Supplementary Figure 1 and Supplementary Table 6].[23,24,27,29,37,39] The concerns for these high-risk RCTs were related to deviations from the intended interventions (4 trials), missing outcomes data (3 trials), outcomes measurements (3 trials), and selection of the reported results (1 trial). All but one of the trials included in the SLR were assessed as having some concerns related to the selection of the reported results. For 2 of the gefapixant trials, these concerns were due to the results having being reported only in conference abstracts and a conference presentation at the time of the literature search, with no full-text publication or clinical trial registry report yet available.[31,32,34] However, these specific concerns have been mitigated by the subsequent publication of both trials.[50]

Discussion

This SLR defined and assessed an RCC or UCC clinical trial evidence base that comprised 20 publications reporting on 19 unique trials of drugs with regulatory approval for any indication, or doses of gefapixant that are currently approved or under consideration for approval. Fourteen of the 17 included RCTs were placebo-controlled; 2 of the other 3 RCTs compared the intervention of interest to another pharmacological intervention, while the third compared the intervention plus SPT to SPT alone. With the exception of 2 of the 3 placebo-controlled gefapixant trials (n = 730 and n = 1314) and the RCT comparing gabapentin to baclofen (n = 234), most trials were small,

with ≤64 participants. There was considerable variation between the included trials in their definitions of RCC and UCC; inclusion and exclusion criteria; study design; study length; outcomes measurement timepoints; and outcomes measures used to assess cough frequency, cough severity, PROs, and safety.

While several trials reported significantly improved outcomes compared to baseline and/or compared to placebo at a single on-treatment timepoint, these improvements did not persist in any of the trials that also included follow-up (post-treatment) outcomes measures. All included RCTs had at least some concerns related to risk of bias, with 6 having a high risk of bias.

In addition to the 19 trials of treatments with existing FDA or EMA approval for any indication and doses of gefapixant that are currently approved in Japan or under consideration for regulatory approval elsewhere, the literature search also identified 23 publications related to 15 unique trials of diverse interventions that have not yet been submitted for consideration for regulatory approval for any medical indication. Although these publications were not described in detail in the current review, they represent evidence that the development of new treatments for RCC or UCC is an active area of clinical research. Further development and regulatory approval of new treatments will require rigorous comparison of candidate interventions to each other and any treatments approved in the future. However, the small size of most of the studies included in the SLR, and the high degree of study design and sample population heterogeneity between trials of RCC or UCC treatments, currently limit the generalizability of the current clinical trial evidence base.

Some of the observed sample population heterogeneity may be due to the lack of specific diagnostic codes for chronic cough, RCC, UCC, other difficulties in making this diagnosis, and inconsistent use of diagnostic codes for acute cough.[51,52] The recent introduction of new International Classification of Diseases codes for chronic cough in the US and Germany may facilitate more consistent sample population identification methods for future trials.[53,54]

In the absence of a licensed treatment for RCC or UCC,[16] the most common comparator across all controlled trials was placebo. Placebo will likely continue to be the most relevant comparator for RCC or UCC drug trials until an approved treatment becomes more widely available and established as the standard of care. However, a powerful placebo effect has been observed in many RCTs of treatments for cough and other respiratory disorders, potentially related to the voluntary control and the conscious and unconscious mechanisms of cough suppression.[50,55-62] Benchmarking this placebo response across large trials would facilitate the design and interpretation of placebo-controlled cough treatment studies. In contrast to the placebo comparator, no consistent pattern emerged from the SLR with respect to the length of RCC or UCC trials, with the time spans of the included studies ranging from 1 to 24 weeks. The optimal study length for a rigorous assessment of efficacy and safety outcomes thus remains undefined.

The primary strength of this SLR is its design and conduct in accordance with PRISMA guidelines. The literature identification process used highly sensitive searches of the peer-reviewed literature, supplemented with searches of clinical trial registries and relevant recent conference proceedings to capture additional completed trials that had not yet been published in full on the search date. As with any review, however, this SLR may be limited by incomplete capture of relevant eligible trials, for example by potentially excluding studies that were recently published but not yet indexed in the selected databases on the date of the search, and those published in languages other than English. Publication bias may also have affected the available content included in the databases used for the literature search.

In conclusion, published RCC or UCC clinical trials were generally small, and there was a high degree of variation between trials in terms of study design, study population, definition of chronic cough, and the outcomes measured. Placebo remains the most common and relevant comparator for trials of potential treatments of RCC or UCC. Due to the limited generalizability of the published trial outcomes, further meta-analyses of published RCC or UCC trials - such as anchored indirect treatment comparisons of relative treatment effects - may not be possible at present.

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Conflicts of interest

Vishal Bali, Ada Adriano, and Aidan Byrne are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and shareholders in Merck & Co., Inc, Rahway, NJ, USA.

Peter Kardos reports receiving honoraria from Bionorica SE and Neumarkt.

Clive Page reports receiving consulting fees, payment, or honoraria from EpiEndo, Eurodrug, Accelerated Enrollment Solutions (Synexus), Helperby Therapeutics, Recipharma, PrEP Biopharma, The Cough and Cold Company Ltd, Clinical Trials Worldwide, and Tianli.

Paola Rogliani reports receiving consulting fees or honoraria from Almirall, AstraZeneca, Biofutura, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini Group, Mundipharma, and Novartis.

Luigino Calzetta reports receiving consulting fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Novartis, Ockham Biotech, Edmond Pharma, Verona Pharma, and Zambon. Adekemi Adeyemi was an employee of PRECISIONheor, a scientific consultancy contracted by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA to conduct this research at the time of the study.

Andrew Frederickson is an employee of PRECISIONheor, a scientific consultancy contracted by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA to conduct this research.

Jonathan Schelfhout was an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and shareholder in Merck & Co., Inc, Rahway, NJ, USA at the time of the study.

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Supplementary Table 1: Literature search strategies

Term (s)	Hits
Embase	
Exp chronic cough/	4177
((chronic adj3 cough) or (unexplained adj3 cough) or (idiopathic adj3 cough) or (refractory adj3 cough) or (unexplained adj3 cough) or (intractable adj3 cough) or (persistent adj3 cough) or (cough adj3 syndrome)).mp	11,598
1 or 2	11,598
Clinical trial/	985,208
Randomized controlled trial/	622,762
Controlled clinical trial/	464,765
Multicenter study/	263,591
Phase 3 clinical trial/	48,824
Phase 4 clinical trial/	4006
Exp RANDOMIZATION/	88,562
Single blind procedure/	40,363
Double blind procedure/	176,401
Crossover procedure/	64,535
PLACEBO/	355,465
Randomi?ed controlled trial$.tw.	238,786
rct.tw.	38,680
(random$ adj2 allocat$).tw.	44,304
single blind$.tw.	25,654
double blind$.tw.	212,846
((treble or triple) adj blind$).tw.	1226
placebo$.tw.	313,636
Prospective Study/	630,435
or/4–22	2,379,719
Case Study/	72,196
case report.tw.	424,398
abstract report/or letter/	1,166,493
Conference proceeding.pt.	0
Conference abstract.pt.	3,873,805
Editorial.pt.	667,420
Letter.pt.	1,139,580
Note.pt.	816,327
or/24–31	6,955,001
23 not 32	1,763,773
3 and 33	908
Limit 34 to English language	839
Medline	
((chronic adj3 cough) or (unexplained adj3 cough) or (idiopathic adj3 cough) or (refractory adj3 cough) or (unexplained adj3 cough) or (intractable adj3 cough) or (persistent adj3 cough) or (cough adj3 syndrome)).mp.	6513
exp cough/	16,042
(chronic or unexplained or idiopathic or refractory or unexplained or intractable).mp.	1,662,858
1 or (2 and 3)	8169
Randomized Controlled Trials as Topic/	136,604
randomized controlled trial/	514,078
Random Allocation/	103,665
Double Blind Method/	160,040
Single Blind Method/	29,092
clinical trial/	525,019
clinical trial, phase i.pt	20,851
clinical trial, phase ii.pt	33,495
clinical trial, phase iii.pt	17,273
clinical trial, phase iv.pt	1959
controlled clinical trial.pt	93,863
randomized controlled trial.pt	514,078

Contd...

Supplementary Table 1: Contd...

Term (s)	Hits
Medline	
multicenter study.pt	279,895
clinical trial.pt	525,019
exp Clinical Trials as topic/	346,466
or/5-19	1,383,470
(clinical adj trial$).tw	381,142
((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw	176,538
PLACEBOS/	35,106
placebo$.tw	220,440
randomly allocated.tw	29,800
(allocated adj2 random$).tw	33,167
or/21-26	655,625
20 or 27	1,665,941
case report.tw	328,358
letter/	1,101,323
historical article/	360,360
or/29-31	1,773,852
28 not 32	1,628,281
4 and 33	833
Limit 34 to English language	760
Cochrane central register of controlled trials	
((chronic adj3 cough) or (unexplained adj3 cough) or (idiopathic adj3 cough) or (refractory adj3 cough) or (unexplained adj3 cough) or (intractable adj3 cough) or (persistent adj3 cough) or (cough adj3 syndrome)).mp.	930
exp cough/	1296
(chronic or unexplained or idiopathic or refractory or unexplained or intractable).mp.	178,283
1 or (2 and 3)	1038
Limit 4 to English	552

Supplementary Table 2: Characteristics of included studies evaluating doses of gefapixant that are not currently under consideration for regulatory approval

Trial name, ID (s) and publication (s)*	Intervention	*n*	Study design		Location		Dates	Crossover permitted
			Phase	Masking	Country	Multi-site		
EPICC[1,2] (NCT01432730)	Gefapixant (1200 mg) versus Placebo	24	II	Double	UK	No	2011–2013	Yes
MK-7264-021[3] (NCT02612623)	Gefapixant (30, 60, or 100 mg) versus Placebo	24	II	Quadruple	US	Yes	2015–2016	No
MK-7264-010[4,5] (NCT02349425)	Gefapixant (30–200 or 400–800 mg) versus Placebo	59	II	Quadruple	US	Yes	2015–2016	Yes
Morice 2019[6,7] (NCT02476890/ EudraCT 2015-002034-47)	Gefapixant (100 mg) versus Placebo	24	II	Triple	UK	No	2015–2016	Yes
Smith, 2020[8-10] (NCT02612610)	Gefapixant (15, 40, or 100 mg) versus Placebo	253	IIb	Double	UK and US	Yes	2015–2016	No

*NCT, US NIH clinical trial registry (https://clinicaltrials.gov). All trials administered gefapixant orally. Dosages represent total daily dose. UK: United Kingdom, US: United States

Supplementary Table 3: Characteristics of included studies evaluating interventions with no regulatory approval for any indication

Trial ID (s)*	Intervention		*n*	Study design		Location		Dates	Crossover permitted
	Class	Treatment		Phase	Masking	Country	Multi-site		
NCT02233699/EudraCT 2014-000306-36[11]	TRPV1 antagonist	XEN-D0501 versus placebo	19	II	Double blind	UK	Yes	2014–2015	Yes
EudraCT 2006-002165-39[12]	NOP1 agonist	SCH486757 versus placebo	31	II	Double blind	UK	No	2007–2007	Yes
EudraCT 2013-002728-17[13]	NR	GRC 17536 potassium versus placebo	52	IIa	Double blind	UK	Yes	2013–2014	No
EudraCT 2014-005074-11[14]	GABA-B agonist	Lesogaberan versus placebo	22	II	Double blind	UK	No	2015–2017	Yes
NCT03372603/EudraCT 2017-002265-21[15]	NR	GSK2798745	17	I/II	Double blind	UK	Yes	2018–2018	Yes
EudraCT 2017-003108-27[16]	NR	AX-8	12	NR	NR	UK	NR	2017–2018	No
EudraCT 2010-021642-22[17]	TRPV1 antagonist	SB-705498	21	NR	Double blind	UK	No	2011–2012†	Yes
NCT03310645[18,19]	P2X3 antagonist	BAY1817080 versus placebo	40	I/II	Double blind	UK	Yes	2017–2019	Yes
NCT03282591[20]	NK1-R antagonist	Serlopitant versus placebo	185	II	Quadruple	UK	NR	2017–2018	No
JapicCTI-184027[21]	P2X3 antagonist	S-600918 versus placebo	31	II	Double blind	Japan	Yes	2018–2019†	Yes
NCT01899768/EudraCT 2012-004891-20[22]	Sodium channel blocker	GSK2339345 versus placebo	16	II	Double blind	UK	Yes	2014–2014	Yes
VOLCANO-1 (Eudra CT 2014-003947-36)[23]	NK-1 antagonist	Orvepitant	13	II	Open-label	UK	No	2015–2015	No
VOLCANO-2 (NCT02993822)[24]	NK-1 antagonist	Orvepitant	315	IIb	Quadruple	UK	Yes	2017–2019	No
ChiCTR-TRC-00000152[25]	NR	Methoxyphenamine	240	NR	Open-label	China	No	2008–2009†	No
ChiCTR-ONC-13003067[26]	NR	Step 1: Asmeton + cetrizine Step 2: Prednisone + budesonide Step 3: Omeprazole + domperidone	102	NR	NR	China	No	2005–2006†	No

*ChiCTR: Chinese clinical trial registry (http://www.chictr.org.cn/enindex.aspx), EudraCT: European union drug regulating authorities clinical trials database (https://eudract.ema.europa.eu/), JapicCTI: Japanese pharmaceutical information center clinical trials information (https://rctportal.niph.go.jp/en/), NCT, US NIH clinical trial registry (https://clinicaltrials.gov), †Dates of first and last participant enrollment. NR: Not reported, UK: United Kingdom

Supplementary Table 4: Key eligibility criteria and definitions for the studies included in the systematic literature review

Trial name	Inclusion criteria			Exclusion criteria			
	Unexplained/ idiopathic*	Refractory	Underlying etiology	Duration of cough	History of smoking	Known respiratory disease	Use of ACEis
RCTs of P2X3 antagonists							
COUGH-1	Unexplained[†]	Yes[M]	NR	≥1 year	Yes	Chronic bronchitis, FEV1/FVC <60%, RTI	Yes
COUGH-2	Unexplained[†]	Yes[M]	NR	≥1 year	Yes	Chronic bronchitis, RTI	Yes
MK-7264-033	Unexplained[‡]	Yes[‡]	NR	≥1 year	Yes	Chronic bronchitis, RTI	Yes
RCTs of corticosteroids							
Chaudhuri, 2004	Idiopathic[§]	No	NR	>1 year	Yes	URTI	Yes
Evald, 1989	Idiopathic[‡]	No	NR	NR	NR	NR	NR
Ribeiro, 2007	Idiopathic[‡]	No	NR	≥8 weeks	NR	Asthma, COPD, FEV1/FVC <70%, GERD, postnasal drip, RTI	No
Pizzichini, 1999	Idiopathic[I]	No	GERD, postnasal drip	≥1 year	Yes	Chest disease, chronic bronchitis, RTI	No
Sadeghi, 2018	Idiopathic[‡]	No	NR	≥8 weeks	Yes	Asthma, bronchiectasis, cystic fibrosis, COPD, LRTI	Yes
RCTs of β-adrenergic agonists							
Ellul-Micallef, 1983	Idiopathic[¶]	Yes[N]	Allergy	≥3 months	Yes	Lung disease	No
RCTs of antibiotics							
Hodgson, 2016	Idiopathic[‡]	No	NR	≥2 months	Yes	RTI	No
Yousaf, 2010	Idiopathic[‡]	No	GERD	>8 weeks	Yes	NR	No
RCTs of mast cell stabilizers							
Birring, 2017	Idiopathic**	No	Asthma, GERD, postnasal drip	>8 weeks	NR	RTI	No
RCTs of neuromodulators							
Dong, 2019	No	Yes[O]	GERD	>2 months	Yes	Cough variant asthma, eosinophilic bronchitis, UACS, URTI	No
Morice, 2007	Idiopathic[††]	No	NR	>3 months	NR	Lung disease	NR
Ryan, 2012	Idiopathic[‡‡]	No	Asthma, GERD, rhinitis	>8 weeks	Yes	COPD, RTI, untreated asthma	Yes
Vertigan, 2016	Idiopathic[J]	Yes[P]	GERD, postnasal drip, withdrawal of ACEis (if used)	≥8 weeks	Yes	Active respiratory disease, RTI	Yes
RCTs of NK-1 antagonists							
Schering-Plough, 2007	Idiopathic[K]	No	Asthma, GERD, postnasal drip	>6 months	Yes	Asthma, COPD	Yes
Single-arm trials of neuromodulators							
Xu, 2013	Idiopathic[‡]	No	GERD	NR	NR	Cough variant asthma, eosinophilic bronchitis, UACS	No
Single-arm trials of NMDA antagonists							
MEM-COUGH-1	Idiopathic[L]	Yes[Q]	NR	>8 weeks	Yes	URTI	Yes

*Studies have been categorized as "idiopathic" if they were conducted before "RCC and UCC" were defined in the 2016 ACCP guidelines on the treatment of UCC,[27] [†]Defined as no diagnosed condition associated with cough, [‡]Definition not reported in study, [§]Defined as cough lasting >1 year (persistent cough), [I]Defined as no improvement on treatment of symptomatic GERD, [¶]Defined as cough of at least 3 month's duration that was unaccompanied by dyspnea or wheezing, **Defined as not responsive to targeted therapies for possible underlying triggers, [††]Defined as failure to respond to specific antitussive therapy, [‡‡]Defined as negative response to previous investigations or trials of treatments for asthma, GERD, and rhinitis, [J]Defined as no associated diagnoses, [K]Defined as unresponsive to 8 weeks of targeted treatment for identified underlying triggers, [L]Defined as no objective evidence of an underlying trigger, [M]Defined as persistent cough despite treatment of conditions associated with cough, [N]Defined as wheezing, [O]Defined as cough that failed to improve with an 8-week course of omeprazole 20 mg twice daily and domperidone 10 mg 3 times daily, [P]Defined as persistent cough after treatment of associated diagnoses of asthma, rhinitis, or GERD, [Q]Defined as cough that was unresponsive to standard treatment for identified underlying trigger (s). ACEi: Angiotensin-converting enzyme inhibitor, COPD: Chronic obstructive pulmonary disease, FEV/FVC: Forced expiratory volume/forced vital capacity, GERD: Gastroesophageal reflux disease, LRTI: Lower respiratory tract infection, NR: Not reported, NK-1: Neurokinin-1, NMDA: N-Methyl-D-aspartate, RTI: Respiratory tract infection, UACS: Upper airway cough syndrome, URTI: Upper respiratory tract infection, UCC: Unexplained chronic cough, RCC: Refractory chronic cough, ACCP: American College of Chest Physician

Supplementary Table 5: Individual adverse events of interest

Trial	Intervention	*n*	Percentage AEs of interest											
			Ageusia/ hypo geusia	Dysgeusia	Dry mouth	Naso pharyngitis	Nausea	Head ache	Allergic reaction	Chest pain	Cough	Dizziness	Drowsiness	Rash
RCTs of P2X3 antagonists														
COUGH-1	Gefapixant 15 mg	244	0.8	7.4	2.0	7.8	2.9	9.8	NR	NR	NR	NR	NR	NR
	Gefapixant 45 mg	243	13.2	33.7	5.8	7.4	5.3	9.5						
	Placebo	243	0.0	2.1	1.6	10.3	3.3	8.6						
COUGH-2	Gefapixant 15 mg	404	2.7	12.2	3.4	16.8	5.7	14.3	NR	NR	NR	NR	NR	NR
	Gefapixant 45 mg	399	15.9	43.2	7	13.2	8.9	15						
	Placebo	406	1.4	6.5	2.5	13.9	6.2	14.1						
MK-7264-033	Gefapixant 45 mg	11	NR	63.6	NR	9.1	9.1	NR	NR	NR	NR	NR	NR	9.1
	Placebo	12		0.0		0.0	0.0							0.0
RCTs of antibiotics														
Hodgson, 2016	Azithromycin	22	NR	NR	NR	NR	4.5	NR	NR	NR	NR	NR	NR	NR
	Placebo	22					4.5							
RCTs of mast cell stabilizers														
Birring, 2017	Sodium cromoglicate	25	NR	NR	12.0	NR	NR	4.0	NR	NR	12.0	0.0	NR	NR
	Placebo	27			0.0			4.0			11.0	4.0		
RCTs of neuromodulators														
Dong, 2019	Gabapentin	117	NR	NR	NR	NR	3.4	NR	NR	NR	NR	23.9	NR	NR
	Baclofen	117					1.7					11.1		
Morice 2007	Morphine sulfate	27	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	25.0	NR
	Placebo	NR											NR	
Ryan 2012	Gabapentin	17	NR	NR	12.0	NR	24.0	6.0	NR	NR	NR	18.0	NR	NR
	Placebo	6			17.0		33.0	0.0				17.0		
Vertigan 2016	SPT + Pregabalin	20	NR	NR	10.0	NR	0.0	NR	NR	NR	NR	45.0	NR	5.0
	SPT	20			5.0		10.0					5.0	NR	10.0
RCTs of NK-1 antagonists														
Schering-Plough 2007	Rolapitant	30	NR	NR	13.3	NR	10.0	20.0	NR	NR	NR	NR	NR	NR
	Placebo	32			3.1		9.4	15.6						
Single-arm trials of neuromodulators														
Xu 2013	Baclofen	16	NR	NR	NR	NR	6.3	NR	NR	NR	NR	12.5	NR	NR
Single-arm trials of NMDA antagonists														
MEM-COUGH-1	Memantine	14	NR	NR	NR	28.6	21.4	35.7	NR	NR	7.1	71.4	NR	NR

Only those trials that reported safety outcomes are included in the table. The frequencies of AEs have been categorized and color-coded according to the European Medicines Agency's ranking of AEs. NK-1: Neurokinin-1, NMDA: N-Methyl-D-aspartate, NR: Not reported, SPT: Speech pathology treatment, AEs: Adverse events

Very common (≥1/10)
Common (≥1/100–<1/10)
Uncommon (≥1/1000–<1/100)
No AEs

Supplementary Table 6: Cochrane risk of bias (RoB2) assessment of included randomized controlled trials

Trial	Treatment	Randomization process	Deviations from intended interventions	Missing outcome data	Outcome measurement	Selective outcome reporting	Overall risk
RCTs of P2X3 antagonists							
COUGH-1	Gefapixant versus placebo	Some concerns	Low risk	Some concerns	Low risk	Some concerns	Some concerns
COUGH-2	Gefapixant versus placebo	Some concerns	Low risk	Some concerns	Low risk	Some concerns	Some concerns
MK-7264-033	Gefapixant versus placebo	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
RCTs of corticosteroids							
Chaudhuri, 2004	Fluticasone versus placebo	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Evald, 1989	Beclomethasone dipropionate versus placebo	Some concerns	High risk	High risk	High risk	Some concerns	High risk
Ribeiro, 2007	Beclomethasone dipropionate versus placebo	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Pizzichini, 1999	Budesonide versus placebo	Low risk	High risk	Low risk	Low risk	Some concerns	High risk
Sadeghi, 2018	Montelukast versus prednisolone	Low risk	Some concerns	Low risk	Low risk	Some concerns	Some concerns
RCTs of β2-adrenergic agonists							
Ellul-Micallef, 1983	Terbutaline sulfate versus placebo	Some concerns	High risk	High risk	Low risk	Some concerns	High risk
RCTs, of antibiotics							
Hodgson, 2016	Azithromycin versus placebo	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Yousaf, 2010	Erythromycin versus placebo	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
RCTs, of mast cell stabilizers							
Birring, 2017	Sodium cromoglicate versus placebo	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
RCTs of neuromodulators							
Dong, 2019	Gabapentin versus baclofen	Some concerns	Some concerns	Low risk	High risk	Some concerns	High risk
Morice, 2007	Morphine sulfate versus placebo	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns
Ryan, 2012	Gabapentin versus placebo	Low risk	Low risk	Low risk	High risk	High risk	High risk
Vertigan, 2016	Pregabalin + SPT versus SPT	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
RCTs of NK-1 antagonists							
EudraCT 2006-0021 64-26 2007	Rolapitant versus placebo	Some concerns	High risk	High risk	Low risk	Some concerns	High risk

NK-1: Neurokinin-1, RCT: Randomized controlled trial, SPT: Speech pathology treatment

Supplementary Figure 1: Cochrane risk of bias 2 assessment of included randomized controlled trials

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