Efficacy and safety of pharmacotherapy for refractory or unexplained chronic cough: a systematic review and network meta-analysis

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Summary

Background Refractory chronic cough (RCC) has a significant impact on patient's health-related quality of life and represents a challenge in clinical management. However, the optimal treatment for RCC remains controversial. This study aimed to investigate and compare the efficacy and safety of the current pharmacological therapeutic options for RCC.

Methods A systematic review was performed by searching PubMed, Web of Science, Embase, and Ovid databases from January 1, 2008 to March 1, 2023. All randomised control trials (RCTs) reporting outcomes of efficacy or/and safety were included in the Bayesian network meta-analysis. Here, we compared the effects on Leicester Cough Questionnaire (LCQ), Visual Analogue Scale (VAS), and objective cough frequency of patients with RCC. Besides, we also compared the incidence of adverse events (AEs) for analysis of safety. PROSPERO registration: CRD42022345940.

Findings 19 eligible RCTs included 3326 patients and 7 medication categories: P2X3 antagonist, GABA modulator, Transient Receptor Potential (TRP) modulator, NK-1 agonist, opioid analgesic, macrolide, and sodium cromoglicate. Compared with placebo, mean difference (MD) of LCQ and 24 h cough frequency for P2X3 antagonist relief were 1.637 (95% CI: 0.887–2.387) and –11.042 (P = 0.035). Compared with placebo, effect sizes (MD for LCQ and cough severity VAS) for GABA modulator were 1.347 (P = 0.003) and –7.843 (P = 0.003). In the network meta-analysis, gefapixant is the most effective treatment for patients with RCC (The Surface Under the Cumulative Ranking Curves (SUCRA) is 0.711 in LCQ, 0.983 in 24 h cough frequency, and 0.786 in cough severity VAS). Lesogaberan had better efficacy than placebo (SUCRA: 0.632 vs. 0.472) in 24 h cough frequency. Eliapixant and lesogaberan had better efficacy than placebo in cough severity VAS. However, TRP modulator had worse efficacy

Abbreviations: RCC, refractory chronic cough; AEs, adverse events; CC, chronic cough; UCC, unexplained chronic cough; ICC, idiopathic chronic cough; LCQ, leicester cough questionnaire; VAS, visual analogue scale; GRADE, grading of recommendations assessment, development and evaluation; WMD, weighted mean difference; MD, mean difference; CI, confidence interval; RR, risk ratio; SD, standard difference; PRISMA, preferred reporting items for systematic reviews and meta-analysis; RCT, randomised control trials; ACCP, American College of Chest Physicians; ERS, European Respiratory Society; TRP, transient receptor potential; NK-1, neurokininin-1; BMI, body mass index; CSD, cough severity diary; SUCRA, surface under the cumulative ranking; CNS, central nervous system

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than placebo. In the meta-analysis of AEs, the present study found P2X3 antagonist had a significant correlation to AEs (RR: 1.129, 95% CI: 1.012–1.259), especially taste-related AEs (RR: 6.216, P < 0.05).

Interpretation In this network meta-analysis, P2X3 antagonist showing advantages in terms of efficacy is currently the most promising medication for treatment of RCC. GABA modulator also showed potential efficacy for RCC but with AEs of the central system. Nevertheless, the role of TRP modulator needed to be revisited. Further research is needed to determine the potential beneficiary population for optimizing the pharmacological management of chronic cough.

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Keywords: Network meta-analysis; Refractory chronic cough; Pharmacotherapy; Efficacy

Research in context

Evidence before this study

Previous studies suggest that several potential medications may play a role in treatment of refractory chronic cough (RCC). We conducted a systematic search in PubMed, Web of Science, Embase, and Ovid for relevant studies from January 2008 to February 2023, using search terms: "chronic cough", "treatment or therapeutic or therapy", "P2X3", "gabapentin" and "TRP", etc. We found some studies reporting efficacy and safety of different medications in patients with RCC. However, a comprehensive review of the efficacy and safety of these medications, and the evidence supporting optimal choice among those are still lacking.

Added value of this study

This study is the first network meta-analysis that summarizes the efficacy and safety of medications in treatment of RCC and ranks their efficacy with multiple comparisons. Our results indicate that P2X3 antagonist (i.e., gefapixant) with acceptable safety was associated with the best improvement in cough frequency, severity, and related quality of life, compared with other treatments. In addition, GABA modulators (i.e., lesogaberan, gabapentin) showed better improvement than placebo but with adverse events of the central system. Nevertheless, the role of TRP modulator may need to be revisited.

Implications of all the available evidence

P2X3 antagonist (i.e., gefapixant) showing advantages in terms of efficacy is currently the most promising medication for the treatment of RCC. Further research is needed to determine its optimal dose and target patients who will benefit most for promoting clinical application of pharmacotherapy and optimizing the management of RCC.

Introduction

Chronic cough (CC) is defined as a cough lasting for >8 weeks.[1] Currently, CC has an estimated global prevalence of 9.6%.[2] Moreover, up to 46% of patients with CC suffer from persistent cough despite optimal treatment for the disease associated with CC.[3] If the cause of the cough is unknown after investigations, it will be defined as unexplained chronic cough (UCC) and if it does not resolve after empirical or etiology-specific treatment, it will be defined as refractory chronic cough (RCC).[3,4] RCC is an intractable clinical problem that has been associated with decreased quality of life.[1,3] Although the optimal management of RCC is still unclear, pharmacotherapy remains a common and reasonable treatment strategy.

Recent research has suggested several targeted therapeutics that act on various sites related to cough, including neuromodulator, P2X3 antagonist, voltage-gated sodium channel blocker, transient receptor potential (TRP) modulator, and neurokinin-1 (NK-1) antagonist.[5] According to a previous systematic review, gefapixant, a P2X3 antagonist, was found to have favourable anti-tussive outcomes in patients with a chronic cough.[6] However, adverse events (AEs) associated with P2X3 antagonist continue to be obvious, particularly for dysgeusia.[7] Furthermore, there are yet insufficient randomised control trials (RCTs) on NK-1, and the previous RCTs suggested that we may revisit the therapeutic role of TRP modulator.[8–10] Amitriptyline, gabapentin, pregabalin, morphine, and tramadol are all centrally acting neuromodulators that can improve cough-specific quality of life and/or cough severity in patients with RCC. There is still a lack of enough evidence and a high risk of bias to compare the efficacy and safety of various medications for RCC. Overall, the best choice of pharmacotherapy for RCC remains controversial.[1,4,7,11,12]

Therefore, this systematic review and meta-analysis aimed to comprehensively investigate the efficacy and

safety of medications for RCC/UCC and to identify the current optimal medication via network meta-analysis.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[13] and was registered on PROSPERO before the completion of the initial search (Registration No: CRD42022345940). The ethical approval was waived for this study type.

Search strategy

PubMed, Web of Science, Embase, and Ovid databases were systematically searched for RCTs published from January 1, 2008 to March 1, 2023. The search strategy used the following terms: ((“refractory chronic cough”) OR (“unexplained chronic cough”)) AND ((“therapy”) OR (“medication*”)); ((“chronic cough”) OR (“idiopathic chronic cough”)) AND ((“treatment”) OR (“medication*”)). The word “chronic cough” was interchanged with “unexplained cough”, “neurogenic cough”, “chronic refractory cough” and “refractory chronic cough” to repeat the same search. The name of molecular pathways including P2X3, TRPV1, TRPV4, GABA, NK-1, etc. would replace the word “medication” or “therapy” to repeat the same search. In addition, other potentially relevant articles were retrieved by manual search. Complete search strategies are listed in the e-Appendix 1.

Study selection

Inclusion criteria for eligible studies were as follows: (1) studies that included patients who were diagnosed with a chronic refractory cough or unexplained cough according to the cough guidelines proposed by the American College of Chest Physicians (ACCP) or European Respiratory Society (ERS); (2) patients who only received pharmacologic therapies and were followed up for efficacy and/or safety outcomes; (3) studies that reported the estimates of relative risk ratio (RR) and mean difference (MD); (4) study design was a comparative RCTs (vs. placebo or common therapy).

Exclusion criteria were as follows: (1) refractory chronic cough resulting from potential lung disease such as bronchiectasis, interstitial lung disease, etc.; (2) the medication directly targeted at an underlying etiology of chronic coughs, such as gastroesophageal reflux, asthma, eosinophilic bronchitis or upper airway cough syndrome; (3) case reports, letters, comments, conference abstracts and review articles; (4) the full text was not available; (5) articles published in languages other than English.

The search results were screened based on two independent authors’ relevant titles and abstracts. All discordant results were resolved through consensus or consultation with a third reviewer.

Data abstraction

The following data were extracted from eligible studies and recorded in a standardised pro forma sheet: names of the author, year of publication, region, and centre, type of literature, sample size, gender and age of the participants, race and BMI of the participants, types of intervention and cough duration (years). To be precise, we separately extracted subjective outcome data and objective outcome data, where the main subjective outcome data included the Lester Cough Questionnaire (LCQ) and the Visual Analogue Scale (VAS), and the main objective outcome data such as cough frequency, included awake, night-time and 24 h. To establish safety, we extracted the number of adverse events in the treatment and placebo groups; specific types of AEs were classified and counted. AEs were assessed by clinical evaluations and patients were recorded in the comment cards. After extracting the data, we found two trials with the same first author and year of publication, so we used A and B to distinguish between different studies.[14–17] Two of these trials consisted of two studies each, which we reported as four independent studies that were distinguished by S1 and S2.

Quality assessment

Cochrane risk of bias assessment tool,[18] which is based on seven main domains, was used in the present work. Each study was categorised as having low, moderate include unclear, or high risk of bias according to the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and carry-over effect.[19] Sensitivity analysis was performed on the primary outcomes. Publication bias was detected with funnel plot, Egger, and the Begg–Mazudumar tests. The quality of all pooled outcomes was assessed using the GRADE system.[20] Furthermore, meta-regression was employed to explore potential sources of heterogeneity, including publication year, area, study design, and sample size.

Data synthesis and analysis

The evidence was qualitatively synthesised, and random effects model-based meta-analysis[21] were conducted to combine the findings of trials with comparable interventions and outcome measures. We contacted the authors for studies that collected outcomes of interest but did not completely report them and requested additional data. For data where only the median but not the mean was provided, we used the conversion of continuous variables to obtain the mean value.[19,22] The efficacy outcomes were continuous data, and we analysed them as mean difference (MD) and 95% confidence interval (CI) in a random-effects model using the inverse-variance method. We assessed statistical heterogeneity among the pooled studies using the I^2 statistic[23,24]; the moderate

heterogeneity was defined as I^2>50%, and P < 0.05 was considered statistically significant. The safety outcomes were dichotomous data, and we pooled them as relative risk ratio (RR) and 95% CI in a random-effect model using the DerSimonian and Laird method. Moreover, meta-regression was performed to explore potential sources of heterogeneity. Besides, a Bayesian multiple treatment network meta-analysis[25] with random-effects and uninformative priors was performed. Both placebo- and active-controlled trials were taken into consideration, and the effectiveness of different medications was compared using the Bayesian models. To evaluate and rank the efficacy of medications, the rank probabilities that a medication being the best, second-best, or worst for an outcome were calculated using the Surface under the Cumulative Ranking Curves (SUCRA).[26] The SUCRA value would be '0' when a medication's efficacy is certain to be the worst and '1' when it is certain to be the best. Finally, all statistical analyses were conducted with RevMan version 5.3,[27] STATA version 15 (Stata Corporation, College Station, TX), R (version 4.2.1), and JAGS (version 4.3.0).[28]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had responsibility for the decision to submit for publication.

Results

Literature selection and study characteristics

After reviewing 2249 records from all databases, 19 RCTs with 3326 patients met eligibility criteria and were finally included in this meta-analysis.[8–10,14–17,29–40] The PRISMA flow chart is shown in Fig. 1. The included RCTs were published between 2010 and 2023 and were mainly conducted in Europe and the United States. The proportion of male participants ranged from 11.8% to 37.3%. The mean age of participants was 59.4 (95% CI: 57.9–60.9), with a mean cough duration of 10.6 years. All the included studies were placebo-controlled trials. A total of 13 medications were studied in these RCTs, representing the following classes of therapies: P2X3 antagonist, GABA modulator, TRP modulator, NK-1 antagonist, opioid analgesic, macrolides, and sodium cromoglicate. Gefapixant was the most frequently studied P2X3antagonist, followed by eliapixant and sivopixant. Detailed characteristics of the included studies are shown in Table 1. Network meta-analysis was conducted if studies had the comparable interventions and comparators, and pooling the results was appropriate. The duration of RCC, inclusion criteria, design, and device for cough monitor in included studies were summarised in Table 2.

Risk of bias assessment

Most studies were graded as having a low risk of bias, while only two were identified as having a high risk of bias. Some concerns about the risk of bias were noted for multiple studies in the following domains: random sequence generation (n = 1), allocation concealment (n = 1), blinding of participants and personal (n = 3), blinding of outcome assessment (n = 1), and incomplete outcome data (n = 1). The risk of bias graph is shown in Fig. 2.

Efficacy outcome: a meta-analysis

The major results of the efficacy outcome were shown in Table 3. For P2X3 antagonist, the most commonly used indicator of efficacy outcome was cough severity VAS (n = 8, WMD: −11.08, 95% CI: −19.18 to −3.19, P = 0.006), followed by LCQ (n = 7, WMD: 1.64, 95% CI: 0.53–2.63, P < 0.001), CSD total score (n = 6, WMD: −1.63, 95% CI: −3.10 to −0.15, P = 0.031), 24 h cough frequency (n = 5, WMD: −11.04, 95% CI: −21.31 to −0.78, P = 0.035), Awake/night-time cough frequency (n = 4, WMD: −15.48, 95% CI: −28.36 to −2.59, P = 0.019), and urge to cough VAS (n = 3, WMD: −13.16, 95% CI: −21.94 to −4.38, P = 0.003). All of the overall effect estimates revealed significant differences from both efficacy outcome indicators, except for night-time cough frequency (WMD: −1.78, 95% CI: −5.81 to 2.25, P = 0.386). The subgroup analysis for patients with gefapixant showed similar results to the primary analysis. The details of the results were reported in e-Table S7 of Supplement.

Three studies reported on the efficacy outcome of a TRP modulator. Compared with the placebo group, cough severity (Urge to cough VAS: WMD: 0.16, 95% CI: −3.58 to 3.90, P = 0.933) and cough-specific quality of life (LCQ: WMD: −0.29, 95% CI: −2.35 to 1.78, P = 0.787) did not improve after treatment with the medication. The overall pooled results of day-time cough frequency (WMD: 5.24, 95% CI: 3.41–7.08, P < 0.001), 24 h cough frequency (WMD: 2.60, 95% CI: 0.39–4.80, P = 0.021), and cough severity VAS (WMD: 5.34, 95% CI: 3.45–7.23, P < 0.001) suggested were worse in the treatment group than the placebo group.

A total of 2 studies reported on the efficacy of GABA modulator. The overall pooled results of LCQ and cough severity VAS significantly favoured the medication group over the placebo group (LCQ: WMD: 1.35, 95% CI: 0.47–2.23, P = 0.003; Cough severity VAS: WMD: −7.84, 95% CI: −13.02 to −2.66, P = 0.003). However, there were no significant differences in 24 h cough frequency between a placebo and a GABA modulator (WMD: −12.93, 95% CI: −33.86 to 8.00, P = 0.226).

The overall effect estimates of the LCQ score showed a significant variance between the two groups favouring the macrolide group (WMD: 1.59, 95% CI: 0.25–2.93, P = 0.02). Although the rest of the studies lacked the

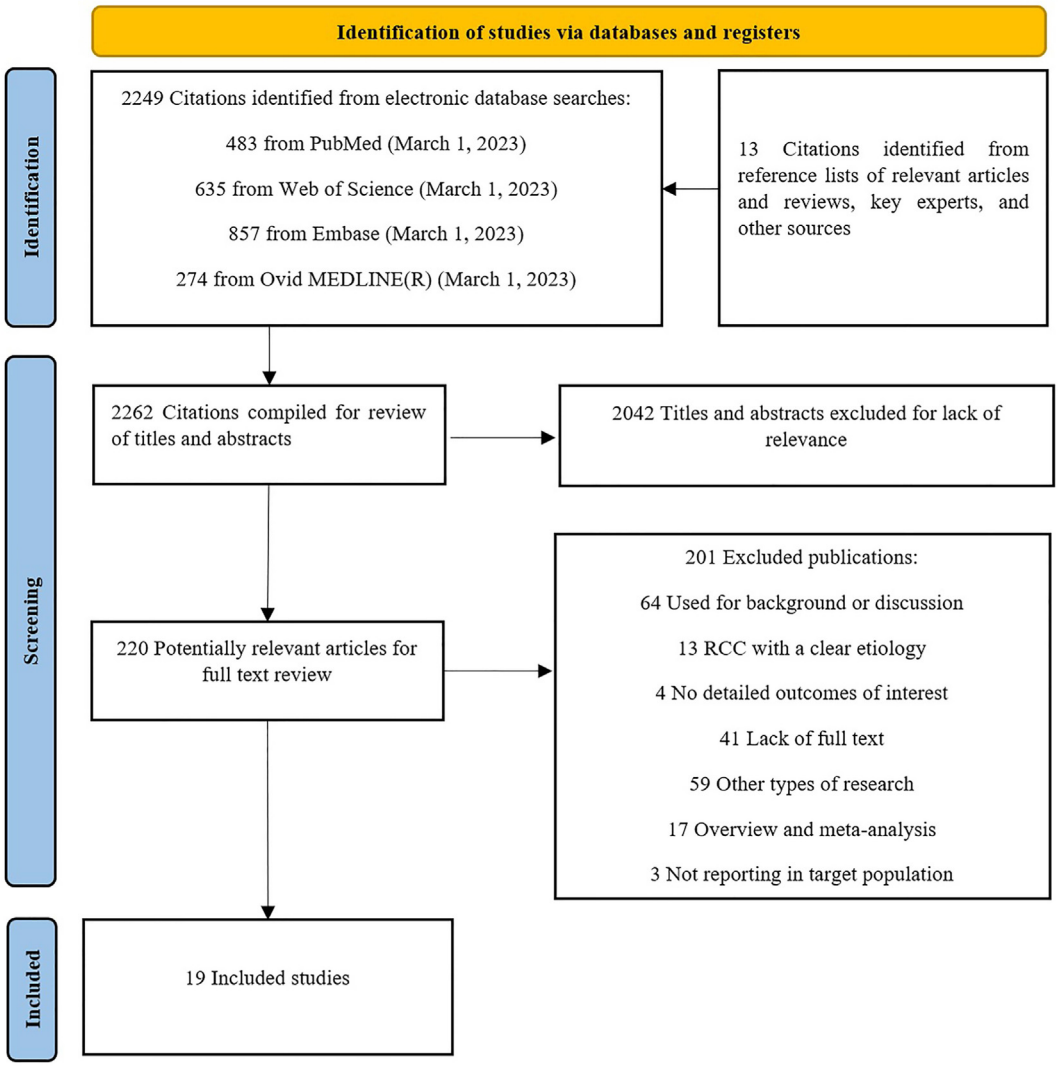

Fig. 1: Flow chart showing study inclusion and exclusion.

data needed for meta-analysis, both showed potential ability in cough remission.

Efficacy outcome: network meta-analysis

Among the 19 RCTs that assessed cough, the three most common outcome measures were LCQ, 24 h cough frequency, and cough severity VAS. Hence, they were identified as the outcome index for network meta-analysis in the present study. The network plots for the outcome of RCC are shown in Fig. 3.

LCQ

LCQ scores were reported for 2379 patients with RCC included in 11 studies. Compared with the placebo group, there were no significant increases in the LCQ score. SUCRA analysis provided a ranking of each intervention according to their LCQ (Table 4). The top-ranked interventions for LCQ were gefapixant (SUCRA score, 0.71), azithromycin (SUCRA score, 0.67), and eliapixant (SUCRA score, 0.56).

24 h cough frequency

A total of 6 unique medications and placebo were included in our network meta-analysis of 24 h cough frequency (Fig. 3B). Pooled network MD values indicated that gefapixant (network MD, −19.2; 95% CI: −25.4 to −11.6) had significantly superior 24 h cough frequency compared to placebo. SUCRA analysis provided a ranking of each medication class according to its efficacy in reducing 24 h cough frequency (Table 4). The three top-ranked interventions for reducing 24 h cough frequency included gefapixant (SUCRA score, 0.98),

Author	Year	Area	Centre	Total	Male/Female	White/Other	Age[a]	BMI (kg/m^2)[ab]	Cough duration (years)[a]	Medication	Category of medication
McGarvey	2023	Mix	Multiple	400	105/295	288/112	57.1 ± 0.7	27.8 ± 0.4	10.4 ± 6.1	Sivopixant	P2X3 antagonist
Niimi A[c]	2022	Asia	Multiple	31	11/20	–	50 ± 14.6	24.1 ± 5.0	8.1 ± 8.6	Sivopixant	P2X3 antagonist
Niimi B[c]	2022	Asia	Multiple	169	63/106	0/169	58 ± 15	24.1 ± 4.2	9.2 ± 10.5	Gefapixant	P2X3 antagonist
McGarvey	2022	Mix	Multiple	2044	518/1526	1627/417	59.6 ± 11.7	–	11.35 ± 0.21	Gefapixant	P2X3 antagonist
Morice	2021	Europe	Multiple	40	9/31	39/1	61.5 ± 10.5	26.8 ± 3.4	–	Eliapixant	P2X3 antagonist
Smith A[c]	2020	Mix	Multiple	253	60/193	234/19	60.2 ± 9.9	27.7 ± 4.7	14.5 ± 11.7	Gefapixant	P2X3 antagonist
Smith B[c]	2020	Mix	Multiple	59	10/49	56/3	62.1 ± 1.45	26.6 ± 0.6	15.4 (14–55.3)	Gefapixant	P2X3 antagonist
Morice	2019	Europe	Single	24	3/21	–	61.1	–	14.6 ± 9.89	Gefapixant	P2X3 antagonist
Abdulqawi	2015	Europe	Single	24	6/18	24/0	54.5 ± 11.1	25.9 (20–35)	9.0 (3.0–25.0)	Gefapixant	P2X3 antagonist
Ludbrook	2021	Europe	Multiple	17	2/15	16/1	61.0 ± 9.85	27.61 ± 4.96	–	GSK2798745	TRP modulator
Belvisi	2017	Europe	Multiple	20	5/15	20/0	63.1 ± 9.4	28.0 ± 5.0	–	XEN-D0501	TRP modulator
Khalid	2014	Europe	Single	21	6/15	21/0	53 (34–70)	26.6 (22.3–31.7)	–	SB-705498	TRP modulator
Badri	2022	Europe	Single	22	6/16	–	63.7 ± 7.2	25.8 ± 4	10.5 (5.8–17.0)	Lesogaberan	GABA modulator
Ryan	2012	Oceanic	Single	62	22/40	–	61.8 ± 1.7	28.9	3.0 (1.5–12.5)	Gabapentin	GABA modulator
Abdulqawi	2020	Europe	Single	26	4/22	–	53.5 ± 12.1	–	10.0 (7.0–16.0)	Lidocaine	Opioid analgesic
Smith	2019	Europe	Single	13	2/11	13/0	60.1 ± 8.36	–	13.1 ± 6.7	Orvepitant	NK-1 antagonist
Birring	2017	Europe	Multiple	27	6/21	25/2	62 (23–73)	27.7 ± 5.7	9.9 ± 9.8	PA-101	Sodium cromoglicate
Hodgson	2016	Europe	Single	44	14/30	–	58.0 ± 1.5	28.1 ± 0.7	–	Azithromycin	Macrolide
Yousaf	2010	Europe	Single	30	6/24	–	62.0 ± 1.6	26.8 ± 0.9	11.6 ± 0.8	Erythroycin	Macrolide

[a]Data expressed as mean (SD). [b]Calculated as weight in kilograms divided by height in metres squared. [c]Two trials with the same first author and year of publication, then we use A and B to distinguish between different studies.

Table 1: **Characteristics of the randomised controlled trials included in the meta-analysis.**

lesogaberan (SUCRA score, 0.63), and placebo (SUCRA score, 0.47).

Cough severity VAS

A total of 10 RCTs with 1915 patients were included in the meta-analysis of cough severity VAS by individual treatment. A total of 7 unique treatments were included in the analysis. Gefapixant was the most commonly investigated intervention. The pooled network outcome that was obtained by comparing each intervention against the placebo revealed that all interventions were statistically equivalent to the placebo (e-Table S6 in Supplement). Nonetheless, although all interventions were equivalent to placebo, the three top-ranked interventions for improving cough severity VAS score were gefapixant (SUCRA score, 0.79), followed by eliapixant (SUCRA score, 0.67), and lesogaberan (SUCRA score, 0.60).

The details of the SUCRA analysis are presented in Table 4 and e-Figure S10. All the results showed moderate heterogeneity, and there were no inconsistent tests due to a lack of direct comparisons. The forest plots (e-Figures S1–S5), league table (e-Tables S4–S6), and cumulative probability plots (e-Figure S9) are shown in the Supplement.

Safety outcomes

The incidence and the proportion for each AEs are presented in e-Table S2 in Supplement. Due to limitations associated with the size of the studies, only the P2X3 antagonist was included in the meta-analysis. For P2X3 antagonist, the incidence of AEs was 80.8% (95% CI: 70.4–89.4), and 49.3% (95% CI: 37.3–61.3) for AEs related to treatment. The most common AEs were taste-related events (50.5%), and the pooled incidence was 39.0% (95% CI: 27.6–51.0). The overall estimates presented a significant variance between the P2X3 antagonist group and placebo group regarding any AEs (RR: 1.140, 95% CI: 1.016–1.279, $P < 0.05$) and AEs related to treatment (RR: 2.314, 95% CI: 1.728–3.100). Compared with the placebo, the P2X3 receptor antagonist resulted as a risk factor of taste-related events, dysgeusia, hypogeusia, and ageusia (both $P < 0.05$).

Subgroup analysis was performed based on pharmacological interventions. Significant differences were found among gefapixant, eliapixant, and sivopixant. Also, significant differences were found in the incidence of any AEs between gefapixant (85.7%, 95% CI: 80.2–90.5) and eliapixant (44.9%, 95% CI: 36.9–5.3). Eliapixant (16.7%, 95% CI: 11.2–23.5) or sivopixant (12.9%, 95% CI: 3.6–29.8) were associated with lower incidence of treatment-related AEs compared to gefapixant (59.7%, 95% CI: 50.5–68.5). Patients who received eliapixant (7.1%, 95% CI: 4.0–11.7 and 6.1%, 95% CI: 3.2–10.5) and sivopixant (26.2%, 95% CI: 22.0–30.9) treatment had a lower incidence in taste related events and dysgeusia than those who received gefapixant treatment (45.2%, 95% CI: 35.3–55.3 and 27.7%, 95% CI: 21.5–34.3). Additionally, eliapixant treatment was not associated with any of the included AEs, while gefapixant was identified as a risk factor for major AEs, including taste-related events (RR: 6.444, 95% CI: 4.973–8.351, $P < 0.001$), dysgeusia (RR: 7.144,

Author	Year	Selection criteria				Design				Outcome measure
		Age	VAS (mm)	Cough duration (months)	Diagnosis	Blind	Crossover/ Parallel	Duration of interventions at each stage	Washout period	
McGarvey	2023	18–80	≥40	≥12	R/UCC	Double	Parallel	2 weeks	–	Cough frequency (VitaloJAK cough monitor)
Niimi A	2022	20–75	≥40	≥6	R/UCC	Double	Crossover	2 weeks	2–3 weeks	LCQ, VAS, cough frequency (VitaloJAK cough monitor)
Niimi B	2022	≥20	–	≥4	R/UCC	Double	Parallel	52 weeks	–	LCQ, cough frequency (VitaloJAK cough monitor)
Badri	2022	>18		>2	RCC	Double	Crossover	2 weeks	1–2 weeks	Cough frequency (VitaloJAK cough monitor)
McGarvey	2022	≥18	≥40	≥12	R/UCC	Double	Parallel	52 weeks	–	LCQ, VAS, cough frequency (VitaloJAK cough monitor)
Ludbrook	2021	18–75	≥40	≥12	R/ICC	Double	Crossover	1 weeks	2–3 weeks	Cough frequency (VitaloJAK cough monitor)
Morice	2021	≥18	≥40	≥12	RCC	Double	Crossover	3 weeks	3–4 weeks	LCQ, VAS, cough frequency (VitaloJAK cough monitor)
Abdulqawi	2020	≥18	–	–	RCC	Double	Crossover	2 weeks	1.5–2 h	VAS, cough frequency (VitaloJAK cough monitor)
Smith A	2020	18–80	≥40	≥12	R/UCC	Double	Parallel	12 weeks	–	LCQ, VAS, cough frequency (VitaloJAK cough monitor)
Smith B	2020	–	≥40	≥12	CC	Double	Crossover	16 days	1–3 weeks	LCQ, VAS, cough frequency (VitaloJAK cough monitor)
Morice	2019	18–80	–	≥12	RCC	Double	Crossover	1 day	2 days	VAS
Smith	2019	18–75	–	>3	RCC	No	Parallel	4 weeks	–	VAS, cough frequency (VitaloJAK cough monitor)
Belvisi	2017	–	–	–	RCC	Double	Crossover	2 weeks	2 weeks	LCQ, VAS, cough frequency (VitaloJAK cough monitor)
Birring	2017	18–75	≥40	>2	CC	Double	Crossover	15 days	2 weeks	LCQ, VAS, cough frequency (Leicester cough monitor)
Hodgson	2016	–	–	–	–	Double	Parallel	8 weeks	–	LCQ, cough frequency
Abdulqawi	2015	–	–	>2	RCC	Double	Crossover	2 weeks	2 weeks	VAS, cough frequency (VitaloJAK cough monitor)
Khalid	2014	–	–	>2	RCC	Double	Crossover	3 days	4 weeks	VAS, cough frequency (VitaloJAK cough monitor)
Ryan	2012	–	–	>2	CC	Double	Parallel	12 weeks	–	LCQ, VAS, cough frequency (Leicester cough monitor)
Yousaf	2010	–	–	>2	CC	Double	Parallel	12 weeks	–	LCQ, VAS, cough frequency (Leicester cough monitor)

Abbreviations: VAS, visual analogue score; RCC, refractory chronic cough; UCC, unexplained chronic cough; ICC, idiopathic chronic cough; CC, chronic cough.

Table 2: **The summary of the methodology in the included studies.**

95% CI: 4.308–11.846, P < 0.001), and hypogeusia (RR: 7.144, 95% CI: 4.308–11.846, P < 0.001). Most pooled RR was not heterogeneous (I^2 < 50%), and the certainty in pooled RR by gefapixant was moderate to high. Table 5 contains more detailed results. The relevant forest plots were shown in e-Figures S6–S8 of the Supplement.

Evidence of quality, sensitivity, and meta-regression analysis

The quality of evidence (GRADE) for each WMD and risk ratio were assessed as shown in Tables 3 and 5. Most of the pooled outcomes (77.6%) were of moderate and high-quality evidence, while the remaining ones were of low and very low quality. Sensitivity analysis of the switching model showed that our results were generally robust. Meta-regression analyses were also conducted to explore the effects of potential confounders, revealing no correlation between pooled results and study (i.e., year, sample size) while patients' characteristics (i.e., age, sex) may be the potential resources in LCQ for the efficacy of P2X3 antagonist. The details of meta-regression were shown in e-Table S1 for efficacy results and e-Table S3 for safety results.

Discussion

This systematic review and network meta-analysis comprehensively analysed the pooled efficacy and safety of pharmacotherapy for RCC, and ranked their efficacy with multiple comparisons. Our study found that P2X3 antagonist (mainly gefapixant) probably provided the optimal improvement effect on RCC, although it was associated with an increased risk of AEs. Moreover, GABA modulator, PA-101, and macrolide also had a certain efficacy, but similar improvement was not observed in TRP modulator. To our knowledge, this study is the first network meta-analysis to compare the efficacy among various medications currently available. All included studies were RCTs, with most results being high quality according to GRADE system, suggesting the reliability of our findings. The studies included in this review were RCTs and most of the these were of high quality in GRADE. And the results were considerable reliable. Overall, this study demonstrates precise estimates of the efficacy and safety for current pharmacological treatments, and may provide evidence supporting the selection and application of therapeutic options for RCC.

This network meta-analysis revealed the largest number of studies involving P2X3 antagonist, with the highest level of evidence and significant effectiveness. Considering the role of P2X3 receptor in the activation of sensory neurons central to the cough reflex,[41,42] as well as an emerging understanding of the role of afferent sensitization in airway dysfunction in patients with CC, antagonism of the P2X3 receptor is currently being assessed as a potential therapeutic target for the RCC. In

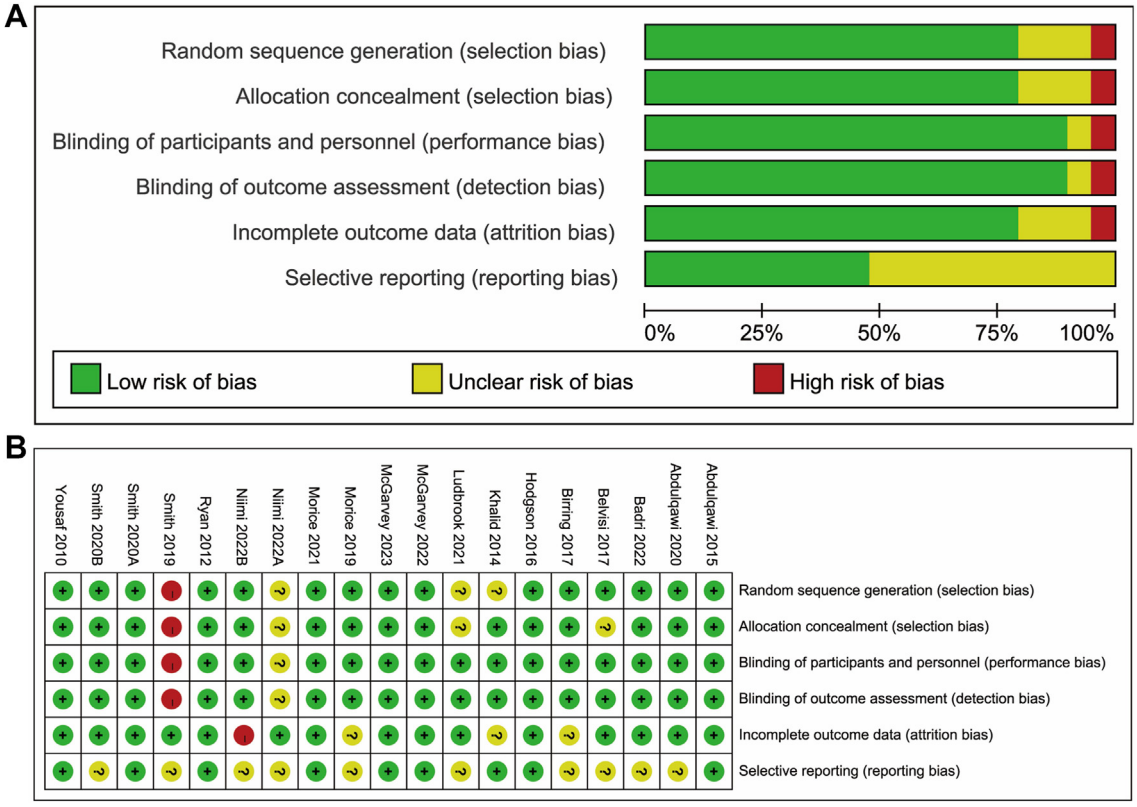

Fig. 2: The results of the Cochrane tool for assessing the risk of bias. (A) Risk of bias graph. (B) Risk of bias summary. Colour of each circle shows different risk of bias. Red circle reflects high risk of bias, yellow reflects unclear risk of bias, and green reflects low risk of bias.

this study, the P2X3 receptor antagonist included the first-in-class P2X3 and P2X2/3 antagonist gefapixant, as well as the recently developed eliapixant and sivopixant. Besides, gefapixant is the first such compound that successfully completed phase III trials. Also, a previous meta-analysis proved its efficacy in reducing cough counts. Compared with the study of Abu-Zaid et al.[6] we found that P2X3 receptor antagonist had favourable efficacy in patients with RCC by improving the frequency of cough (awake and 24 h), cough severity VAS, urge to cough VAS, and CSD total score. Although P2X3 antagonist did not achieve minimal clinical differences in VAS,[43] it still achieves differences in LCQ scores.[44] Besides, gefapixant showed significant differences in improving the LCQ, 24 h cough frequency, and cough severity VAS among other medications included. Eliapixant was associated with improvement in LCQ and cough severity VAS; however, the analysis based on 24 h cough frequency showed worse effectiveness compared to placebo, ranking 4 during 6 types of intervention.

On the other hand, we observed that compared with a placebo, gefapixant was associated with the higher incidence of AEs. Although serious complications were rarely observed, a certain percentage of taste-related complications (37.7%), especially taste disorders (24.4%), was still found. However, we also found no appreciable differences between gafapixant and placebo in terms of the prevalence of nasopharyngitis, nausea, headaches, upper respiratory infections, and oral system disorders. In addition, the difference of AEs among various P2X3 antagonists is not only in terms of incidence but also in terms of severity. This difference may depend on the varying degrees of selectivity for the P2X3 receptor. According to earlier investigations, gefapixant has marginal selectivity for P2X3 over P2X2/3 heterotrimers in the taste buds.[1,29,45,46] P2X2/3 receptors were related with transmission of taste information,[47] the taste disturbance may be due to the off-target effect of gefapixant on them. Besides, eliapixant, a compound more selective for the P2X3 homotrimeric receptor, has been associated with better tolerability than gefapixant. Thus, compounds with high selectivity of P2X3 receptor may need to be developed in the future. Although significant placebo effects complicated the interpretation of the results, these results were also significant in our network meta-analysis. Notably, the ranges of 95% CI for pooled VAS were large, reflecting variability in

Score system	Study (n)	No. of placebo (n)	No. of treatment (n)	Pooled score change (95% CI)	P-value	Certainty in pooled estimates
P2X3 antagonist						
LCQ	7	771	1510	1.637 (0.887, 2.387)	<0.001	High
Awake cough frequency (c/h)	4	162	352	−15.476 (−28.358, −2.594)	0.019	Moderate
Night-time cough frequency (c/h)	4	119	117	−1.782 (−5.813, 2.248)	0.386	Moderate
24 h cough frequency (c/h)	5	182	370	−11.042 (−21.306, −0.778)	0.035	Moderate
Cough severity VAS (mm)	8	761	1069	−11.075 (−17.496, −5.914)	<0.001	High
Urge to cough VAS (mm)	3	107	238	−13.16 (−21.938, −4.381)	0.003	Moderate
CSD total score	6	741	1381	−1.625 (−3.098, −0.151)	0.031	Moderate
TRP modulator						
LCQ	2	37	35	−0.285 (−2.353, 1.783)	0.787	Moderate
Day-time cough frequency (c/h)	2	38	38	5.244 (3.405, 7.082)	<0.001	Moderate
24 h cough frequency (c/h)	2	41	41	2.597 (0.393, 4.800)	0.021	Moderate
Cough severity VAS (mm)	2	38	36	5.337 (3.445, 7.229)	<0.001	Moderate
Urge to cough VAS (mm)	3	57	54	0.159 (−3.583, 3.901)	0.933	Moderate
GABA modulator						
LCQ	2	54	52	1.347 (0.466, 2.229)	0.003	Moderate
24 h cough frequency (c/h)	2	54	52	−12.929 (−33.858, 8.000)	0.226	Low
Cough severity VAS (mm)	2	52	48	−7.843 (−13.023, −2.663)	0.003	Moderate
Macrolide						
LCQ	2	37	37	1.589 (0.245, 2.932)	0.02	Moderate

Abbreviations: WMD, weighted mean difference; CI, confidence interval; LCQ, leicester cough questionnaire; VAS, visual analogue score; CSD, cough severity diary. Some medicines and outcomes were not available for meta-analysis due to the limited number of literatures. Pooled score change, the absolute difference between the mean value in medication and placebo. The certainty in pooled estimate was evaluated by GRADE.

Table 3: **The results of meta-analysis for cough score change (WMD).**

efficacy between populations. In conclusion, our results provided support that patients with RCC may benefit from gefapixant and eliapixant. Gefapixant has passed phase 3 trials, which indicates that this medication may enter the market and become used in clinical practice. Further clinical studies are needed to precisely characterise the population that benefits most from P2X3 antagonist, both in terms of efficacy and safety.

Transient receptor potential (TRP) channels are abundantly present in the airways. Among particular interest to cough are members of the vanilloid (TRPV1, TRPV4), ankyrin (TRPA1), and melastatin (TRPM8) families.[48] There are different profiles of cough hypersensitivity mediated by TRPV1, TRPA1, TRPV4, and TRPM8 in patients with chronic cough, suggesting that selective or combined antagonists therapy targeting TRPV1, TRPA1, or other cough receptors might be effective.[49–51] Previous studies suggested that patients with RCC may not benefit from present medications.[49,52,53] Also, the pharmacologic modulation of TRP channels should be further investigated as a potential target for CC.

Hence, clinical trials with the TRPV1 and TRPV4 were terminated, mainly due to the following reasons: first, it has become clear in recent years that while evoked cough models are important for elucidating mechanisms and confirming target engagement in both animals and humans, they are poorly predictive of impact on pathological cough in a real-life clinical population. Second, although Khalid et al. reported that treatment with SB-705498 significantly reduced experimentally produced cough responses to capsaicin, there was no discernible improvement in the frequency of spontaneous cough.[9] They argued that increased cough responses to capsaicin might result from neuroplastic changes anywhere along the cough reflex pathway (central or peripheral), rather than as a direct result of changes in TRPV1 expression or activity. The differential sensitivity of cough to antitussive therapies implies the existence of heterogeneity in cough hypersensitivity. The above data suggest that the cough pathway is heterogeneous and that a single type of TRP receptor agonist may only affect a portion of the pathway in the cough neural reflex, as reported by Khalid et al. Although current clinical trials did not indicate the efficacy of TRP modulators in the treatment of RCC/UCC, Tnernesten et al. found that capsaicin powder taken orally could decrease cough sensitivity and symptoms.[54] This effect may due to the reduction of peripheral sensitization of cough via the depletion of TRPV1 receptor in the airway. Further studies are required to elucidate the underlying pathophysiological mechanisms. In order to effectively treat the cough as a neural

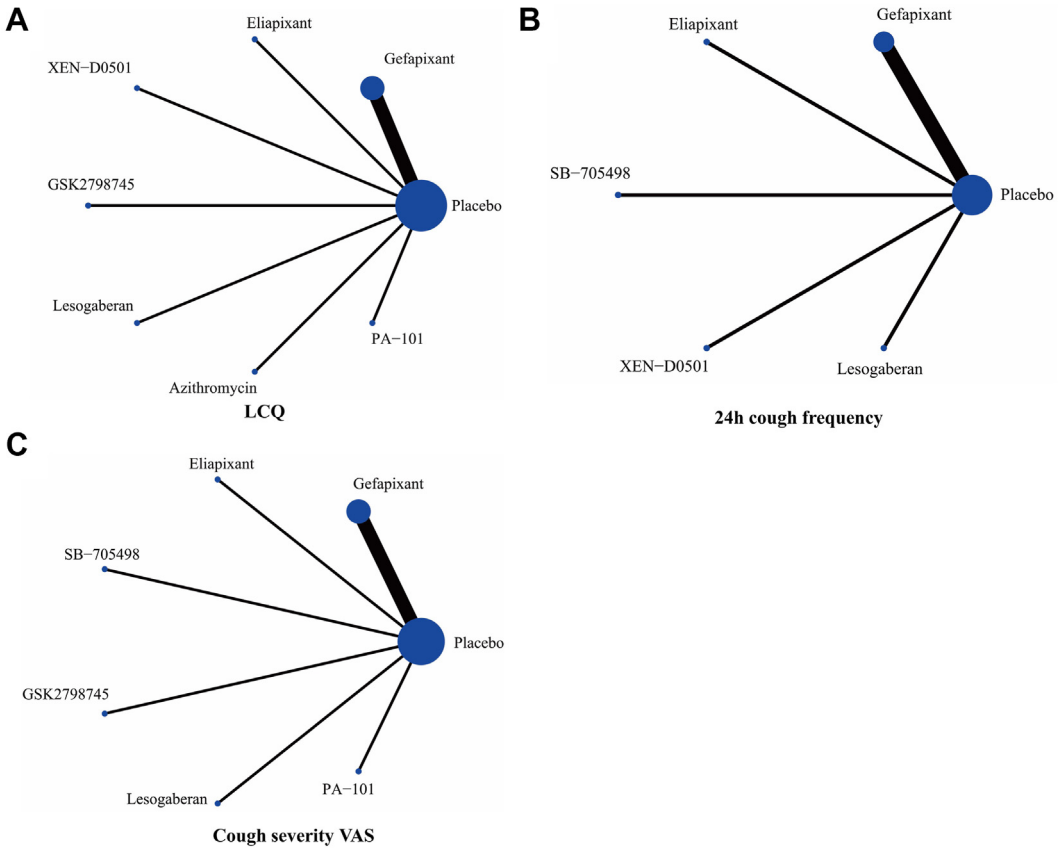

Fig. 3: Network plots of included treatments in terms of remission in LCQ, 24 h cough frequency, and cough severity VAS for patients with RCC/UCC. (A) LCQ; (B) 24 h cough frequency; (C) cough severity VAS. The lines between nodes represent direct comparisons in various trials. The size of each node is proportional to the size of the population involved in each specific treatment. The thickness of the lines is proportional to the number of trials connected to the network. Abbreviations: LCQ, leicester cough questionnaire; VAS, visual analogue score.

reflex as a whole, a combination of multiple TRP receptor antagonists may be necessary. Indeed, the involvement of a complex suite of neurobiological processes involving the peripheral nervous system and central nervous system (CNS) in the cough as a reflex.[55] The treatment of cough as a neural reflex may have a potential therapeutic effect if peripheral receptor blockers are combined with drugs that affect the CNS component of cough hypersensitivity. After all, there is substantial preclinical evidence for the involvement of TRPV1, TRPA1, and now TRPV4 in the cough mechanism.[8,9]

The sensorimotor phenomenology of cough suggests the involvement of a complex suite of neurobiological processes involving the peripheral nervous system, brainstem, and higher brain in this phenomenon.[55] Consequently, neuromodulators such as gabapentin and morphine are effective in treating RCC.[38] Gabapentin is a GABA analogue that binds to the voltage-gated calcium channels, centrally inhibiting neurotransmitters, while lesogaberan is a GABA agonist. As both have an impact on GABA receptors, they were included in the meta-analysis. In the previous meta-analysis, whose selection

Treatment	LCQ	24 h cough frequency	Cough severity VAS
Placebo	0.327	0.472	0.425
Gefapixant	0.711	0.983	0.786
Eliapixant	0.555	0.392	0.667
XEN-D0501	0.39	0.192	ND[a]
GSK2798745	0.304	ND[a]	0.284
SB-705498	ND[a]	0.328	0.331
Lesogaberan	0.529	0.632	0.601
Azithromycin	0.671	ND[a]	ND[a]
PA-101	0.514	ND[a]	0.397

Abbreviations: SUCRA, surface under the cumulative ranking curve; LCQ, leicester cough questionnaire. [a]ND, this medication was not included in the network meta-analysis.

Table 4: **The results of network meta-analysis for SUCRA.**

Variable	Study	Patients with treatment	Patients with placebo	Pooled RR	P-value	I^2 (%)	GRADE
	(n)	(n)	(n)	(95% CI)			
Any AEs	8	1977	956	1.140 (1.016–1.279)	0.026	83.8	Moderate
Gefapixant	7	1821	916	1.186 (1.060–1.326)	0.003	82.8	Moderate
Eliapixant	1	156	40	0.690 (0.518–0.919)	0.011	–	Very low
AEs related to treatment	7	1803	866	2.314 (1.728–3.100)	<0.001	58.9	Moderate
Gefapixant	5	1616	795	2.529 (1.863–3.433)	<0.001	65.1	Moderate
Eliapixant	1	156	40	1.333 (0.547–3.253)	0.527	–	Very low
Sivopixant	1	31	31	1.000 (0.274–3.645)	1.000	–	Very low
Taste related events	6	1775	838	6.375 (4.930–8.243)	<0.001	0	High
Gefapixant	5	1619	798	6.444 (4.973–8.351)	<0.001	0	High
Eliapixant	1	156	40	3.333 (0.449–24.731)	0.239	–	Very low
Sivopixant	1	298	102	1.711 (1.135–2.581)	0.010	–	Very low
Dysgeusia	9	1863	924	6.591 (4.157–10.451)	<0.001	22.6	High
Gefapixant	9	1707	884	7.144 (4.308–11.846)	<0.001	29.4	High
Eliapixant	1	156	40	2.821 (0.375–21.207)	0.314	–	Very low
Hypogeusia	7	1797	859	6.591 (4.157–10.451)	<0.001	22.6	High
Gefapixant	6	1641	819	7.144 (4.308–11.846)	<0.001	29.4	High
Eliapixant	1	156	40	2.821 (0.375–21.207)	0.314	–	Very low
Ageusia	5	1616	795	13.181 (4.500–38.611)	<0.001	0	High
Upper respiratory tract infection	4	1257	569	1.575 (0.665–3.730)	0.302	39.7	Moderate
Gefapixant	3	1101	524	1.904 (0.578–6.277)	0.290	59.5	Low
Eliapixant	1	156	40	1.282 (0.154–10.668)	0.818	–	Very low
Nasopharyngitis	4	1555	744	1.055 (0.870–1.280)	0.584	0	Moderate
Gefapixant	3	1525	715	1.063 (0.875–1.292)	0.537	0	Moderate
Eliapixant	1	30	29	0.641 (0.129–3.183)	0.587	–	Very low
Nausea	4	1251	557	1.942 (0.645–5.844)	0.238	44.5	Low
Gefapixant	3	1095	517	2.828 (0.601–13.313)	0.188	61.8	Low
Eliapixant	1	156	40	0.769 (0.082–7.199)	0.818	–	Very low
Headache	6	1774	836	1.038 (0.829–1.300)	0.746	0.0	Moderate
Gefapixant	5	1618	796	1.082 (0.875–1.339)	0.466	0	Moderate
Eliapixant	1	156	40	0.470 (0.185–1.194)	0.112	–	Very low
Oral-system diseases	7	494	249	2.108 (0.933–4.764)	0.073	60.7	Low
Gefapixant	6	338	209	2.710 (1.141–6.439)	0.024	55.4	Moderate
Eliapixant	1	156	40	0.641 (0.212–1.938)	0.431	–	Very low

N > 30 and well-defined AEs are analysed. Relative risk, RR, the ratio of the risk of disease among those exposed to a risk factor to the risk among those not exposed. RR > 1 represents the medicine as the activator of the AEs. P-values of <0.05 were defined as statistically significant summarized treatment effect. Abbreviations: AEs, adverse events; RR, relative risk ratio. The certainty in pooled estimate was evaluated by GRADE.

Table 5: **The results of meta-analysis of risk ratio for adverse events.**

range dated from 1998 to 2012, 3 studies confirmed the efficacy of gabapentin in patients with RCC.[56] The present study focused on the studies published in recent years. This meta-analysis showed that compared with the placebo, the medication effect on a GABA receptor was significantly associated with improved LCQ and decreased cough severity VAS in patients with RCC. However, in network meta-analysis, the rank of lesogaberan was higher than placebo in LCQ, 24 h cough frequency, and cough severity. In addition, the two most common AEs were digestive system events (26.4%) and dizziness (7.9%), and the incidence of digestive system events for gabapentin was lower compared to lesogaberan (18.8% vs. 32.6%), which could be due to the inhibition of peripheral nerves. Our results suggested that the GABA receptor was an effective target for CC, which could be used as a valuable reference for further investigation of medications.

PA-101 (a novel formulation of cromolyn sodium) was thought to act as a mast cell stabiliser. The present work included only 1 study that addressed PA-101.[32] In the network meta-analysis, it ranked 5 among 8 medications in LCQ, surpassing the placebo. However, the results of cough severity VAS revealed that PA-101 had a worse effect than the placebo. Hence, there is no evidence that patients with RCC would benefit from PA-101. Due to a lack of data, orvepitant (an NK-1 receptor agonist) and lidocaine (an opioid analgesic) were not

included in the meta-analysis and network meta-analysis; however, some previous studies reported that both of them were potentially effective.[30,39] Azithromycin and erythromycin belong to the class of macrolide,[33,40] with anti-inflammatory actions. Our results suggest that macrolides are potential pharmacological interventions for patients with RCC, which could be due to the following reasons: 1) Inflammation can also cause plasticity of airway mucosal innervation. 2) Animal studies also suggest that neural plasticity during pulmonary pathologies may be related to neuro-inflammation within the vagus nerve or ganglia, this phenomenon has not been confirmed in humans, but it was hypothesised as a cause of cough in some patients. On the other hand, it also suggests that RCC may be related to inflammation.[55] In summary, macrolides reduce cough symptoms in patients with RCC/UCC by suppressing inflammation.

The present study has several limitations. First, the absence of head-to-head (direct) comparison studies is the reason for the current network meta-analysis. Although the network meta-analysis is a useful tool for comparative effectiveness research, the potential bias due to the complexity and the assumption of transitivity needs to be considered during the process and the interpretation. The present study using random effects meta-analysis summarised the comparisons between medication and placebo, and network meta-analysis integrated the indirect evidence. Besides, sensitive analysis and meta-regression were also used to improve the quality of the results. Second, this study inevitably received a placebo effect which may complicate the interpretation of the results. Despite these, the efficacy of many medications remains significant (i.e., gefapixant). Third, the data mainly come from US and Europe, which limits the worldwide generalizability. This may be due to the potential differences in the demographics, etiological composition, and management of people with chronic cough in the US and Europe compared with other regions. Finally, partial pooled results with heterogeneity may need to be interpreted with caution due to inevitable differences in interventions between trials (e.g., design, dose and duration). Though, this network meta-analysis of RCTs was performed in strict accordance with PRISMA and presents the best available evidence. It may provide reliable qualitative and quantitative data for the efficacy and safety of pharmacotherapy in RCC.

In this network meta-analysis, P2X3 antagonist showing advantages in terms of efficacy is currently the most promising medication for treatment of RCC or UCC. GABA modulator also showed potential efficacy but with AEs of the central system. Nevertheless, the role of TRP modulator needed to be revisited. Further research is needed to determine the potential beneficiary population for optimizing the pharmacological management of chronic cough.

Contributors

SL, WS, and RC designed the study. ZZ, JH, ZX, TW, and XL conducted the literature search and searched the articles. SX, ZL, and KT contributed to the data extraction process. ZZ, JH, ZX, and AM analysed or interpreted the data. ZZ, ZX, ZL, and SX verified the underlying data. ZZ, JH, ZX, TW, and XL drafted the manuscript. All the authors revised the article and approved the final version. All authors had full access to all the data in the study and accept responsibility for decision to submit for publication.

Data sharing statement

Review protocol has been available via PROSPERO website. All extracted data are available upon appropriate requests by emailing to co-corresponding authors.

Declaration of interests

All authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102100.

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