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Review article

Management of non-pharmacologic therapy for chronic refractory cough: Mechanism, composition, applicable population, and assessment

Yanzi Peng [1], Tongyanzi Zhang [1], Lingdan Yuan [1], Xianghuai Xu [*], Li Yu [**]

Department of Pulmonary and Critical Care Medicine, Tongji Hospital, School of Medicine, Tongji University, No. 389 Xincun Road, Shanghai 200065, China

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ABSTRACT

Chronic cough is common in the clinic and can seriously affect the quality of life of patients. Following the existing guidelines for treatment, refractory chronic cough is defined as a clinical condition in which the cause of the cough remains unclear after comprehensive examination and treatment, or the cause is clear but symptomatic treatment is ineffective.

It has been found that non-pharmacologic therapy can effectively improve the quality of life and reduce the frequency of coughing for some patients with refractory chronic cough. Compared with pharmacological therapy, non-pharmacologic therapy has no obvious adverse effects; therefore, non-pharmacologic therapy has good application prospects in the diagnosis and treatment of refractory chronic cough. This paper summarizes the composition, indication, action and mechanism of non-pharmacologic therapy in the diagnosis and treatment of refractory chronic cough and prospects for research on non-pharmacologic therapy.

Text：A cough as the only or main symptom that lasts longer than 8 weeks and has no obvious abnormality on chest X-ray is defined as a chronic cough [1]. A chronic cough that lacks definite causes according to the procedures recommended by guidelines and is not alleviated with empirical treatment, or has a clear etiology but poor therapeutic effects, is known as a refractory chronic cough [2,3].

The prevalence of chronic cough in the population is estimated to be 9.6% [4]. Chronic cough can have negative effects on physical, psychological, and social wellbeing, not only causing vomiting, headaches, throat injuries, and urinary incontinence, but also causing anxiety, depression, and a social burden. In addition, chronic cough causes an economic burden and has a profound impact on quality of life [5,6].

Current treatments for refractory chronic cough include etiologic treatment, medications, non-medications, and emerging treatment modalities [7]. Etiologic treatment is mainly aimed at refractory chronic cough with a clear etiology. The common causes of chronic cough include cough variant asthma, upper airway cough syndrome, eosinophilic bronchitis, gastroesophageal reflux cough, and allergic cough [8–10]. Medication or non-pharmacologic therapy is needed for refractory chronic cough with an unknown etiology or treatment failure. Pharmacologic therapies for refractory chronic cough include opioids, such as morphine, as well as neuromodulators, such as gabapentin, pregabalin, and amitriptyline. The adverse reactions to pharmacologic therapies are well known and

* Corresponding author.
** Corresponding author.
E-mail addresses: 05849@tongji.edu.cn (X. Xu), 96778@tongji.edu.cn (L. Yu).
[1] These authors have contributed equally to this work and share first authorship.

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include drowsiness, loss of consciousness, and constipation [7]. Non-pharmacologic therapy includes physical therapy and speech and language therapy. Compared to pharmacologic therapy, there are no apparent adverse reactions [5,7]. Emerging treatments, including P2X3 receptor antagonists, NK-1 receptor antagonists, and TRP receptor blockers, have specific application prospects, but the effectiveness and safety must be further confirmed in clinical trials [7,9]. Non-pharmacologic therapy is a potential therapy, especially for the treatment of refractory chronic cough, so we have reviewed the current clinical research involving non-pharmacologic therapy in the diagnosis and treatment of refractory chronic cough. We have searched Medline, Embase, LILACS (Latin American and Caribbean Health Sciences Literature), Wanfang Med Database, China National Knowledge Infrastructure, Chinese VIP Information Database and Chinese Biomedical. For English databases, subject headings and text-word searches were used, and the search details included "language therapy", "non-pharmacologic therapy", "refractory cough" and "chronic cough". For Chinese databases, free text terms were used, such as "yu yan zhi liao" (which means language therapy in Chinese), "fei yao wu zhi liao" (which means non-pharmacologic therapy in Chinese) and "ke sou" (which means cough in Chinese). Studies included in this paper were published before July 1, 2022. Only 9 clinical trials that investigated the efficacy of non-pharmacologic treatment studies of refractory chronic cough were included.

The basic characteristics of each study are presented in Table 1.

1. Introduction The concept of non-pharmacologic therapy

Non-pharmacologic therapy for chronic cough mainly includes physiotherapy and speech and language intervention (PSALI). PSALI is a method that relies on behavioral interventions to treat coughing. PALSI integrates a series of concepts studied by Vertigan et al. [11] and Patel et al. [15] and includes therapists' provision and guidance on the completion of multiple interventions, including maintaining throat hygiene and hydration, laryngeal massage techniques, and chest physiotherapy. PALSI also includes health education, psychoeducational counseling, cough suppression technology, and breathing exercises to help patients control coughing independently. In recent years, other treatments, such as acupuncture therapy, pain stimulation therapy, and capsaicin desensitization treatment, have become new options for non-pharmacologic therapy.

Table 1
Basic characteristics of non-pharmacologic therapy studies on refractory chronic cough.

author	a particular year	research design	sample number	control group	test team	population		
						Sex (M/F)	Age, years	Duration of RCC, months
Vertiganet al. [11]	2006	RCT	n = 87	Healthy lifestyle education	Physiotherapy and speech and language intervention	64/23	Mean = 59.4	Not mentioned
Vertigan et al. [12]	2008	RCT	n = 83	Healthy lifestyle education	Physiotherapy and speech and language intervention	22/61	Mean = 54.5	Not mentioned
Ryan et al. [13]	2009	Uncontrolled trial	n = 24	own control	Physiotherapy and speech and language intervention	5/19	CC + PVFM group: median = 56 , CC group: median = 58	Median = 24
Ryan et al. [14]	2010	Uncontrolled trial	n = 17	own control	Physiotherapy and speech and language intervention	8/9	Median = 61	Median = 60
Patel et al. [15]	2011	Uncontrolled trial	n = 23	own control	Physiotherapy and speech and language intervention	10/13	Mean = 60	Mean = 42
Vertigan et al. [16]	2016	RCT	n = 40	Placebo + speech and language therapy	Pregabalin plus physiotherapy and speech and language intervention	13/27	Control group: mean = 64 , Test group: mean = 61	Control group: mean = 151 , Test group: mean = 94
Chamberlain Mitchell et al. [17]	2017	RCT	n = 75	Healthy lifestyle education	Physiotherapy and speech and language intervention	24/51	Control group: median = 56 , Test group: median = 61	Control group: median = 48 Test group: median = 60
Kapela et al. [18]	2020	RCT	n = 18	Speech and language therapy alone	Supplementary prerecorded video group	2/16	Mean = 58	Median = 36
Wright et al. [19]	2021	Uncontrolled trial	n = 27	own control	Physiotherapy and speech and language intervention	8/19	Mean = 58	Mean = 60

2. Possible mechanisms underlying non-pharmacologic therapy

2.1. Inhibition of heightened cough sensitivity

The pathologic mechanism underlying increased cough sensitivity is thought to be nerve damage caused by an inflammatory stimulus [20]. Increased sensitivity of the cough receptor, remodeling of the afferent nerve, and abnormal functional areas of the central brain cause patients with chronic coughing to produce a hyperactive cough reflex to low levels of stimulation [21]. A small amount of lampblack, dust, odor, and cold air stimulation, and even when speaking or nervous, can cause coughing. The motivation of cough-like symptoms caused by these stimuli is referred to as "urge-to-cough". Importantly, urge-to-cough mediates the cognitive responses of airway stimulation prior to coughing [22]. The intensity of the urge-to-cough has been positively correlated with that of an actual cough. Furthermore, a decrease in the intensity of an urge-to-cough is often accompanied by an increased cough reflex threshold [23]. Therefore, blocking this mechanism is an important basis for treating chronic cough [24]. Among these therapies, reducing laryngeal irritation, maintaining laryngeal hydration, and laryngeal massage can reduce peripheral cough sensitivity. The mechanism involves increasing the resistance of the vocal cords to injury and reducing or avoiding cough-induced stimulation, reducing activation of the airway sensory nerve receptors (TRPV1 and TRPA1), reducing the cough impulse, increasing the cough threshold, and reducing peripheral cough sensitivity [25]. The management of depression and anxiety in psychoeducational counseling can be associated with reduced central cough sensitivity [15].

2.2. Inhibition of the laryngeal hypersensitivity reaction

Laryngeal hypersensitivity is an inappropriate or abnormally enhanced laryngeal response to external sensory triggers, whereas many symptoms described by chronic cough patients are confined to the throat and upper chest. These symptoms are usually caused by non-specific environmental triggers, which have an inseparable relationship [26]. A survey showed that most patients with refractory chronic cough had laryngeal paresthesia, including pharyngeal itching, pharyngeal foreign body sensation, and a mucus adhesion sensation [27,28]. In addition, there is evidence linking chronic cough to laryngeal dysfunction diseases. Other studies have reported that 40%–47% of refractory chronic cough patients will have abnormal vocal cord function, such as repeated abnormal vocal cord movement and mediolateral laryngeal muscle contraction during pronunciation [29,30]. Milgrom et al. [31] suggested that approximately 25% of subjects with chronic cough had contradictory vocal cord movement (i.e., inappropriate vocal cord adduction). Andrianopoulos et al. [32] reported that coughing is a common symptom in patients with laryngospasm, which is characterized by abnormal or "enhanced" laryngeal adductor reflex. As a result, there is an overlap with the clinical diagnosis and treatment of chronic cough. Reducing laryngeal stimulation can slow the speed of reaching the cough threshold, and maintaining laryngeal hydration and laryngeal massage can reduce the laryngeal hypersensitivity response, thus reducing the laryngeal muscle spasm or vocal cord abnormal movement caused by laryngeal stimulation and reducing the risk of subsequent injury. Breathing exercises are conducive to reducing adductor activity during expiration, thus reducing coughing [33].

2.3. Automatic control and inhibition of coughing

Several studies have confirmed that coughing is controlled by the central nervous system and that humans can control and suppress coughing [32,34,35]. Functional brain imaging has also revealed that multiple brain regions are activated during automatic control or cognition of coughing and cough suppression [20]. While functional neuroimaging in chronic cough patients has revealed decreased activity in the forebrain regions, including the dorsal, prefrontal, and middle anterior cingulate cortex, these same areas appear to be involved in the controlled suppression of capsaicin-induced coughing [36]. Cho et al. [37] studied the ability of chronic cough patients to suppress coughing during the capsaicin challenge test and verified diminished controlled suppression of coughing in patients with chronic cough. Psychoeducational counseling and cough suppression techniques can influence cognitive behavior, which emphasizes increased autonomous control of cough impulses and stimulating the brain higher center to process cough reflex sensory input while enhancing downward control, thus inhibiting the occurrence of coughing [38].

3. Composition of non-pharmacologic therapy

Non-pharmacologic therapy mainly includes physiotherapy and speech and language intervention. Physiotherapy includes maintaining throat hygiene and hydration and laryngeal massage. Speech and language therapy includes education, cough suppression techniques, reduced laryngeal stimulation, and psychoeducational counseling. Non-pharmacologic therapy is performed by a language pathologist or physiotherapist for 1–2 months in four sessions, with 30–60 min for each session. The course content is implemented step-by-step according to the non-pharmacologic model, and patients are encouraged to practice at home after class. There is no unified standard, however, for treatment time, the number of courses, or the content of non-pharmacologic therapy. There is personalized adjustment according to the patient's condition, so there are differences in the implementation of non-pharmacologic therapy, but the therapies are basically similar. In recent years, other treatments, such as acupuncture, pain stimulation therapy, and capsaicin desensitization treatment, have become new options for non-pharmacologic therapy.

3.1. Education

The purpose of education lays the theoretical foundation for subsequent behavioral therapy. First, education helps patients to understand the mechanism and development process of chronic cough and the purpose and principle of physical therapy and speech and language therapy, thus improving their enthusiasm and compliance to participate in the treatment [17]. This process emphasizes that repeated coughing has no physiologic benefits but has negative effects, such as laryngeal injury, increased irritation, and persistent cough circulation. Education also emphasizes that cough suppression does not hurt the body [39,40].

Another aim of education is to establish the goal of treatment (i.e., cough suppression) [40]. It is recommended that patients attempt to suppress their cough, even if they want to cough [12,41]. However, some patients believe that coughing acts as a reflex and is not under self-control. Therefore, patients should understand the cough reflex principle and that coughing can be proactively controlled. In this way, willingness to control coughing independently will be strengthened [34].

3.2. Cough suppression technology

Cough suppression techniques are used to help patients identify signs of an impending cough and to prevent or block the occurrence of a cough by inhibiting or replacing the cough. The first step is to identify the triggers of coughing, such as mental stress, air pollution, abnormal smells, and other physical or chemical stimuli. Identifying these cough triggers can help to predict the timing of coughing. Second, strategies to suppress or replace the cough are implemented when the cough is about to occur, including swallowing or diverting attention, lip contraction and abdominal breathing, and nasal breathing [2,5,15,17,42]. The person can swallow hard instead of coughing [17]. The methods of distracting attention include drinking water, sucking on ice cubes, chewing gum, and sucking lollipops to increase the frequency and amount of saliva swallowing [39]. Cough suppression techniques should be taught through multiple courses and require patients to practice at home to ensure the accuracy of the cough suppression techniques. When patients are proficient in the techniques, they can attempt to expose themselves to cough triggers and implement strategies to control their coughing [5]. Increasing evidence has confirmed that cough suppression can increase downward control, reduce the vagus nerve cough reflex arc hypersensitivity response, and stimulate the cough receptor [25]. According to the close innervation relationship between coughing and voice, cough suppression treatment can also improve voice disorders that traditional pharmacologic therapy cannot cure [43]. This fact is significant for patients with co-morbid chronic cough and voice disorders. Slovarp et al. [44]reported that among patients with refractory chronic cough who were referred to cough suppression therapy because pharmacologic therapy was not effective, 70.1% showed significant improvements in symptoms and 58% reported satisfaction with the treatment outcomes. Indeed, early intervention in cough suppression could be a cost-effective and efficient option for patients with chronic cough.

Breathing exercises are also important insofar as they involve changing the breathing pattern to control cough, and training abdominal, diaphragm, and reduced lip contraction breathing. Breathing exercises have been widely used in coughing and abnormal vocal cord movement by relaxing laryngeal muscle tone and avoiding neck, shoulder, and upper chest muscle tension through breathing [42]. Patients should be relaxed, place the left hand on the chest and the right hand on the abdomen, inhale with the nose, keep the chest motionless when inhaling, bulge the abdomen, push downward on the diaphragm, and inhale air. Then, the patient should pout and exhale slowly, maximize the flow through the throat, perform vocal cord abduction, or emit an “S” sound during breathing, cause airway resistance to transfer from the throat to the mouth, exhale with abdominal depression, push upward on the diaphragm, and exhale the air [15,16,42,45]. The focus of breathing should be on exhalation rather than inspiration. Among these steps, exercising the diaphragm can also strengthen the pressure of the esophagogastric junction and improve reflux [46]. Breathing exercises have been supported by strong evidence in improving the quality of life of asthma patients and correcting hyperventilation [37,38]. The respiratory retraining therapy developed by Nacci [47] and Murry [48] has also achieved ideal results in the long-term treatment of contradictory vocal cord dysfunction, which is closely related to chronic cough. Eherer et al. [49] conducted a randomized, controlled study on the effect of abdominal breathing on gastroesophageal reflux disease. The outcome confirmed that through breathing practice and active training, abdominal breathing effectively enhances the anti-reflux barrier and improves chronic cough characterized by gastroesophageal reflux. In a breathing exercises study involving refractory cough [50], patients received 2–7 respiratory retraining sessions. The mean severity score changed from 9.2 before treatment to 1.3 posttreatment. All patients subjectively described an improvement in cough severity. Yang et al. [51] focused on aerodynamics in evaluating behavioral therapy, and concluded that a decreased cough severity index, prolonged maximal vocal duration, decreased mean estimated subglottic air pressure, and reduction in oral airway resistance all demonstrated the effectiveness of breathing exercises for chronic cough.

3.3. Psychoeducational counseling

Psychoeducational counseling provides patients with psychological education guidance, helps patients to establish particular goals, and motivated patients to reach the goals. Psychoeducational counseling can also eliminate patient tension and anxiety about psychological pressure and encourage patients to control coughing independently. If necessary, patients can also receive hypnotherapy. During speech and language therapy, patients should assume the ultimate responsibility for controlling symptoms. Patient adherence to treatment is necessary to achieve optimal treatment outcomes. It is necessary to enhance patient awareness of the controllability of coughing, emphasizing the view of coughing as a response to stimuli rather than an uncontrollable phenomenon [52]. In addition, patients should be encouraged to set realistic goals, such as the purpose of treatment being to control, rather than completely eliminate, coughing, while understanding that treatment is not easy and cannot work immediately. In this way, speech and language therapy can prevent patients from abandoning non-pharmacologic therapy because non-pharmacologic therapy is not effective in the

short term, thus patient compliance is enhanced [12].

Studies have shown that chronic cough patients have higher levels of depression, anxiety, fatigue, and somatic symptoms than participants without a chronic cough. Individuals with a refractory cough scored higher for fatigue and depression than those with a definite cough cause [53]. Chronic cough patients with long-term coughing are difficult to treat and are usually complicated by anxiety, depression, irritability, and other negative emotions [53,54]. Therefore, it is also necessary to provide psychoeducational counseling, such as using anxiety and stress management to relieve bad emotions, stabilize emotions, strengthen the confidence in a cure, and improve the coordination of patients in treatment [17,39,55]. Vertigan et al. [39] pointed out that the effectiveness of psychotherapy as monotherapy depends on whether chronic cough patients have psychogenic causes because psychotherapy is more effective for adult somatic cough syndrome and children's psychological cough and habitual cough. In a study that used hypnosis to cure children's habitual cough, six of nine cases had a significant reduction in coughing episodes or stopped coughing altogether [56].

3.4. Reduce laryngeal irritation

The purpose of reducing laryngeal irritation is to lower the cough threshold and reduce the occurrence of coughing [57]. Patients must identify and avoid exposure to smoke, pungent odors, cold air, chemicals, and other cough-inducing physical and chemical stimuli. Patients are also encouraged to stop smoking or avoid passive smoke and to minimize exposure to substances that dry the throat, such as alcohol and caffeine [12,25]. Gastroesophageal reflux patients are managed to reduce acid reflux and irritation [12].

3.5. Throat hydration and laryngeal massage

The purpose of laryngeal hydration and laryngeal massage is to moisten the larynx and reduce the sensitivity of the larynx to irritation. Patients should avoid breathing with the mouth. The nose has the effect of moist suction air inhalation, thus patients should attempt to inhale with the nose to moisten the air [42]. Steam inhalation and increased intake and frequency of water, drinking at least

Table 2
Inclusion and exclusion criteria for non-pharmacologic treatment studies of chronic refractory cough.

author	inclusion criteria	exclusion criteria
Vertigan et al. [11]	(1) > 18 years old; (2) cough persisting for more than 2 months after pharmacological treatment; (3) cough persisting after treatment for chronic cough-related diseases (asthma, postnasal drip syndrome, gastroesophageal reflux) and withdrawal of ACEI (if used); (4) normal chest X-ray; (5) ability to travel to the hospital	(1) Recent upper respiratory tract infection (2)untreated chronic cough-related diseases, such as allergy, postnasal drip syndrome, asthma, gastroesophageal reflux, eosinophilic bronchitis, lung pathology, abnormality on the chest radiograph, pulmonary disease, chronic obstructive pulmonary disease, and neurological voice disorders; (3) abnormal chest X-ray
Vertigan et al. [12]	(1) > 18 years old; (2) cough persisting for more than 2 months after pharmacological treatment; (3)cough persisting after treatment for chronic cough-related diseases (asthma, postnasal drip syndrome, gastroesophageal reflux) and withdrawal of ACEI (if used); (4) normal chest X-ray; (5) ability to travel to the hospital	(1) Recent upper respiratory tract infection; (2) untreated chronic cough-related diseases, such as allergy, postnasal drip syndrome, asthma, gastroesophageal reflux, eosinophilic bronchitis, lung pathology, abnormality on the chest radiograph, pulmonary disease, chronic obstructive pulmonary disease, and neurological voice disorders; (3) abnormal chest X-ray
Ryan et al. [13]	(1) 18–80 years old; (2) coughing lasting more than 8 weeks; (3) nonsmokers or ex-smokers with fewer than ten pack years; (4) no other active respiratory or cardiac diseases; (5) coughing persisting after treatment for chronic cough-related diseases (asthma, postnasal drip syndrome, gastroesophageal reflux) and withdrawal of ACEI (if used); (6) normal chest X ray	(1)current smokers; (2)untreated chronic cough-related diseases (such as asthma, postnasal drip syndrome, gastroesophageal reflux) and the use of ACEI; (3) abnormal chest X-ray
Ryan et al. [14]	(1)18–80 years old; (2)cough lasting more than 8 weeks; (3)nonsmokers or ex-smokers with fewer than ten pack years; (4) no other active respiratory or cardiac diseases; (5) cough persisting after treatment for chronic cough-related diseases (asthma, postnasal drip syndrome, gastroesophageal reflux) and withdrawal of ACEI (if used); (6) normal chest X ray	(1)current smokers; (2)untreated chronic cough-related diseases (such as asthma, postnasal drip syndrome, gastroesophageal reflux) and the use of ACEI; (3) abnormal chest X-ray
Patel et al. [15]	(1) > 18 years old; (2) cough lasting more than 8 weeks; (2) idiopathic chronic cough or cough due to asthma, upper airway cough syndrome or GERD refractory to intensive therapy; (3) nonsmokers; (4) normal chest X-ray	(1) current smokers; (2) recent upper respiratory tract infection (within 4 weeks); (3) use of ACEIs; (4)significant change in cough severity in the preceding 4 weeks; (5) abnormal chest X-ray; (6) abnormal lung function tests
Vertigan et al. [16]	(1) 18–80 years old; (2) cough persisting after treatment for chronic cough-related diseases (asthma, postnasal drip syndrome, gastroesophageal reflux) and withdrawal of ACEI (if used); (3)nonsmokers; ④ no respiratory diseases	(1)recent upper respiratory tract infection; (2) coughing with mucus purulent sputum; (3) pregnant or lactating women; (4) significant psychiatric or neurologic disorder; (5) previous speech pathology management in the previous 12 months
Chamberlain Mitchell et al. [17]	(1) > 18 years old; (2) cough lasting more than 8 weeks; (3) cough persisting after treatment for chronic cough-related diseases (asthma, postnasal drip syndrome, gastroesophageal reflux) and withdrawal of ACEI (if used); (4) normal chest X-ray	(1)current smokers; (2)upper respiratory tract infection in the previous 4 weeks; (3) use of ACEIs (4) known respiratory disease (such as lung cancer, pneumonia, pulmonary fibrosis, sarcoidosis, pleural effusion, bronchiectasis)
Kapela et al. [18]	(1) > 18 years old; (2) cough lasting more than 8 weeks; (3) etiology is unclear or coughing persisted after treatment for chronic cough-related diseases (asthma, postnasal drip syndrome, gastroesophageal reflux) and withdrawal of ACEI (if used).	(1) cognitive impairment.; (2) untreated diseases (such as asthma, sinusitis, gastroesophageal reflux, lung disease); and the use of ACEIs

2 L per day, can keep the larynx moist and clean [39,40]. Previous studies have shown through modeling calculations that liquid pressure accumulation in the membrane region of the vocal cords can lead to considerable tissue damage during vibration. Increasing the hydration effect can reduce the sound threshold pressure, and the vibration driving force can be reduced, thus reducing fluid pressure accumulation and laryngeal damage [58]. If excessive coughing leads to muscle tension, laryngeal massage can be performed.

Table 3
Indicators and efficacy of non-pharmacologic treatment studies of refractory chronic cough.

author	Main research objectives	outcome index	curative effect
Vertigan et al. [11]	Effects of physiotherapy and speech and language intervention on chronic cough symptoms	Coughing, breathing, voice, upper airway symptoms, daily life limitations and total symptoms	Coughing, breathing, sound, upper airway symptoms and limitation scores decreased significantly after the intervention. Although the scores of the control group also decreased, the improvement was significantly greater in the treatment group. The rate of outcome success was 88% in the treatment group and 14% in the control group.
Vertigan et al. [12]	Effect of physiotherapy and speech and language intervention on voice quality	perceptual voice profile, acoustic and electroglottographic analysis	The perceptual voice profile were significantly improved in the treatment group compared to the control group. The maximum phonation time, jitter, and harmonic-to-noise ratio in the treatment group were significantly improved from pre- to postintervention in the treatment group. Fundamental frequency in connected speech, closed phase of vocal fold vibration basal frequency standard deviation and phonation range had no significant differences from pre- to postintervention either in the treatment group or the control group.
Ryan et al. [13]	physiotherapy and speech and language therapy's effects on other laryngeal problems	LCQ, forced expired nitric oxide, hypertonic saline challenge, capsaicin cough reflex sensitivity testing, fiber optic laryngoscopy	After treatment, cough-related quality of life and cough reflex sensitivity showed significant improvement. Extrathoracic airway hyperresponsiveness and PVFM showed significant reduction for subjects with chronic cough and PVFM.
Ryan et al. [14]	Effects of physiotherapy and speech and language intervention on chronic refractory cough	LCQ, laryngeal dysfunction symptom questionnaire (LDQ), cough score, total symptom score, cough frequency, and capsaicin cough reflex sensitivity	After treatment, the cough-related quality of life, cough frequency, and cough reflex sensitivity improved significantly.
Patel et al. [15]	Effects of physiotherapy and speech and language intervention on the quality of life of patients with chronic cough	LCQ, cough frequency, and sleep disturbance	Cough-specific quality of life improved significantly after treatment. Both the cough frequency score and the sleep disturbance scores decreased significantly. There were no adverse reactions observed.
Vertigan et al. [16]	comparing the efficacy of pregabalin + physiotherapy and speech and language intervention	Cough frequency, VSA, LCQ, and capsaicin cough reflex sensitivity	Cough severity, cough frequency, and quality of life improved in both groups after treatment. The improvement in LCQ and VSA scores was greater in the physiotherapy and speech and language therapy combined with pregabalin group than in the physiotherapy and speech and language therapy alone group, but there was no significant difference in cough frequency between the two groups.
Chamberlain Mitchell et al. [17]	Effects of physiotherapy and speech and language intervention on chronic refractory cough	LCQ, cough frequency, capsaicin cough reflex sensitivity, VSA, VPQ, and HADS-anxiety, HADS-depression	Cough-related quality of life improved significantly in the treatment group compared to the control group, with a 41% reduction in cough frequency and more pronounced reduction in the severity of coughing. The improvement within the treatment group lasted 3 months. There was no significant difference in cough reflex sensitivity, VPQ, HADS-anxiety, or HADS-depression between the treatment and control groups. No adverse events were reported.
Kapela et al. [18]	benefits of providing supplemental prerecorded video about physiotherapy and speech and language intervention	ratings of participants' accuracy in performing the therapy techniques, the number of therapy sessions until treatment goals were achieved, Symptom Frequency and Severity Rating Scale scores, LCQ,CAPE-V.	Both groups showed significant improvement before and after treatment, but there was no significant difference in the degree of improvement between the two groups.
Wright et al. [19]	Follow-up on the long-term efficacy of patients receiving physiotherapy and speech and language intervention	LCQ、self-report score	After six months or longer of treatment, the severity of the cough improved for a long time.

Patients assume a sitting position, massage the front part of the neck and the sternocleidomastoid muscle section, place their fingers on both sides of the thyroid cartilage, and massage from top to bottom while the fingers gently press the thyroid cartilage and larynx [59]. This process can help relax the laryngeal muscles and reduce the sensitivity of the laryngeal receptors to stimulation [7].

3.6. Chest physical therapy

Chest physiotherapy is a widely used intervention in patients with airway diseases. The primary goal is to promote secretion transport, thus reducing secretion retention in the airway by reducing airway obstruction caused by secretions that occupy the airway lumen and reducing cough symptoms, including a combination of forced expiration (directed cough or exhalation), postural drainage, percussion, and/or shaking [60,61].

3.7. Other physical therapy

Acupuncture, moxibustion, and other traditional Chinese medicine physical therapies are quite effective in the treatment of chronic cough, and can effectively regulate the inflammatory response and reduce the proinflammatory factors in the plasma. Cui et al. [62] used moxibustion to treat 68 pediatric patients with chronic cough, with a cure rate of 79.2%. In treatment using acupuncture for postoperative chronic cough in patients with non-small cell lung cancer lung cancer, the study showed that the Leicester cough score (Leicester cough questionnaire [LCQ]) in the acupuncture treatment group 10 weeks after surgery was significantly higher than the group with no treatment [63]. In the latest study, Shen et al. [64] effectively cured chronic cough in a prospective, randomized, controlled trial. In addition, studies have shown that pain stimulation in healthy subjects reduces cough and cough impulsivity [65]. The results of another randomized, controlled study suggested that coughing and the cough impulse caused by capsaicin inhalation in healthy people and refractory cough patients were suppressed by inducing the activation of pain mechanisms [66]. A new study of patients with refractory chronic cough published in 2022 showed that using progressive doses of capsaicin combined with cough suppression for cough desensitization treatment reduced cough frequency by up to 97% [67].

4. Suitable populations for non-pharmacologic therapy

According to the 2016 ACCP and 2020 ERS guidelines, non-pharmacologic therapy is recommended for adults with unexplained chronic cough. Patients with chronic refractory cough who want to replace pharmacologic therapy should consider multimodality physiotherapy or speech and language therapy because they are difficult to treat. It is recommended to identify patients with chronic cough, pharyngeal dysphagia, or the presence of conditions associated with a high risk of inhalation because they are potential candidates for non-pharmacologic therapy [68,69].

Currently, relevant clinical studies of non-pharmacologic treatment of chronic cough are mainly performed in individuals with refractory cough. The specific inclusion and exclusion criteria for each study are shown in Table 2. Although the inclusion and exclusion criteria vary, there were some common factors. According to the inclusion and exclusion criteria of eight studies, the inclusion criteria were as follows: (1) adults 18–80 years of age; (2) unclear etiology, no relief after pharmacologic therapy for coughing due to GERD, sinusitis, asthma, or no response after withdrawal of an angiotensin converting enzyme inhibitor (ACEI); (3) normal chest X ray or chest CT; and (4) no respiratory disease and no upper respiratory tract infection in nearly 4 weeks. The exclusion criteria were as follows: (1) current smokers or ex-smokers within 10 years; (2) untreated chronic cough-related diseases (such as asthma, postnasal drip syndrome, and GERD) and the use of an ACEI; (3) abnormal chest X ray or chest CT; (4) a previous history of lung disease (such as lung cancer, pneumonia, pulmonary fibrosis, sarcoidosis, pleural effusion, and bronchiectasis); and (5) cognitive impairment.

5. Evaluation indicators and efficacy of non-pharmacologic therapy

Existing studies have shown that the effectiveness of non-pharmacologic therapy in chronic refractory cough shows good application prospects, but the current studies use multiple interventions. It is still unclear which component of non-pharmacologic therapy is most beneficial. The main evaluation indicators include the visual analog scale (VAS), cough-related quality of life, cough frequency, and cough reflex sensitivity. In addition, some studies have evaluated other indicators, such as voice quality and adverse effects of non-pharmacologic therapy. The evaluation indicators and efficacy of related studies for non-drug therapy are shown in Table 3.

5.1. Visual analog scale

Cough severity was measured by the visual analog scale (VAS). The VAS evaluates the severity of coughing with a 100-mm scale line. Patients mark the scale between 0 and 100 according to their self-feeling. The larger the value is, the more severe the cough is [70]. Vertigan et al. [16] found an improvement in cough severity in both the non-pharmacologic treatment and non-pharmacologic treatment + pregabalin groups. Mitchell et al. [17] reported a reduction in VAS cough severity in the non-pharmacologic and control groups. The difference between the non-pharmacologic and control groups approached statistical significance. The reason for the discrepancy in results is unclear and could be related to the small sample size. Therefore, a larger study needs to be conducted. Compared to the LCQ and cough frequency monitoring, the VAS is less effective and reliable, and it is not recommended as the main index to assess coughing [71].

5.2. Cough-related quality of life

Cough-related quality of life was assessed by the LCQ. The LCQ is a self-report questionnaire with 19 items involving physical, psychological, and social health. The cough severity was assessed according to seven grades from "always will" to "completely no," and the total score ranged from 3 to 21 for the scores on three domains. The higher the score, the lower the severity of coughing and the better the quality of life [70]. Non-pharmacologic treatment can improve cough-related quality of life, but the long-term quality of life improvement remains unclear due to the limitation of a short study duration of follow-up. A study showed that the difference between the non-pharmacologic and control groups disappeared after 3 months. Therefore, the long-term outcomes of non-pharmacologic treatment warrant further evaluation [17].

5.3. Cough frequency

Cough frequency monitors or autonomous reports of cough frequency are used to evaluate the effect of non-pharmacologic treatment on cough frequency. The former is an objective evaluation and more widely used clinically, while the latter is a subjective evaluation [14–17]. Non-pharmacologic treatment can reduce the frequency of coughing by up to 41% and the reduction lasts 3 months. Non-pharmacologic treatment effectively improves cough symptoms. However, repeated trials to verify the duration of non-pharmacologic treatment efficacy are still lacking [17].

5.4. Cough reflex sensitivity

Cough reflex sensitivity is objectively measured using the capsaicin cough challenge [14–18]. Cough reflex sensitivity refers to the difficulty in causing coughing by chemical or physical substances [72]. The capsaicin cough challenge uses cough stimulants, such as capsaicin, to induce coughing. When $\geq$2 or $\geq$5 coughs are induced, the inhalation concentration (C2 or C5) is taken as the index of cough sensitivity [70].

Cough hypersensitivity syndrome is defined as a severe cough response caused by low-dose exogenous stimulation, which is one of the main characteristics of chronic cough [73]. Chronic cough with improved cough reflex sensitivity and typical stimulation symptoms and sensation, also known as chronic cough hypersensitivity syndrome (CCHS), is a new direction for studying the underlying mechanism and treatment of chronic cough [74]. There are differences in the results of relevant non-pharmacologic treatment studies that use similar physiotherapy, and speech and language therapy. Some studies have shown that non-pharmacologic treatment could increase the cough threshold and reduce cough reflex sensitivity [14–16]. However, other studies [17] have found that there was no significant reduction in cough reflex sensitivity. The reasons for the discrepancy are unclear and might be related to the small sample sizes, different severity of chronic cough, and conscious control of patients. These studies, however, suggest that the mechanism underlying non-pharmacologic therapy might be related to cough reflex sensitivity, which should be further studied and interpreted.

5.5. Voice-related indicators

Voice abnormalities are common in chronic refractory cough, such as dysphonia and hoarseness, which can affect the quality of life [12]. This fact could be related to irritable larynx syndrome (ILS), which is the result of laryngeal stimulation by various stimuli that cause laryngeal muscle spasms and paradoxical vocal fold movement (PVFM). PVFM manifests as chronic cough, dysphonia, a foreign body sensation in the throat, and laryngospasm [75,76]. Voice quality is currently evaluated by subjective or objective methods. Subjective methods include perceptual voice analysis, the vocal performance questionnaire (VPQ), and the Consensus Auditory Perceptual Evaluation of Voice (CAPE-V). Objective methods include acoustic and electroglottographic analyses. A study by Vertigan et al. [11] involving the efficacy of physiotherapy, and speech and language therapy for chronic cough showed an improvement in coughing, breathing, sounds, upper airway symptoms, and daily life limitations in the physiotherapy group, and speech and language therapy group. Subsequently, Vertigan et al. [12] studied the impact on voice quality and reported that breathiness, roughness, strain, and glottal fry in the physiotherapy group, and speech and language therapy group were significantly improved compared with the control group. The maximum phonation time, jitter, and harmonic-to-noise ratio in the treatment group were significantly improved from pre-to post-intervention in the treatment group. Kapela et al. [18] used the CAPE-V to subjectively assess voice quality, which showed a significant improvement from pre-to post-intervention. Mitchell et al. [17] used the VPQ to self-evaluate the degree of voice impairment and quality of life, although there was no significant difference between the treatment and control groups.

5.6. Untoward effects

No current non-pharmacologic studies have reported adverse effects, such as pulmonary infection, nor any pharmacologic treatment-related adverse effects, such as lethargy, loss of consciousness, and constipation [15,17]. Therefore, the safety of non-pharmacologic treatment is higher, and it is more conducive to improving the quality of life of patients. The adverse effects were not evaluated in some studies, so subsequent relevant studies should pay closer attention to the evaluation.

In summary, VAS, cough-related quality of life, cough frequency, and the cough reflex sensitivity measure the short designated time availability of non-pharmacologic treatment. Recent studies have assessed the efficacy of non-pharmacologic therapy more comprehensively through aerodynamic analysis, perceptual voice analysis, auditory judgment, acoustic analysis, and the cough

threshold. The short-term efficacy (4–6 weeks) has been considered good [77]. On this basis, Wright et al. [19] reported the long-term outcomes of non-pharmacologic treatment in individuals who were treated for chronic cough for ≥6 months. According to improvement in LCQ scores, non-pharmacologic treatment has sustained effectiveness for most patients. However, according to self-symptom assessments, 44% of patients did not achieve long-term benefits. The explanation could be that reducing the frequency of non-pharmacologic treatment impacts the efficacy, or that other new health events related to chronic cough might have occurred.

A meta-analysis of non-pharmacologic treatment [6] selected and included two randomized, controlled studies with 162 participants and showed that the health-related quality of life and the objective cough count were improved significantly after 4 weeks of non-pharmacologic treatment compared to the control group, but not maintained at the follow-up from 4 weeks to 3 months after the treatment. The effect of treatment on the subjective measures was uncertain, and there was no significant difference between the two groups in the cough severity index. Therefore, more high-quality studies are needed to further evaluate subjective cough measures, cough severity, and long-term efficacy.

6. Summary and prospects

In conclusion, non-pharmacologic therapy is effective for chronic cough, especially for refractory chronic cough patients. Non-pharmacologic therapy can effectively improve the quality of life and reduce the frequency of coughing. Compared to pharmacologic therapy, non-pharmacologic therapy has no apparent adverse reactions. As such, non-pharmacologic therapy has good application prospects in the diagnosis and treatment of refractory chronic cough.

Nevertheless, the current relevant research is imperfect. The sample size is still small, and the mechanism of action and long-term efficacy must be verified by large-sample clinical studies. The methods used for non-pharmacologic therapy vary, and the specific application standards of each different therapy, the adaptation object, and the frequency and cycle of treatment require further standardization. First, the scarcity of professional language pathology counselors and instructors has hampered the promotion of treatments. Second, patient compliance has a great impact on efficacy, especially for patients, in whom hospitalization is difficult. Achieving standardized rational management is yet another challenge. In addition, further study is warranted on jointly using the various methods and combining the methods with pharmacologic therapy for chronic cough to achieve better efficacy. In addition, non-pharmacologic therapy studies remain limited to patients with chronic cough, especially refractory chronic cough. Whether this therapy can be used in other chronic respiratory diseases, such as asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and sarcoidosis, should be further explored.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations List

Purinergic-receptor 2X3 P2X3
Neurokinin-1 NK1
Transient receptor potential TRP
Physiotherapy and speech and language intervention PSALI
Transient receptor potential vanilloid 1 TRPV1
Transient receptor potential ankyrin 1 TRPA1
Leicester cough questionnaire: LCQ

American College of Clinical Pharmacists ACCP
European Respiratory Society ERS
Gastroesophageal reflux disease GRED
Angiotensin converting enzyme inhibitor ACEI
Visual analog scale VAS
Concentrations of the cough agonist causing one/two/five coughs in the cough challenge tests C1/2/5
Chronic cough hypersensitivity syndrome: CCHS
Irritable larynx syndrome: ILS
Paradoxical vocal fold motion PVFM
Vocal performance questionnaire: VPQ
Hospital Anxiety and Depression Scale HADS
Consensus Auditory Perceptual Evaluation of Voice CAPE-V
laryngeal dysfunction symptom questionnaire: LDQ

Appendix A. Supplementary data

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