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Outcome Measures for Chronic Cough: A Literature Review

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Abstract

Background: Approximately 9-10 percent of adults experience chronic cough. Chronic cough is a cough that lasts greater than eight weeks, with significant impacts on an individual's quality-of-life in social, psychological, and physical domains. Current treatment is not successful for all patients, and a lack of validated outcome measures makes it challenging to determine the efficacy of experimental chronic cough interventions.

Aims: The purpose of this review is to determine the optimal protocols for outcome measures needed to ascertain the efficacy of chronic cough treatment.

Main contribution: Inconsistent correlations were found between objective and subjective outcome measures. The strongest outcome measure correlations were found between cough-specific quality-of-life questionnaires and objective cough frequency counting. Methods of objective measures vary and require further investigation.

Conclusions: Data from both subjective and objective outcome measures are needed to determine a cough treatment's efficacy due to the different constructs measured by each tool, and the inconsistent correlations found between subjective and objective outcome measures. Additionally, further standardization is needed for subjective outcome tools.

Keywords: chronic cough, outcome measures, treatment efficacy

Introduction

Cough is a common respiratory complaint for which patients seek medical attention, with a significant portion of health-care dollars spent annually to alleviate cough symptoms (Chung et al., 2003; Irwin et al., 1998; Lee & Birring, 2012). Typically, coughing serves as a defense mechanism from the inhalation of unwanted or harmful agents and excess secretions into the airway (Hsu et al., 1994; Irwin et al., 1998; McGarvey & Gibson, 2019). The cough is a visceral reflex tied to the afferent vagal nerve (cranial nerve X), with higher cortical control. This arrangement allows the cough mechanism to be both voluntary and involuntary (Irwin et al., 2006). A cough is typically comprised of three phases; an initial inspiratory stage, the compressive phase, and the explosive phase (McGarvey & Gibson, 2019; Pramono, Imtiaz, & Rodriguez-Villegas, 2016).

Chronic cough is a cough that lasts greater than eight weeks and is reported by 9-10% of adults (Lee & Birring, 2012; Song et al. 2015). Chronic cough can have significant impacts on quality-of-life in social, psychological, and physical domains (Morice, McGarvey & Povard, 2006; Vertigan, Theodoros, Gibson & Winkworth, 2006). It may lead to mild troubles such as hoarse voice, sleep disturbance, chest pain, self-consciousness or more severe disturbances such as stress urinary incontinence, abdominal muscle ruptures, or loss of consciousness (Irwin et al., 1998; Morice et al., 2006; French, Fletcher, & Irwin, 2006). Patients with chronic cough may cough anywhere from one hundred to one thousand times per day, with Hsu et al. (1994) finding that patients coughed an average of 794 times in a day, ranging from 64-3,639 coughs per participant.

Chronic cough may have several etiologies, including respiratory conditions and non-respiratory conditions. Respiratory conditions include asthma, upper airway disease,

gastroesophageal reflux disease (GORD), and chronic obstructive pulmonary disease (COPD). Non-respiratory conditions may consist of rhinosinusitis and gastroesophageal reflux (Morice et al., 2006; Irwin et al., 2006; Smith & Woodcock, 2017). Clinicians utilize client medical history, clinical examination, spirometry, and chest radiography or high resolution computed tomographic scanning of the thorax to identify or eliminate conditions that may underlie the patient's cough (Lee & Birring, 2012; Morice et al., 2006; Smith & Woodcock, 2017). When cough persists despite appropriate investigation and treatment, it is termed idiopathic (ICC) or unexplained (UCC), meaning cough with no underlying diagnosable condition. A cough that persists despite best treatment for the assumed associated conditions is termed refractory chronic cough (RCC) (Irwin et al., 2006; McGarvey & Gibson, 2019). In specialty pulmonary clinics, between 20-42% of patients experience unexplained cough (Morice et al., 2006; Vertigan, Theodoros, Gibson & Winkworth, 2006).

Chronic cough is difficult to treat due to the multiplicity of possible underlying conditions or causes, with treatment effectiveness varying by etiology. Because underlying diagnoses remain unknown for many patients, targeted intervention is not always effective or feasible. As researchers continue to investigate medical treatment and alternative management of chronic cough, they rely on multiple measures (subjective and objective) to assess cough and describe treatment outcomes for patients. Subjective outcome measures are outcome measures that collect data from patient self-report. Objective outcome measures are instruments that collect data independent of the patient's experience. While objective measures are the gold standard to determine efficacy for clinical trials, they may be limited to a laboratory setting and time consuming (Nguyen, Bacci, Dicpinigaitis, & Vernon, 2020; Spinou & Birring, 2014). Additionally, objective measures may be unable to measure aspects of cough that have a

legitimate impact on the individual, such as cough severity or disruption (Faruqi, Thompson, Wright, Sheedy, & Morice 2011; McCrory, Coeytaux, Yancy, & Schmit 2013; Spinou & Birring, 2014). Subjective outcome measures are commonly used by researchers investigating chronic cough to measure severity and frequency. However, most severity and frequency outcome measures used in chronic cough research fail to be validated or standardized (Boulet et al., 2015; Kelsall et al., 2011; Lee et al., 2012; McCrory et al., 2013).

Accurate and responsive outcome measures are necessary for the determination of treatment effectiveness. Without valid or repeatable outcome measures, the confidence of research examining treatments for chronic cough remains uncertain, and the impact on patients is unclear. The purpose of this review is to evaluate the currently available outcome measures used in order to determine optimal protocols needed to ascertain the efficacy of chronic cough treatment.

Outcome Measures

Subjective Measures

Until recently, only subjective parameters were available to researchers investigating outcomes of chronic cough treatment. Subjective tools used to measure cough outcomes include visual analog scales (VAS), cough scores, and health-related quality-of-life questionnaires (HRQOL) (Schmit et al., 2013; Decalmer et al., 2007; Birring & Spinou, 2015; Boulet et al., 2015; Marsden et al., 2008). Both cough severity VAS and HRQOL questionnaires can be easily applied in clinical practice and are frequently used by investigators as outcome measures in research (Birring & Spinou, 2015). The scope of subjective measures includes patient perception of cough intensity, frequency, cough severity, quality-of-life, and response to treatment. However, not all subjective measures have been validated, and may, therefore, be prone to bias

as they vary with the temperament of the participant, the patient's ability to recall symptoms, and the participant's expectations of treatment (Kelsall et al., 2011; Marsden et al., 2008).

Cough severity visual analog scales (VAS). A subjective tool, visual analog scales (VAS) have been adapted to measure cough severity. With cough severity VAS, the patient reports a rating by marking on a horizontal or vertical line that ranges from "no cough" to "worst cough" (Marsden et al., 2008). VAS may be given in paper or electronic form and may provide complementary data to cough-specific health-related quality-of-life questionnaires. Additionally, VAS has been shown to be a highly responsive tool (Birring & Spinou, 2015; Faruqi et al., 2011). However, VAS has not been psychometrically tested or well-researched, lacking a minimally important difference (MID) for chronic cough (although a 17mm MID has been reported by researchers for acute cough) (Boulet et al., 2015; Spinou & Birring, 2014). There is insufficient strength of evidence for VAS validity and repeatability (Boulet et al., 2015; McCrory et al., 2013). The American College of Chest Physicians (CHEST) guidelines recommend VAS scales be standardized to address the issue of validity. Standardization of the VAS includes the use of a 100mm closed-end scale with the word "cough" on both ends indicated with perpendicular lines (Boulet et al., 2015).

Cough severity measures. Cough severity may be measured via the Cough Severity Diary (CSD) or through cough scores (also known as Cough Symptom Scores or Cough Severity Scores). The Cough Severity Diary is a seven-item diary wherein individuals rate their cough severity across three domains (frequency, intensity, and disruptiveness) across a 24-hour period. The scores on the three domains range from 0-10 (0=never to 10=constantly), with the total score taken as an average of the three domains. A higher score signifies a greater cough severity (Vernon, Kline Leidy, Nacson, & Nelsen, 2010; Nguyen et al., 2020). Nguyen et al. (2020)

found that the CSD was valid, reliable, and responsive to change with a preliminary clinically meaningful difference of a $\geqslant$ 1.3 score change. A more diverse sample size is needed to confirm the clinically meaningful difference and validity of the measure.

Cough scores, Cough Symptom Scores, or Cough Severity Scores are two-part questionnaires that differentiate between both day and night cough (Birring & Spinou, 2015: Spinou & Birring, 2014). The cough scores use a numeric scoring system (0-5) (Hamutcu, Francis, Karakoc, & Bush, 2002; Hsu et al., 1994; Marsden et al., 2008). Each number is followed by a brief description (ex. Hsu et al. (1994): "(0) no cough during the day, (1) cough for one short period, (2) cough for more than two short periods (3) frequent coughing, which did not interfere with usual daytime activities (4) frequent coughing, which did interfere with usual daytime activities, and (5) distressing cough most of the day"). The descriptions are altered to match night/sleep disturbance for the nighttime part of the questionnaire. Cough scores have application in a busy clinic because they are easy and quick to administer. However, cough scores are not validated or standardized and are subject to bias (Kelsall et al., 2011). Furthermore, the minimally important difference for cough severity scores is unknown (Spinou & Birring, 2014).

Health-related quality-of-life questionnaires (HRQoL). Health-related quality-of-life (HRQoL) questionnaires measure the patient's perception of the impact of health and disease on several domains (French et al., 2003). QoL questionnaires range from specific to non-specific, focusing on general health, or domains impacted specifically by cough (Irwin et al., 2006). Cough specific questionnaires include the Leicester Cough Questionnaire (LCQ), Cough-Specific Quality-of-Life Questionnaire (CLQC), Chronic Cough Impact Questionnaire, Cough-Specific Quality-of-Life Questionnaire (CQLQ), Pediatric Cough Questionnaire (PCQ), and

Adverse Cough Outcome Survey (ACOS) (McCrory et al., 2013; Schmit et al., 2013). Non-specific HRQoL questionnaires are not recommended for clinical research of chronic cough. Instead, The American College of Chest Physicians (CHEST) cough guidelines recommend cough-specific HRQoL questionnaires as the measurement of cough's impact on patients, as they are validated and reliable (Boulet et al., 2015).

Researchers often use the Leicester Cough Questionnaire (LCQ) for cough-specific quality-of-life. Composed of 19 items, the LCQ measures physical, psychological, and social domains. Patient score within the domains ranges 1-7, with a total score that falls between 3-21. A higher score demonstrates a better health status (Lee et al., 2012). For its preliminary validation, the LCQ underwent item generation using preexisting HRQoL questionnaires, item reduction via patient rating (1-5) for the importance of each item and analysis under the clinical impact factor method. Additionally, repeatability and responsiveness were tested and confirmed (Birring et al., 2003). The Leister cough questionnaire is brief. On average, the LCQ takes five minutes for the patient to complete (Birring et al., 2003; Spinou & Birring, 2014).

Correlations between cough-specific quality-of-life questionnaires with objective measures are well-researched. For instance, a fair to moderate correlation was found between the LCQ and the Cough-Specific Quality-of-Life Questionnaire (CLQC), suggesting their interchangeability (McCrory et al., 2013; Schmit et al., 2013). However, cough specific QoL measures were not designed to measure cough severity directly. They may be, therefore, unable to fully capture the impact of cough severity for individuals with chronic cough (Vernon et al., 2010).

Objective Measures

In response to the lack of objective methods capable of quantifying cough frequency for chronic cough, researchers have designed objective outcome measure tools. (Decalmer et al., 2007; Lee et al., 2012). Objective cough counting has become more accessible in recent years, with programs such as the Automated Device for Asthma Monitoring and Management (ADAMM), which allow users to track their disease state in real-time through an app on their phone (Sterling, Rhee, & Bocko, 2014). The scope of objective measures includes cough frequency and cough reflex sensitivity. Moreover, a study by Kelsall et al. (2011) found that objective measures are useful for the examination of chronic cough by lowering the sample size needed to demonstrate statistically significant results in parallel or cross over designs.

Cough counting. Objective cough measures include ambulatory measures of cough such as the Leicester Cough Monitor (LCM) or custom-built cough recorders, like those used by Decalmer et al. (2007) and Kelsall et al. (2011). Both video recording and audio may be used to count cough objectively. Cough counters, however, are currently unable to describe aspects of cough that may significantly impact a patient, such as cough severity or quality-of-life.

Objective cough counting ranges from automated (such as the LCM) to manual cough counting (used by the VitaloJack). Both manual cough counters and automated cough counts have been found by researchers to correlate well (Hamutcu et al., 2002; Hsu et al., 1994). Researchers Hsu et al. (1994) were able to demonstrate a strong correlation between manual and audio cough counts with EMG signals. Nevertheless, while there is a strong correlation between the two methods, manual cough counts can be difficult to implement for large data sets as they are time-consuming and labor inducive, and therefore limit the feasibility of their application (Decalmer et al., 2007; Smith et al., 2006).

Cough frequency may be quantified through time spent coughing (cough seconds), total cough counts, or cough epochs (also known as cough bouts) (Marsden et al., 2008; Kelsall et at., 2008). Cough seconds and total cough count qualification measures are considered to be interchangeable due to their sufficient correlation and moderate agreement with cough-related quality-of-life questionnaires and cough severity scores. Cough epochs demonstrated a lower correlation, and therefore serve as a weaker alternative (Kelsall et al., 2008).

Although most cough frequency recorders measure 24-hour periods, shorter cough duration recordings of four hours and six hours were found by Lee et al. (2012) to correlate well with 24-hour recordings and subjective measures. Birring (2011) reported that 80% of patient's coughs occur during the daytime, suggesting that shorter duration cough monitoring may be sufficient in demonstrating therapy effectiveness. Currently, the most useful duration for cough monitoring is unknown (Boulet et al., 2015).

A cough counter commonly used in chronic cough research is the Leicester Cough Monitor (LCM). The LSM is a semi-automated ambulatory (audio) device that uses computer software to analyze 24-hour MP3 recordings. These recordings take an average of one hour to process (Birring et al., 2003; Birring & Spinou 2015; Chamberlain et al., 2017; Sterling et al., 2014). LCM measures cough frequency with a sensitivity and specificity of 91% and 99%, respectively, and has been found to be repeatable (Birring et al., 2008; Birring & Spinou, 2015; Lee et al., 2012). As a barrier to its use in research and clinical application, the LCM is not commercially available, making analysis costly.

While cough counting devices are objectively able to demonstrate reduction of cough during clinical trials, it is currently unknown if audio cough counters can accurately account for

cough severity. CHEST guidelines recommend cough counting be used only to assess cough frequency and not cough severity (Boulet et al., 2015).

Cough challenge testing. Cough challenge testing, also known as cough sensitivity testing or cough reflex sensitivity testing, examines the sensitivity of an individual's cough reflex. Typically, this is accomplished using increasing (or doubling) doses of citric acid or capsaicin and placebo doses of saline given in vapor form through a nebulizer. Citric acid or capsaicin serve as cough stimulants, inducing coughing (Decalmer et al., 2007). Researchers record doses that trigger two coughs (C2) and five coughs (C5) within one minute as an individual's baseline sensitivity (Decalmer et al., 2007; Marsden et al., 2008). Of objective testing, cough challenge testing is the most commonly used. Researchers have found cough challenge testing to be reproducible in patients (Birring, 2011; Spinou & Birring, 2014). However, cough challenge testing has been found by some studies to be unreliable in discriminating patients with chronic cough from healthy patients, possibly due to the protocols that terminate challenge testing after the C5 endpoint (Hilton et al., 2013; Spinou & Birring, 2014). Additionally, other studies report that cough challenge testing may be unable to detect the effect of antitussive therapy if the therapy targets a different reflex pathway (Birring, 2010).

Correlation Between Objective Cough Counting and Subjective Measures.

Several studies examined the correlation between cough measures, with varying results. The correlation between subjective measures and objective cough frequency counting tools varied by subjective instrument type and range, from no correlation to a moderate correlation. Unvalidated forms of subjective outcome measures, such as the VAS and cough scores reflected greater variability than validated tools such as the LCQ (a cough specific QoL tool).

Quality-of-life questionnaires. A moderate to strong correlation between cough counting tools and subjective outcome measures and QoL questionnaires was demonstrated by several studies (Decalmer et al., 2007; Faruqi et al., 2011; Kelsall et al., 2011; Lee et al. 2011; Marsden et al., 2008; Schmit et al., 2013). Lee et al. (2011) found a moderate correlation between 24-h and 4-h recordings with HRQoL questionnaires. When compared to other subjective measures, Marsden et al. (2008) found the closest relation between cough counts and the LCQ. Additionally, Decalmer et al. (2007) and Faruqi et al. (2011) found the strongest correlation between the LCQ and manual cough counting measures, with a moderate correlation (Decalmer et al. (2007) $r=-0.62$, $P<0.001$, and Faruqi et al. (2011) $r= -0.6$, $P < 0.001$). Kelsall et al. (2011) were able to demonstrate a response to change via both cough rates and LCQ.

Cough severity visual analog scale (VAS). Researchers found a weak to strong correlation between VAS and cough frequency, varying between total VAS score, day VAS score, and night VAS score (Chamberlain et al., 2017; Decalmer et al., 2007; Faruqi et al., 2011; Kelsall et al., 2011; Key, Holt, Hamilton, Smith, & Earis, 2010; Lee et al., 2012; Marsden et al., 2008; Schmit et al., 2013). Key et al. (2010) found a strong correlation between VAS scores and cough counts with a day score of Pearson's $r = 0.80$ and $p < 0.001$, and a night score of $r = 0.71$, $p = 0.001$. In their study, Lee et al. (2012) reported a moderate correlation of VAS to 24-hour and 4-hour cough frequency recordings. Decalmer et al. (2007) found a moderate positive correlation between VAS scores and objective cough measure for both day and night (Pearson's $r=0.46$, $p<0.001$ for day scores and Pearson's $r=0.61$, $p<0.001$). During their single-blinded randomized-controlled trial investigating physiotherapy, speech and language therapy intervention (PSALTI), Chamberlain et al. (2017) found a more significant reduction in VAS score within the PSALTI group. However, Marsden et al. (2008) found only a weak correlation

between day and night VAS scores and cough frequency rates (Pearson's r=0.32, p=.002 for day scores, r=.43, p=.003 for night scores), and Kelsall et al. (2011) found that overall decrease in cough frequency did not correlate with changes in day VAS scores. Furthermore, Faruqi et al. (2011) found a weaker degree of reproducibility of VAS when compared to the LCQ.

Cough severity measures. Cough scores and the Cough Severity Diary (CSD) demonstrated anywhere from no correlation to a strong correlation with objective frequency counts, varying by study and tool used (Hsu et al., 1994; Marsden et al.; 2008; Nguyen et al., 2020; Schmit et al., 2013; Smith, Owen, Earis, & Woodcock, 2006). Only Nguyen et al. (2020) analyzed the Cough Severity Diary with objective cough counts. Nguyen et al. (2020) compared awake cough counts with the change in CSD score to assess the responsiveness of the instrument, finding a strong-to-moderate correlation between the two measures.

For cough scores, Hsu et al. (1994) found a significant correlation between daytime cough frequency and cough scores ($p<0.01$). These cough score findings were more strongly correlated for patients with chronic cough than patients with asthma. However, Marsden et al. (2008) only found weak correlations between both day and night cough scores and cough rates (Pearson's r=0.32, p<.002 for the day, and r=0.44, p<.001 for the night). Decalmer et al. (2007) found a moderate correlation between cough scores and cough frequency data with day r =0.50, $p<0.00$, and a night r =0.55, $p<0.001$.

Smith et al. (2006) found no correlation between night cough scores and objective measures, and Hamutcu et al. (2002) found no correlation between cough scores and a cough counting recording device (the LR 100) despite a measured reduction in cough frequency. Furthermore, change in cough frequency was not reflected by either day or night cough scores in the study by Kelsall et al. (2011) (P=.05; Wilcoxon, Z = -1.96 for day, and P=.04; Wilcoxon, Z=

-2.03 for night). Smith et al. (2006) found no correlation between the measured reduction in cough counts and cough scores in either the placebo or codeine group.

Correlation Between Cough Challenge Testing and Other Measures

Cough frequency rate decreases were reflected by an increase in cough challenge testing data in a study by Faruqi et al. (2011). However, cough sensitivity did not correlate well with subjective outcome measures. Marsden et al. (2015) found a weak correlation between daytime cough rates for (C2) but no correlation for (C5) while Decalmer et al. (2007) and Chang, Phelan, Robertson, Roberts, and Sawyer (2003) found an inverse correlation between daytime cough rates and logC5 (Decalmer et al. (2007) reported a Pearson's $r = -0.45$, $p<0.001$, and Chang et al. (2003) reported an $r = -0.38$, $p=0.03$). Furthermore, Chamberlain et al. (2017) found no significant difference between PSALTI group and control group for C2 or C5, suggesting cough challenge testing's inability to differentiate between subjects. The PSALTI group, however, demonstrated a reduction in C5 after treatment that was not reflected by the control group, suggesting cough challenge testing may indicate a response to change.

Discussion

Clinical Implications

The purpose of this review is to evaluate optimal outcome measures necessary to determine the effectiveness of treatment for chronic cough. Currently, most outcome measures used in research fail to be validated or standardized. Overall, the poor to moderate level of correlation between objective and subjective tools suggests that the different outcome measures are not interchangeable and assess different constructs. Furthermore, although some studies found an objective decrease in cough counts, the reduction was not always reflected via

subjective outcome measures. This lack of correlation indicates that a decrease in cough counts may not be the sole factor in dictating a patient's perception of cough impact.

Subjective tools measure a wider scope of constructs than objective cough frequency counting or cough challenge testing because they are able to demonstrate patient perception of intensity, severity of cough, and impact on various domains. However, because of subjective measures' overall lack of standardization, researchers are unable to rely on VAS and cough scores alone. More validated measures, such as the Cough Severity Diary (CSD) and Leicester Cough Questionnaire (LCQ) showed the greatest correlation with objective cough counting and indicated responsiveness to change, suggesting that they may better measure aspects of cough that impact a patient’s perception of response to treatment.

Although objective measures fail to account for all aspects of cough that impact patients, the use of cough frequency counting in combination with subjective measures increases the validity of treatment findings. Therefore, in order to obtain a holistic view of cough, researchers should use data from both subjective and objective instruments when determining cough treatment outcomes.

Future Implications

No device currently measures all domains affected by cough. A device with the ability to measure cough severity/intensity, cough disturbance, and cough frequency might account for the variance between objective and subjective measures. Such a device would be beneficial for future studies and clinical trials and may account for the lack of correlation between measures. Furthermore, additional research on the standardization of subjective measures such as VAS, cough scores, and the CSD is needed to determine the validity of their data. Because of the ease of use in a clinical setting, VAS, cough scores, and the CSD should be further researched.

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