Cochrane for Clinicians

Putting Evidence into Practice

Role of Mucolytics in the Treatment of Chronic Bronchitis or COPD

Jeanmarie B. Rey, MD, and Afsoon A. Anvari, MD, Fort Belvoir Community Hospital, Fort Belvoir, Virginia

Author disclosure: No relevant financial affiliations.

Clinical Question

Are oral mucolytics safe and effective at reducing the number of acute exacerbations, days of disability, and hospital admissions in patients with chronic bronchitis or chronic obstructive pulmonary disease (COPD)?

Evidence-Based Answer

Oral mucolytic agents may reduce the number of acute exacerbations in patients with chronic bronchitis or COPD (number needed to treat [NNT] = 8 over an average of nine months; 95% CI, 7 to 10). Although mucolytics do not appear to impact lung function or quality of life, they are associated with a small reduction in days of disability per month (mean difference [MD] = −0.43 days; 95% CI, −0.56 to −0.30) and decreased hospital admissions (NNT for 17 months = 19; 95% CI, 12 to 59). Mucolytics are not associated with an increase in adverse effects.[1] (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

COPD is the fourth leading cause of death in the United States, with the majority of cases attributed to tobacco use.[1,2] COPD is characterized by persistent respiratory symptoms and chronic airflow limitation due to a mixture of small airway disease and parenchymal destruction.[3] Current clinical practice guidelines require spirometry to establish the diagnosis of COPD.[3] Many patients with chronic bronchitis have COPD. Acute exacerbations are the largest contributor to health care costs related to COPD and are characterized by an increase in the volume or purulence of sputum.[1] The authors of this review sought to determine the potential role of mucolytics in the treatment of chronic bronchitis or COPD.

This Cochrane review included 38 randomized controlled trials (published between 1976 and 2017) involving 10,377 participants.[1] The authors looked for placebo-controlled trials investigating a range of oral mucolytic therapy given for at least two months in adults with chronic bronchitis or COPD. The mean age of participants ranged from 40 years to 71 years. A total of 15 studies investigated the use of mucolytics in participants with COPD only, whereas the remaining 23 studies involved participants with chronic bronchitis, COPD, or both. In 13 studies conducted from 1980 to 1999, the diagnosis of chronic bronchitis was made using the British Medical Research Council definition, which does not require spirometry.[4] The primary outcome measured was a reduction in acute exacerbations and/or days of disability. Secondary outcomes included quality of life, lung function, and adverse effects. Studies investigating children or persons with other pulmonary conditions such as asthma and cystic fibrosis were excluded.

This review showed that patients receiving oral mucolytic therapy had a small reduction in the number of acute exacerbations (odds ratio [OR] = 1.73; 95% CI, 1.56 to 1.91; NNT = 8; 95% CI, 7 to 10; 28 studies; 6,723 participants). These results should be interpreted with caution because of high heterogeneity between studies, with larger effects seen in older studies of mucolytics in chronic bronchitis and smaller effects noted in more recent studies. Of note, the severity of COPD as well as the dose and type of mucolytic agent did not alter the effect size of this primary outcome. Mucolytic use was also associated with fewer days of disability per participant per month (MD = −0.43; 95% CI, −0.56 to −0.30; nine studies; 2,259 participants) and a reduction in the number of participants with one or more hospital admissions over the course of 17 months (OR = 0.68; 95% CI, 0.52 to 0.89; NNT = 19; 95%

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CI, 12 to 59; five studies; 1,833 participants). Subgroup analysis showed no significant difference in groups of participants being treated concurrently with inhaled corticosteroids. This suggests that the effect of mucolytics is independent of inhaled corticosteroid use.

Forced vital capacity was evaluated in 12 studies, with results favoring mucolytics over placebo; however, results were not statistically significant. Pooled results from studies that measured health-related quality of life using the validated St. George's Respiratory Questionnaire favored mucolytics over placebo; however, the effect did not meet the minimum clinically important difference of –4 units, and the MD for this secondary outcome was not statistically significant. Mucolytic agents did not appear to be associated with a significant increase in adverse effects.

Current clinical practice guidelines offer a range of recommendations regarding the use of mucolytic agents in the treatment of COPD.[3,5-8] Most clinical practice guidelines recommend that mucolytic therapy be considered for certain patients with COPD to reduce the number of exacerbations.[3,5-7] This recommendation is consistent with the findings of this Cochrane review. Further research is needed to assess the role of mucolytics in the treatment of chronic bronchitis and COPD with regard to symptom severity, quality of life, disease progression, and mortality.

The practice recommendations in this activity are available at http://www.cochrane.org/CD001287.

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References

1. Poole P, Sathananthan K, Fortescue R. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2019;(5):CD001287.
2. Centers for Disease Control and Prevention. Disease of the week. COPD. Updated November 5, 2019. Accessed November 8, 2019. https://www.cdc.gov/dotw/copd/
3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2019 report). Accessed October 30, 2019. https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf
4. Definition and classification of chronic bronchitis for clinical and epidemiological purposes. A report to the Medical Research Council by their Committee on the Aetiology of Chronic Bronchitis. *Lancet*. 1965;1(7389):775-779.
5. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. NICE guideline [NG115]. Updated July 2019. Accessed October 30, 2019. http://www.nice.org.uk/guidance/ng115
6. Wedzicha JA, Calverley PMA, Albert RK, et al. Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. 2017;50(3):1602265.
7. Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society guideline. *Chest*. 2015;147(4):894-942.
8. Department of Veterans Affairs, Department of Defense. VA/DoD clinical practice guideline for the management of chronic obstructive pulmonary disease. December 2014. Accessed October 30, 2019. https://www.healthquality.va.gov/guidelines/CD/copd/VADoDCOPDCPG2014.pdf

Nicotine Replacement Therapy for Smoking Cessation

Kathleen Barry, MD, and Jorge Finke, MD

University of Massachusetts Medical School, Worcester, Massachusetts

Author disclosure: No relevant financial affiliations.

Clinical Question

Does combining long-acting and short-acting nicotine replacement therapy (NRT) help patients quit smoking? Is any single form of NRT more effective than another?

Evidence-Based Answer

Patients using a combination of nicotine patch and fast-acting NRT are more likely to quit smoking than those on any single therapy alone (number needed to treat [NNT] = 29; 95% CI, 20 to 47). Rates of smoking cessation are not significantly different when directly comparing nicotine patches with fast-acting forms (e.g., lozenges, gum, inhalers, sprays), although dropout rates are higher with fast-acting forms. Rates of smoking cessation do not significantly differ among the various fast-acting forms.[1] (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

In 2017, roughly 47.4 million U.S. adults (19.3%) used tobacco products; cigarettes were the most commonly used product.[2] Tobacco use is a leading cause of preventable illness and death worldwide, accounting for more than 7 million deaths annually.[1] Although two-thirds of smokers are interested in quitting, less than one-third use evidence-based cessation aids, and less than 10% successfully quit annually.[3] The authors of this review sought to determine the effectiveness and safety of different formulations, doses, durations, and schedules of NRT.

This review included 63 randomized controlled trials, involving 41,509 participants, that compared various forms of NRT with a primary outcome of smoking cessation at six months (with or without additional 12-month follow-up) and a secondary outcome of cardiac adverse effects.[1] Participants were 45 years of age on average and smoked at least one pack per day.

High-quality evidence gathered from 14 randomized controlled trials with 11,356 participants suggested that a combination of nicotine patches and fast-acting NRT (e.g., lozenges, gum, inhaler, oral spray) yielded better smoking cessation rates than either single therapy alone (absolute risk reduction [ARR] = 3.5%; 95% CI, 2.1% to 5%; NNT = 29; 95% CI, 20 to 47) with no statistically significant difference in adverse effects. The duration of combination therapy did not appear to impact quit rates. One study of 402 participants comparing 50-week gum use and 10-week gum use found no difference in smoking cessation rates (ARR = 1.7%; relative risk [RR] = 1.04; 95% CI, 0.82 to 1.32). Three studies, with a combined 2,168 subjects, compared treatment durations of patch plus gum at intervals between two and 26 weeks, and found no difference in cessation rates.

Quit rates for 21-mg patches alone were higher than for 14-mg patches alone (NNT = 12), but increasing doses up to 44 mg had no added benefit. Dropout rates were lower with the patch (five per 1,000) compared with fast-acting forms (23 per 1,000; number needed to harm = 56; 95% CI, 17 to 222; RR = 4.23; 95% CI, 1.54 to 11.63; three studies; 1,482 participants). None of the eight studies (3,319 participants) that compared a form of fast-acting NRT with nicotine patches found a statistically significant difference in rates of smoking cessation (RR = 0.90; 95% CI, 0.77 to 1.05). The 4-mg gum alone resulted in greater smoking cessation rates than the 2-mg gum alone (RR = 1.85; 95% CI, 1.36 to 2.50) in high-dependency smokers, but there was no difference in low-dependency smokers, as defined by established dependency scales.

The cost, dosing schedule, and whether the formulation was chosen by the patient or the physician did not affect cessation rates. Other smoking cessation aids, such as bupropion (Wellbutrin) and varenicline (Chantix), were not examined in this review.

The U.S. Preventive Services Task Force (USPSTF) recommends using a combination of behavioral interventions and pharmacotherapy for all nonpregnant smokers who are trying to quit. According to the USPSTF, the best and most effective combinations are those that are acceptable to and feasible for the patient.[4] This review demonstrates that there are multiple effective nicotine replacement interventions, allowing flexibility for patients to choose the method that will work best for them.

The practice recommendations in this activity are available at http://www.cochrane.org/CD013308.

Editor's Note: The numbers needed to treat and harm, confidence intervals, absolute risk reductions, and relative risks reported in this Cochrane for Clinicians were calculated by the authors based on raw data provided in the original Cochrane review.

References

1. Lindson N, Chepkin SC, Ye W, et al. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev.* 2019;(4):CD013308.
2. Babb S, Malarcher A, Schauer G, et al. Quitting smoking among adults—United States, 2000-2015. *MMWR Morb Mortal Wkly Rep.* 2017;65(55):1457-1464.
3. Wang TW, Asman K, Gentzke AS, et al. Tobacco product use among adults — United States, 2017. *MMWR Morb Mortal Wkly Rep.* 2018;67(44):1225-1232.
4. U.S. Preventive Services Task Force. Final recommendation statement: tobacco smoking cessation in adults, including pregnant women: behavioral and pharmacotherapy interventions. September 15, 2015. Accessed December 15, 2019. https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1 ■