

Managing Cough Without Codeine in the Urgent Care Setting

Urgent message: Opioid prescribing and opioid-related deaths have risen during the COVID-19 pandemic. Although supported in some scenarios by the CHEST Diagnosis and Management of Cough and NICE COVID-19 guidelines, it is time to reevaluate the appropriateness of using codeine in suppressing cough.

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Citation: Penner M, Jang H. Managing cough without codeine in the urgent care setting. *J Urgent Care Med.* 2022;17(3):46-47.

Clinical Scenario

A 54-year-old female with a past medical history of diabetes, hypertension, and depression presents to the urgent care center with congestion, nasal discharge, fatigue, and cough with symptoms starting 5 days prior to presentation. The patient is diagnosed with a viral respiratory tract infection and prescribed oral guaifenesin with codeine. The question is, are codeine-based antitussives really the safest and most efficacious agents for treating cough?

Introduction

Codeine is an opioid which exerts its antitussive effect by mediating mu and kappa opioid receptors in the medulla. Although considered a weak opioid, codeine is converted via cytochrome P450 (CYP) 2D6 to morphine and exerts its analgesic effects via this pathway. Codeine is often paired with anticholinergic and/or expectorant medications such as promethazine or guaifenesin to alleviate the symptoms of cough or related pain and congestion.

Therapies for cough are limited, with opioids and dextromethorphan being the two centrally acting antitussives, and benzonatate acting as a peripheral antitussive through local anesthetic effects. Patients often seek care after already trialing over the counter cough



suppressants.

The 2006 CHEST Diagnosis and Management of Cough guidelines recommend against centrally acting cough suppressants such as codeine and dextromethorphan for upper respiratory tract infections (URI) but endorse consideration of short-term therapy for chronic bronchitis, postinfectious cough, and other conditions if alternate agents have failed.¹ Since publication of the 2006 guidelines, CHEST has published

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additional guidelines and expert panel reports regarding cough; however, these subsequent guidelines do not address priority of antitussive therapy utilization.

Management of cough has become critical in the COVID-19 pandemic. The NICE COVID-19 guidelines recommend starting with simple measures for cough management such as consuming honey, but also recommend consideration of a short trial of codeine or morphine.²

It is important to note that these recommendations are based on consensus rather than an evidence-based framework.

Therapeutics

Because of genetic variances in CYP2D6 metabolism, patient response to codeine can be unpredictable. This metabolism and subsequent risk for respiratory depression led to the boxed warning and contraindication for use in children.³

In addition to the variable response, codeine's CYP450 activity poses risk for many drug interactions. Although less potent than other opioids, codeine still carries the typical opioid risks such as constipation, hypotension, sedation, and respiratory depression. (This "low-potency" opioid isn't looking so harmless anymore, right?)

While codeine has shown some effect on time spent coughing compared with given baseline, studies have shown no significant difference when compared with placebo. Additionally, studies have shown no significant differences in cough challenge thresholds or subjective cough measured for codeine compared with guaifenesin and dextromethorphan.^{4,5}

Although limited head-to-head comparisons have been published, the side effects of guaifenesin and benzonatate are minute compared with codeine.

Also, the formulation of codeine combined with promethazine is frequently utilized for cough suppression. This formulation is high risk for respiratory and central nervous system depression and has the associated common name of "purple drank" when being misused for recreational purposes. In addition to the additive central nervous system depression, promethazine carries the risk of anticholinergic side effects such as dry mucous membranes and sedation.

Dextromethorphan, which is structurally related to codeine, is also metabolized by CYP2D6, but exerts its antitussive effects through blockade of sigma opioid receptors rather than the mu and kappa opioid receptors which are associated with analgesia and euphoria. Dextromethorphan also acts as an antagonist at N-methyl-

D-aspartate (NMDA) receptors, which can lead to dissociation effects and hallucinations if misused. This risk escalates when paired with codeine.

Dextromethorphan also has serotonergic properties which should be considered before using for a patient with multiple serotonergic medications at baseline because of the risk of serotonin syndrome. Dextromethorphan cannot be used with a concomitant monoamine oxidase inhibitor (MAOI) or within 2 weeks of its discontinuation.

Benzonatate, a local anesthetic, is FDA-approved for cough management in adults. Side effects are rare, given its local action. Benzonatate requires a prescription.

Guaifenesin does not suppress cough, but acts as an expectorant by reducing viscosity of mucus and increasing hydration of the respiratory tract. Adverse effects with guaifenesin are also rare and usually limited to gastrointestinal irritation.

Many over-the-counter cold medications will contain multiple agents, so it is important to get a detailed history on the ingredients that have been trialed before moving on to opioid therapy. Additionally, non-pharmacologic treatments for cough such as increasing hydration, air humidification, eating 1-2 teaspoons of honey, utilizing cough drops, and breathing techniques should be used along with pharmacologic therapies.

Conclusion

Returning to the reference case: If the patient takes metformin, liraglutide, losartan, atorvastatin, escitalopram, and buspirone at home, how will this impact our medication choice? Both codeine and dextromethorphan will increase the serotonergic effect of escitalopram. Thus, guaifenesin should be trialed first to also assist with the congestion. Benzonatate could also be used. If these fail, dextromethorphan should be trialed before moving on to codeine. Although data regarding efficacy of cough suppressants are sparse, the available literature highlights the risks—and lack of benefits—of opioids. ■

References

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