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# Common Respiratory Diseases

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## KEYWORDS

- Complementary and alternative medicine
- Herbs • Upper respiratory infections
- Chronic obstructive pulmonary disease
- Asthma • Rhinosinusitis

The incidence of acute respiratory conditions in the United States and around the world (eg, West Nile virus, influenza A virus subtype H1N1, severe acute respiratory syndrome) and the burden of chronic respiratory conditions (eg, asthma, chronic obstructive pulmonary disease [COPD]) continue to increase and cause concern.

Human parainfluenza viruses (HPIVs) and respiratory syncytial virus (RSV) are a common cause of upper respiratory tract disease in young children. They spread from contact with respiratory secretions on contaminated surfaces or close contact with infected persons. No curative treatment or vaccines are currently available to protect against infection caused by any of these viruses.

RSV can cause substantial morbidity in older adults. Although RSV and influenza cause considerable individual morbidity, the burden of disease from rhinovirus infections and infections of unknown etiology seems greater. The interval between onset of illness and consultation together with diagnostic difficulties raises concern regarding the role of antiviral drugs in treating influenza.

Asthma is also common. Recent data from the Centers for Disease Control and Prevention (CDC) ([www.cdc.gov](http://www.cdc.gov)) indicate that 16.2 million adults and 6.7 million children currently have asthma, resulting in 10.6 million visits to office-based physicians and a minimum of 444,000 hospital stays.

COPD (a group of diseases characterized by airflow obstruction associated with breathing-related symptoms) was the underlying cause of death for 718,077 persons aged 25 years and older in the United States between 2000 and 2005. From 2000 to 2005, the annual number of deaths from COPD increased 5% among men and 11% among women.

Studies about the use of complementary and alternative medicine (CAM) have documented a high use of CAM therapies for conditions that are chronic and lack

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Prim Care Clin Office Pract 37 (2010) 297–324

doi:10.1016/j.pop.2010.02.007

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a cure such as asthma,<sup>1</sup> rhinosinusitis,<sup>2</sup> and COPD.<sup>3</sup> In this article, the authors review the most common natural therapies used for the treatment of the common cold, rhinosinusitis, asthma, and COPD.

## COMMON COLD

Viral upper respiratory infection (URI) accounts for a high number of people missing work or school, and represents the leading acute diagnosis in the office setting each year in the United States alone.<sup>4</sup> The common cold is caused by several viral organisms such as adenoviruses, myxoviruses, coronaviruses, picornaviruses. The most common viral cause is the *Rhinovirus* (10%–25%). Usually, patients recover in 7 to 10 days. Complications are usually related to extension of infection to the lower respiratory tract (eg, bronchitis, pneumonia) or nasal ostia and eustachian tubes (eg, sinusitis, otitis media). Usual care is mainly symptomatic and supportive. The most commonly known or marketed natural supplements are described in this article. However, health professionals should know that herbalists and natural health care providers most often use a combination of herbs, supplement, aromatherapy, and so forth, to treat symptoms or for their antimicrobial properties. Discussion of such formulas is beyond the scope of this article. A summary is presented in **Table 1**.

### ***Andrographis (Andrographis paniculata)***

*Andrographis paniculata* is an annual herb. The leaves are used traditionally in Asian traditional medicine and particularly Ayurveda to treat fever associated with infections. Approximately 28 species of *Andrographis* are known and indigenous to Asia. *A paniculata* is the most commonly used. *Andrographis* is also used for other medical conditions; for example, digestive problems, blood cleanser, fever, sore throat, and URIs.

In a systematic review by Coon and Ernst<sup>5</sup> in 2004, 7 double-blind controlled trials (N = 896) met the criteria for evaluation of efficacy. All trials scored at least 3 out of 5 in methodological qualities. The dose of *Andrographis* used ranged from 48 to 360 mg. *A paniculata* alone or in combination with *E senticosus* seem promising in the treatment of uncomplicated URI symptoms. In the highest quality study<sup>6</sup> a fixed combination of standardized extract of the leaves of *A paniculata* 60 mg/d and the roots of *E senticosus* 120 mg/d given to patients with uncomplicated URIs within 36 hours of the onset of symptoms. Outcome measures were patient and physician evaluation of severity of symptoms based on predefined criteria. Significant improvement was noted in patient-measured symptoms ( $P = .0006$ ) and physician-measured assessments ( $P = .003$ ). Improvement was noted in symptoms such as muscle ache, cough frequency, presence of productive cough, fever, and sore throat.

Another meta-analysis published in the same year identified 4 qualifying studies (N = 433) and reported similar improvements in symptom severity in favor of the combination *A paniculata* and *E senticosus*.<sup>7</sup> A large (N = 200) nonrandomized study, using the same fixed combination of standardized extract (leaves of *A paniculata* 60 mg/d and the roots of *E senticosus* 120 mg/d) given for 5 days, found a significant difference between the mean symptom scores between groups at the end of the treatment ( $P < .001$ ).<sup>8</sup> Headaches, nasal and throat symptoms, and general malaise showed the most improvement. In another 2 randomized controlled trials, subjects received 60 mg/d of *A paniculata* with 48 to 72 hours of the onset of URI symptoms; statistically significant improvement in symptoms was reported within 4 to 5 days.<sup>9,10</sup> In a study comparing 180 or 360 mg/d of *A paniculata* with paracetamol (3.9 g/d), subjects randomized to paracetamol and high-dose *A paniculata* reported statistically significant improvement in symptoms by day 3.

| <b>Name</b>                                | <b>Suggested Dose</b>                    | <b>Drug Interactions</b>   | <b>Side Effects</b>  | <b>Scientific Evidence of Efficacy</b>             |
|--|--|--|--|--|
| <i>Andrographis paniculata</i>             | 48–360 mg/d                              | No specific interactions noted. In vivo and in vitro can inhibit the activity of CYP2C9 and CYP3A4               | Allergic reaction; 3 reports of anaphylactic shock (1) or reaction (2)<br>Avoid if attempting to conceive    | Good evidence of effectiveness                     |
| Vitamin C (ascorbic acid)                  | 2–8 g/d                                  |  | Diarrhea, renal lithiasis in high doses  | Equivocal  |
| Goldenseal ( <i>Hydrastis canadensis</i> ) | 250–500 mg/d of extract or dried root    | Interacts with CYP450–3A4 in vivo, but no known evidence in vitro  | Well tolerated. Low evidence of gastrointestinal problems, ulceration, nephritis. Avoid during breastfeeding | No well-designed studies                           |
| <i>Echinacea</i> sp                        | 1–5 g/d in 3 divided doses of crude herb | No documented drug interaction, but is known to inhibit activity of CYP450–3A4                                   | Well tolerated. Caution if allergic to daisies   | Supportive for treatment; equivocal for prevention |
| Zinc gluconate                             | 4.5–23.7 mg                              | Increases level of zinc: amiloride<br>Decreases level of zinc: ACE inhibitors; antibiotics; cisplatin; thiazides | Lowers HDL; potential urinary problems (BPH and lithiasis). Caution with nasal spray gel: loss of smell      | Equivocal  |

Abbreviations: ACE, angiotensin-converting enzyme; CYP, cytochrome.

The safety profile of *A paniculata* is very favorable with a few reports of allergic reaction and 1 report of anaphylactic shock and 2 reports of anaphylactic reaction in the early 1990s from Sweden. Data are lacking about the safety of *A paniculata* for pregnant or breastfeeding women and should be avoided. In addition, some experimental reports indicate that *A paniculata* might have a contraceptive effect; therefore, its use should be avoided in men or women attempting to conceive.

Overall, the evidence suggests that *A paniculata* alone or in combination with *E senticosus* could be effective in the treatment of uncomplicated acute upper respiratory tract infection.

### ***Vitamin C (Ascorbic Acid)***

Ascorbic acid is a water-soluble vitamin necessary to form collagen, cartilage, absorption of iron, and formation of blood vessels. It is found naturally in fruits (eg, citrus) and vegetables.

Interest in the use of vitamin C for the treatment and prevention of the common cold was heightened following the publication in 1970 of Nobel Prize winning scientist Linus Pauling's book *Vitamin C and the common cold*. He followed that by conducting several meta-analyses demonstrating a decrease in the incidence and in the number of days of illness following the use of vitamin C. Since then, controversy has arisen with several trials reporting a benefit (mainly in populations who had low vitamin C intake or < physical stress) and others reporting no benefit. Initial reviews indicated that despite the heterogeneity of the studies, supplementation with vitamin C at doses of 1 g/d or more consistently decreased the duration or alleviated the symptoms of the common cold.<sup>11,12</sup> In 2007, a meta-analysis by the Cochrane review group<sup>13</sup> attempted to answer the question: does vitamin C in doses of 0.2 g daily or more, reduce the incidence, duration, or severity of the common cold when used either as continuous prophylaxis or at the onset of cold symptoms.

Data from 11 different trials involving 3294 cold episodes where participants initiated supplementation at the onset of cold symptoms were included. The data from the therapeutic trials do not provide convincing evidence of reduced duration of colds when treatment commenced after common cold symptoms began. Eight trial arms, which included 2753 separate respiratory episodes for which cold severity was assessed, were also reviewed. Analysis of these results similarly found no meaningful difference between vitamin C and placebo groups in the severity of cold episodes when treatment commenced after common cold symptoms began.

Questions remain about the overall efficacy of vitamin C in the treatment of common cold symptoms. Although no firm conclusions can be drawn, some evidence suggests the following strategies could be helpful: (1) vitamin C is more effective in reducing cold symptoms and duration if the initiation of treatment is within 24 hours of the onset of symptoms; (2) vitamin C may be more effective in subjects with a low level of vitamin C or who are undergoing high physical or mental stress; (c) higher doses of vitamin C (4 g or higher) are more effective than lower doses. None of the vitamin C common cold trials reported evidence that vitamin C is harmful in doses that were tested.

### ***Echinacea (Echinacea angustifolia, Echinacea purpurea, Echinacea pallida)***

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*Echinacea* species is widely used and marketed to improve the immune system response during colds and flu. The exact mechanism of action for the immune-stimulating effects of *Echinacea* preparations remains unclear. Four compounds are believed to contribute to the immunomodulatory activity of *Echinacea* extracts: alkaloids, glycoproteins, polysaccharides, and caffeic acid derivatives. These seem to activate the alternate complement pathway components, and increased levels of T lymphocytes and natural killer cells.<sup>14</sup> In addition, *Echinacea* extracts increase the macrophage proliferation and phagocytosis, as well as secretion of interferon, tumor necrosis factor, and interleukin-1 (in vitro and in vivo).<sup>15-17</sup> A Cochrane Review identified 9 trials (N = 1126) with a total of 10 *Echinacea* groups diagnosed with common cold symptoms, randomized and treated with *Echinacea*.<sup>18</sup> Pressed juices (stabilized with alcohol), alcohol tinctures, or tablets made from dried extracts were the forms of *Echinacea* used. Outcome measurements were heterogeneous. Treatment groups often used different instruments, timing of measurements, type of analysis, and descriptive statistics. Among the 2 trials with no comparison groups, 1 study among children receiving pressed juice of *E purpurea* herb reported positive results.<sup>19</sup> When *Echinacea* preparations were compared with placebo as treatment, a significant effect was reported in 9 comparisons, a trend in 1, and no difference in 6. Overall, the clinical evidence for the efficacy of *Echinacea* for treating common cold symptoms remains unclear.

### ***Goldenseal (Hydrastis Canadensis)***

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Goldenseal is native to eastern North America and is traditionally used by Native Americans for the treatment of inflammation of the respiratory, digestive, and urinary tracts. The 2 primary alkaloids found in goldenseal are berberine and hydrastatine. Goldenseal has a strong astringent property, which is traditionally used to help ease the discomfort of sore throat. Herbalists often recommend goldenseal in combination with *Echinacea* for the treatment of colds and flu. However, there are currently no well-designed studies evaluating goldenseal either alone or in combination with *Echinacea*. Goldenseal is not recommended for pregnant or breastfeeding women.

### ***Zinc***

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Zinc is an essential mineral that is naturally present in some foods (mollusks, oysters, meat, poultry, beans, nuts, whole grains, cereals, and so forth), and available as a -dietary supplement. Data from National Health and Nutrition Examination Survey (NHANES III) indicate that 35% to 45% of adults aged 60 years or older had zinc intakes less than the estimated average requirement of 6.8 mg/d for elderly women and 9.4 mg/d for elderly men.<sup>20</sup> Mild to moderate degrees of zinc deficiency can impair the function and activity of the immune system, particular T lymphocytes.<sup>21,22</sup> Zinc is commonly used for a variety of conditions such as wound healing, skin ulcers, and smell and taste disorders. It is also marketed in a variety of forms for treatment of viral infections such as herpes simplex and URI.

Initial evidence from rigorous scientific trials of zinc and its effects on cold symptoms came from inoculation studies.<sup>23,24</sup> Neither trial found a direct effect on viral shedding, in either magnitude or duration. A more recent randomized, double-blind, controlled trial of 100 employees of the Cleveland Clinic using zinc gluconate (13.3 mg) every 2 hours reported significant reduction in the duration of symptoms of the common cold.<sup>25</sup> A 7-month placebo-controlled trial<sup>26</sup> (15 mg zinc sulfate daily as a prophylactic, 15 mg twice daily after onset of cold and until symptoms resolved) reported a drop in the mean number of colds (1.2 vs 1.7;  $P = .003$ ), the mean number of cold-related absences (0.9 days vs 1.3 days;  $P = .04$ ), and shorter duration of cold symptoms in the zinc group versus placebo ( $P < .0001$ ).

A meta-analysis<sup>27</sup> identified 8 trials using zinc gluconate on patients in whom colds were developing de novo in the community. Doses of zinc gluconate used ranged from 4.5 to 23.7 mg. The odds ratio for the presence of any cold symptoms at 7 days was 0.52 (95% confidence interval, 0.25–1.2) indicating that the evidence for effectiveness of zinc lozenges in reducing the duration of common colds is still lacking. Overall, the current evidence is weak for the efficacy of zinc gluconate lozenges in reducing cold duration.

Zinc is considered relatively safe when taken at recommended doses. Few studies report side effects such as nausea, vomiting, or diarrhea. High-dose zinc has also been associated with a potential reduction in (1) serum copper level, (2) lymphocyte stimulation, and (3) high-density lipoprotein (HDL) and a higher incidence of urinary problems among men, such as benign prostatic hyperplasia (BPH) and renal lithiasis. Recent warnings regarding intranasal gel/spray have been posted by the US Food and Drug Administration for possible loss of smell.

### ***Other Therapies***

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Chinese herbs and formulas have also been evaluated for their potential benefit in treating the common cold. A Cochrane meta-analysis<sup>28</sup> identified 14 studies involving 2440 patients. All studies were rated of low or poor quality. There was high probability

of biases in all of the studies included. Different Chinese herbal preparations were tested in nearly all trials. In 6 studies, 5 herbal preparations were found to be more effective at enhancing recovery than the control; in the other 8 studies, 5 herbal preparations were shown to be equal to the control. Based on this review, the investigators concluded that they were unable to recommend any kind of Chinese herbal preparation for the common cold.

Recently, over-the-counter products (such as Airborne) marketed for the treatment and prevention of the common cold have gained particular notoriety and popularity. A review of this product reveals that it contains several ingredients such as zinc (8 mg), *Echinacea* (350 mg), and vitamins A, C, E, riboflavin, minerals (sodium, magnesium, selenium, potassium) as well as other herbs such as ginger, Chinese vitex, forsythia, and so forth. A review of the literature and the manufacturer's Web site highlight several testimonials but no scientific evidence of efficacy.

### **RHINOSINUSITIS/ALLERGIC RHINITIS**

The CDC defines rhinosinusitis (previously referred to as sinusitis) as an inflammation of the mucosa of the sinuses and paranasal structures. It affects 31 million individuals in the United States each year with an estimated annual cost of \$5.8 billion.<sup>29</sup> Patients with bacterial sinusitis often report symptoms for more than 7 days, facial and/or teeth tenderness and purulent nasal discharge. Viruses account for most cases of rhinosinusitis and most cases resolve spontaneously. Rhinosinusitis remains the fifth leading reason for which antibiotics are prescribed. Antibiotics should be reserved for patients with bacterial symptoms. Surveys indicate that 24% to 32% of subjects with chronic rhinosinusitis use herbal therapy either alone or in combination with other treatments.<sup>30</sup>

Allergic rhinitis is a common condition. Current estimates indicate that more than 50 million people in the United States suffer from allergic rhinitis. It is the most prevalent chronic condition in patients less than 18 years of age. People affected by the condition often report fatigue and upper respiratory symptoms. Allergic rhinitis also leads to 40% to 80% of cases of chronic rhinosinusitis.<sup>31</sup>

In this section, the most common natural supplements marketed for the treatment of rhinosinusitis are reviewed.

#### ***Vitamin C (Ascorbic Acid) and Other Vitamins***

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Vitamin C is reported to inhibit histamine secretion by white blood cells.<sup>32</sup> There seems to be an inverse relationship between the ascorbic acid levels in the plasma and histamine levels. Initial studies show that oral supplementation of vitamin C can reliably lower blood histamine levels.<sup>33</sup> In a prospective trial, blood levels of several vitamins and minerals were evaluated in children ( $n = 24$ , mean age 9.2 years) with chronic rhinosinusitis and compared with healthy controls ( $n = 20$ ). Vitamin C, vitamin E, copper, and zinc levels were significantly lower in the chronic sinusitis group compared with controls.<sup>34</sup> Vitamin C might hold promise in the management of rhinosinusitis; however, evidence at this time does not allow for a definite conclusion.

#### ***Urtica dioica (Stinging Nettle)***

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*Urtica dioica*, also known as stinging nettle, has been traditionally used to treat allergic rhinitis. The exact mechanism of action is not known; however, studies do indicate that the plant is nutrient dense and that histamine, serotonin, and acetylcholine are present in the plant's hairs.<sup>35</sup> The authors could not identify any clinical studies on the use of stinging nettle for sinusitis; however, in 1 randomized, double-blind clinical trial,

subjects (n = 69) who took freeze-dried (300 mg twice daily) *Urtica dioica* for the treatment of allergic rhinitis achieved positive results. All treated subjects reported improved global assessments, with 58% noting symptom abatement and 48% recording equivalent or increased response with *Urtica dioica* compared with previous medicine.<sup>36</sup> The safety of stinging nettle for women who are pregnant or breastfeeding has not been established. Caution is advised for patients with diabetes, bleeding disorders, and those on diuretics.

### ***Bromelain***

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Bromelain, a proteolytic enzyme obtained from pineapple, has commonly been used to treat rhinosinusitis as an antiinflammatory and mucolytic.<sup>37</sup> Bromelain seems to thin nasal secretions<sup>38</sup> in addition to its proteolytic activity at inflammatory sites, which is believed to promote the inhibition of proinflammatory prostaglandin biosynthesis.<sup>39</sup>

A study of children with acute sinusitis reported faster symptom recovery in children on bromelain compared with standard treatment.<sup>40</sup> This confirmed findings from an earlier double-blind study in which 85% of patients with acute and chronic sinusitis receiving bromelain had complete resolution of inflammation of the nasal mucosa ( $P < .05$ ) compared with 40% in the placebo group.<sup>41</sup> Initial studies on bromelain seem to be encouraging but more evidence is needed.

Bromelain oral dosage is typically 500 to 1000 mg/d. Side effects include allergic reaction to bromelain, indigestion, nausea, and diarrhea. The safety of bromelain for pregnant or nursing women, children, or people with liver or kidney disease is not known.

### ***Quercetin***

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Quercetin is found in many foods such as onions and apples. Its antiinflammatory activity seems to be a result of its antioxidant and inhibitory effects on inflammation-producing enzymes.<sup>42,43</sup> Quercetin is also found to stabilize mast cells, which inhibit release of histamine.<sup>44,45</sup> Clinically, quercetin seems to be helpful in the management of allergic rhinitis and seems to be therapeutically similar to cromolyn sodium and oral antihistamine. In a small study (n = 12) a nasal spray formulation containing an extract of quercetin was given immediately after the appearance of characteristic allergic nasal symptoms. All patients experienced a rapid and significant symptom relief of nasal symptoms, comparable with the effect of antihistamine and chromoglicate preparations. The effect was felt within minutes after the administration and lasted for several hours.<sup>46</sup> Despite the positive initial evidence, no additional studies have been published to confirm these findings.

The common oral dose of 400 to 500 mg 3 times per day is typically used. Quercetin is generally safe. At large doses, there are some anecdotal reports of joint pain and gastric discomfort.

### ***Butterbur (Petasites hybridus)***

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Butterbur is a plant in the daisy family (Asteraceae). Butterbur is a robust plant with thick rhizomes and large rhubarb-like leaves that contain active compounds believed to be petasins, a group of sesquiterpenes. Butterbur was used traditionally as a remedy for headache and inflammation. Clinical studies suggests that butterbur (standardized extract Ze 339; 1 tablet 3 times daily) may effectively prevent allergic rhinitis similar to fexofenadine (Allegra) and cetirizine (Zyrtec) in susceptible individuals.<sup>47,48</sup> However a study focusing on intermittent rhinitis is conflicting and suggest that it is no better than placebo.<sup>49</sup> The evidence is encouraging that butterburr may prevent allergic rhinitis



but additional studies are needed to confirm this. Patients with liver disease or dysfunction should avoid raw butterbur extract because of the potential for hepatotoxicity. Avoid if pregnant, breastfeeding, or allergic to butterbur.

### **Other Therapies**

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#### **Acupuncture**

The World Health Organization identifies acupuncture as an effective treatment of allergic rhinitis, including hay fever. Several small trials report beneficial effect for allergic rhinitis and allergies. For example a 2004 randomized clinical study compared active versus sham acupuncture for 12 months in 40 consecutive patients with allergic rhinitis and a positive skin test. For 1 allergen, mugwort, a greater reduction in levels of specific immunoglobulin E (IgE) ( $P = .019, 0.039$ ) and skin test reaction ( $P = .004$ ) was seen in the group receiving active acupuncture compared with the group receiving sham acupuncture.<sup>50</sup> However, a recent systematic review identified 7 randomized controlled trials (RCTs), generally of poor quality, with the exception of 2 high-quality studies, as assessed by Jadad scale.<sup>51</sup> A wide variety of outcomes were measured but most assessed symptom severity on a visual analog scale. A meta-analysis failed to show any benefits of acupuncture treatment on symptom severity scores or serum IgE measures that could not have been accounted for by chance alone. Acupuncture studies looking at the treatment of sinusitis did not show an advantage over conventional treatments.<sup>52,53</sup> These findings were confirmed by a recent systematic review of 7 high-quality RCTs.<sup>54</sup> Two RCTs compared acupuncture with oral pharmacologic medications and reported positive results in favor of acupuncture. One study reported favorable effects of acupuncture on a rhinitis symptom score and 1 found positive results for a nasal symptom score compared with placebo acupuncture. Three RCTs failed to demonstrate a beneficial effect of acupuncture in treating or preventing symptoms of allergic rhinitis.

Overall the evidence for the effectiveness of acupuncture for the symptomatic treatment or prevention of allergic rhinitis remains mixed. Studies fail to show beneficial results for seasonal allergic rhinitis although some suggest evidence of effectiveness in the management of perennial allergic rhinitis.

#### **ASTHMA**

Asthma is a chronic inflammatory disease of the airways characterized by reversible airflow restrictions and associated symptoms of wheezing, chest tightness, and shortness of breath.<sup>55,56</sup> In the United States, it affects 22 million people of all ages, races, and ethnic groups, and is 1 of the most common chronic diseases of childhood.<sup>56,57</sup> There are clear allopathic guidelines for treatment according to disease severity,<sup>57</sup> but the use of CAM for asthma is widespread. A survey by the National Asthma Campaign in the United Kingdom found that 60% of people with moderate asthma and 70% with severe asthma had used CAM to treat their condition, and of the minority who had not yet used CAM, 67% indicated they would consider using CAM for their asthma in the future.<sup>55</sup> A survey of CAM use in by people with asthma or rhinosinusitis in the United States found that 42% of the study population had used some form of CAM for their condition in the 12 months before the study.<sup>58</sup>

The most popular forms of CAM for asthma include herbs, breathing techniques (including mind-body relaxation techniques), homeopathy, and acupuncture.<sup>55,59</sup> Studies on why patients turn to CAM treatments reveal a desire for personal control over treatment, the perception of effectiveness, safety, being more natural or holistic,

as well as dissatisfaction with side effects, costs, provider interaction, and approaches of conventional methods (Tables 2 and 3).<sup>60–64</sup>

Given the prevalence of CAM use for asthma, and because most patients (>80%) who use CAM are simultaneously using allopathic treatments,<sup>58,65</sup> it is important for allopathic physicians to be aware of the common types CAM treatments being used, and be able to counsel patients on current evidence for efficacy, risks, and potential interactions between therapies, especially involving herbs and pharmaceuticals.

### **Herbals**

Herbal therapy is 1 of the most popular forms of CAM treatments for asthma.<sup>55,58,59</sup> Four of the 5 classes of drugs currently used to treat asthma ( $\beta_2$  agonists, anticholinergics, methylxanthines, and cromones) have origins in herbal treatments going back at least 5000 years.<sup>66</sup> For example, ephedrine was developed from the traditional Chinese herbal remedy ma huang, tea leaves are the herbal origin of theophylline, and caffeine, found in tea and coffee, is a member of the same family as theophylline, and has been used for centuries as a treatment of asthma.<sup>65,67</sup> Like many CAM treatments, scientific evidence evaluating the effectiveness of herbal therapy for asthma has been marred by poor study quality and flawed study design. Three systematic reviews of herbal therapies for asthma were conducted in the last decade, and although they used slightly different methodologies, they all came to similar conclusions. In the most recent and most comprehensive review,<sup>65</sup> the investigators found 27 studies assessing 21 herbal preparations involving 1925 participants that met the entry criteria of the review. Small sample sizes, disparate outcome measurements, and relatively short-term follow-up prevented any overall clear conclusion as to efficacy and long-term safety of herbal therapy for asthma. Mean duration of therapy was only 8 weeks. There were large variations in the types of pulmonary function measurements, symptom scores, and types of subjective assessments, greatly limiting the ability of the review to perform combined outcome data assessments or subgroup analysis. With these limitations in mind, the results of a few herbs merit comment.

### ***Boswellia serrata***

*Boswellia* is a branching tree found in India, North Africa, and the Middle East, and a close relative of the Biblical incense frankincense. The gummy oleoresin found under the bark has been used for years in Ayurvedic medicine in India and in African countries for the treatment of a variety of diseases, including arthritis and asthma. Its mechanism of action in asthma is believed to be a result of its antiinflammatory properties, because resin extracts inhibit leukotriene synthesis and release.<sup>68</sup> One 6-week randomized controlled trial of 80 adults with asthma reported improvements in forced expiratory volume in 1 second (FEV<sub>1</sub>), forced vital capacity (FVC), number of asthma exacerbations, and wheezing<sup>69</sup> but subsequent reviewers expressed concerns with significant differences in baseline characteristics between groups, raising questions about appropriate randomization, and about whether the groups were comparable. The Cochrane Review identified another small, double-blind RCT of 40 patients that reported improvements in FEV<sub>1</sub> as a percentage of predicted, but translated into only modest changes in actual FEV<sub>1</sub>, and had no improvements in peak expiratory flow rate (PEFR) or FVC%.

*Boswellia* seems to be generally safe, although extensive studies of safety and tolerability are lacking and there have been some references to gastrointestinal side effects in humans (epigastric pain, heartburn, nausea, and diarrhea) and findings of hepatotoxicity in 1 study of mice. Caution is advised in patients taking agents metabolized

**Table 2**  
**Summary of natural supplements used for asthma treatments and their effectiveness**

| <b>Name</b>                       | <b>Suggested Dose</b>                                      | <b>Drug Interactions</b>   | <b>Side Effects</b>  | <b>Scientific Evidence of Efficacy</b>   |
|-----------------------------------|--|--|--|--|
| <i>Boswellia serrata</i>          | 300 mg 3 times daily powdered gum resin capsules           | Inhibitor of cytochrome P450 enzymes. May impair absorption of lipid-soluble medications   | Generally well tolerated, some reports of gastrointestinal symptoms  | Limited evidence, clinical effects likely modest                                       |
| <i>Tylophora indica</i>           | 250 mg once to 3 times daily, 0.1% of tylophorine per dose | No specific interactions noted   | Severe nausea/vomiting, required antiemetic in 1 trial to mask it from placebo (lessened if capsule form rather than whole leaf)           | Limited evidence of short-term effectiveness for FEV <sub>1</sub> and attack frequency |
| Propolis                          | Not known  | May have antiplatelet effects. In vitro studies show additive effects to antimicrobials. Some tinctures have ethanol   | Potent allergen and sensitizing agent, caution in hypersensitive individuals   | Limited evidence of effectiveness in 1 small study                                     |
| Purple passion fruit peel extract | 150 mg/d of extract  | Insufficient information   | None known, limited data   | Equivocal  |
| Selenium                          | Studies: 100 µg/d, (RDA is 50 µg/d for adults)             | Not recommended during chemotherapy or radiation therapy because of potential interference. Combination with β-carotene, vitamins C or E seems to decrease the effectiveness of simvastatin and niacin | Seems well tolerated at noted doses. Chronic high selenium levels may decrease sperm motility, although effects on fertility are not known | Not effective by limited evidence  |

|                              |  |  |   |                                   |
|------------------------------|--|--|---|-----------------------------------|
| Vitamin C                    | Studies used 500 mg to 2 g/d. (RDA is 75 mg/d) |  | Diarrhea, renal lithiasis in high doses   | Not effective by fair evidence    |
| Vitamin E                    | 500 mg/d. RDA is 15 mg/d                       | Caution in combination with anticoagulant and antiplatelet medications. May increase cyclosporine levels | Seems well tolerated up to 1000 mg/d for short periods Not recommended for long-term dosing | Not effective by limited evidence |
| Magnesium                    | 300–400 mg/d                                   | May interact and decrease effectiveness of several antibiotics and thyroid hormone                       | Seems tolerated up to 1200 mg/d   | Equivocal                         |
| Fish oil/omega-3 fatty acids | Variable, 2–3 g/d                              | Theoretic increase in risk of bleeding in combination with ASA or warfarin                               | Seems well tolerated. Caution re: heavy metal contaminants                                  | Not effective by good evidence    |

*Abbreviations:* ASA, acetylsalicylic acid; FEV<sub>1</sub>, forced expiratory volume in 1 second; RDA, recommended daily allowance.

| Name                     | Details                                   | Side Effects                               | Scientific Evidence of Efficacy                          |
|--------------------------|---|--|--|
| Acupuncture              | Variable points chosen depending on study | Rare; generally well tolerated             | Not effective but poor quality studies                   |
| Homeopathy               | Variable agents used                      | Not reported                               | Not effective by good evidence                           |
| Osteopathic manipulation | Various techniques used                   | Not reported                               | Equivocal  |
| Mind-body relaxation     | Various: relaxation, hypnosis, yoga       | Not reported, generally recognized as safe | Limited evidence benefit in quality of life measurements |

by the liver's cytochrome P450 enzymes, as boswellia may moderately or potentially inhibit these enzymes, and in patients taking lipid-soluble medications, because the gum resin of boswellia has been reported to lower cholesterol and triglyceride levels, and may bind to/impair absorption of these medications. Boswellia powdered gum resin capsules 300 mg 3 times daily were used in the original trial.<sup>70</sup>

### ***Tylophora indica***

*Tylophora* is a climbing perennial plant that grows in India. Its mechanism of action seems to be a result of the effects of tylophorine, a major alkaloid of *Tylophora*, on adrenal hormone stimulation, depressing cell-mediated immunity and suppression of IgE mediator release. In the Cochrane Systematic Review, *Tylophora* showed impressive short-term improvements in clinical outcomes of attack frequency and symptom severity, and moderate improvements in lung function measurements but positive effects were not evident after 12 weeks, and investigators noted that this herb may not be suitable for chronic use because it is also associated with severe gastrointestinal side effects, sufficient to lead 1 of the investigators to include an antiemetic agent in the placebo comparator to mask treatment group assignment. In an earlier systematic review<sup>63</sup> identifying 5 randomized clinical trials, 3 demonstrated moderate improvement of symptoms, 1 with improved FEV<sub>1</sub>, and 2 studies showed no significant improvement compared with placebo for the 2-week trials. Different formulations and dosing regimens have been reported from various studies, but doses of 250 mg 1 to 3 times daily, 0.1% of tylophorine per dose, have been standardized. Safety data only exist for 6- to 14-day exposures, and adverse effects mainly seem to be gastrointestinal, including nausea and vomiting, and these seem to be reduced if the leaves are taken in capsule form instead of chewing.

### ***Propolis***

Propolis is a natural flavonoid-rich resin produced from the buds of conifer and poplar trees then incorporated by bees into beeswax in combination with other bee secretions. There is preliminary *in vitro* and *in vivo* evidence that propolis suppresses the lipoxygenase pathway of arachidonic acid metabolism and decreases the synthesis of prostaglandins and leukotrienes involved in inflammation. Propolis has also demonstrated antiinflammatory properties through its free radical-scavenging properties, as well as antimicrobial effects from several flavonoids.

A small clinical trial<sup>71</sup> reported some improvement in lung parameters (FEV<sub>1</sub>, PEFR, and forced expiratory flow 25%–75%), as well as a reduction in nocturnal attacks compared with placebo.

Numerous case reports have demonstrated that propolis may be a potent allergen and sensitizing agent, and therefore it should be used cautiously in hypersensitive individuals. There are no standard dosing recommendations, and preparations have been found to have highly variable compositions.

### ***Purple Passion Fruit Peel Extract***

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A recent short-term Iranian study<sup>72</sup> of 42 patients involving a double-blind, randomized, placebo-controlled trial of 150 mg/d of purple passion fruit peel (PFP) extract, a novel mixture of bioflavonoids, on asthma symptoms showed some promising results. The prevalence of wheeze, cough, and shortness of breath was reduced and FVC improved significantly in the group treated with PFP extract ( $P < .05$ ) compared with placebo; however, the absolute improvement was relatively small, with unclear clinical significance and no significant improvement was observed in FEV<sub>1</sub>. The investigators point to several possible intriguing mechanisms supporting a beneficial effect of PFP on asthma, citing effects of flavonoids in reducing asthmatic inflammation through their known antioxidant, antiallergic, and antiinflammatory properties, as well as an observed effect on lowering nitrous oxide production. There was no adverse effect reported by any of the study participants, making this a compelling compound for further study in larger and longer trials.

### ***Other Herbal Preparations***

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Several other herbs demonstrated improvements in subjective asthma symptoms (eucalyptol, ginger, pulmoflex, Tj-96, Liu-Wei-Di-Huang-Wan, Shen-Ling-Bia-Shu-San, and Jai-Wei-Si-Jun-Zi-Tang) or short-term steroid reduction in severe asthmatics (eucalyptol), but the validity of the study results were significantly undermined by poor study design and reporting quality. Studies of herbal therapies as a part of traditional Chinese medicine (TCM) also had frequent limitations; none of the trials used a placebo control, there were variable or unspecified ingredients, and after direct query by the Cochrane reviewers, it turned out that more than 95% of the study investigators did not understand the concept of randomization, preventing any meaningful conclusion as to their efficacy.

### ***Summary Herbal Treatments for Asthma***

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*Boswellia*, *Tylophora* and purple passion fruit peel extract show some promise in asthma treatment, but further studies of efficacy and side effects that are larger and better designed are needed before these can be recommended for general use.

### ***Supplements***

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Interest in treating asthma through dietary supplements is often based on concepts related to potential antiinflammatory and antioxidant effects as well as the idea that modern western diets are deficient in elements necessary or beneficial to normal lung function. Elements that have been reputed to play potential roles include selenium, vitamins C and E, and omega-3 fatty acids in fish oil.

### ***Selenium***

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Selenium gained interest in treating asthma based on studies that observed asthma patients with lowered selenium status and lowered activity of the selenium-dependent

enzyme glutathione peroxidase in asthma patients along with observational reports that selenium supplementation might be beneficial to patients with intrinsic asthma because of its important role in the cellular elimination of hydroperoxides. A Cochrane Systematic Review of the effects of selenium in asthma from 2004<sup>73</sup> was only able to locate a single, small, double-blind RCT of 24 patients who were receiving standard asthma therapy. Those receiving a daily supplement of 100 µg sodium selenite for 14 weeks showed significant increases in serum selenium level and platelet glutathione peroxidase activity, and improvement in subjective asthma symptoms but failed to demonstrate improvements in objective spirometry measurements. The investigators speculated that although it is possible that the supplemental dose given was too low and that a dose of 200 to 250 µg might be more beneficial based on other observational studies, they concluded that there is insufficient evidence to assess the use of selenium in clinical practice.

A subsequent double-blind RCT in 2007<sup>74</sup> using 100 µg for 24 weeks in 97 patients, documented significant increases in selenium serum levels, but showed nonsignificant improvements in quality of life and no significant changes in lung function testing, leading the investigators to conclude that selenium supplementation offered no clinical benefit in chronic asthma.

### ***Vitamin C***

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As 1 of the key antioxidant vitamins that is abundant in the extracellular fluid, vitamin C has been a supplement of interest in asthma, especially because adults and children with asthma have been found to have lower concentrations of vitamin C compared with normal subjects, and prior observational studies have showing that low vitamin C intake is associated with pulmonary dysfunction. It has been speculated that patients with asthma may have low supplies of vitamin C or an increased demand for vitamin C in the face of an oxidant load resulting in depletion. A 2009 Cochrane Review<sup>75</sup> of vitamin C use in seasonal, exercise-induced, and chronic asthma located a 9 studies meeting review criteria, with varying study protocols ranging from single dosing between 500 and 2000 mg, to daily supplementation between 500 and 1500 mg for time ranges of 1 week to 6 months. Because of poor data reporting and variable methodology, the investigators were only able to combine data for FEV<sub>1</sub> measurements in 4 of the studies, and commented that the method of randomization, allocation concealment, and blinding was not always clear, leaving the results open to bias. They found essentially no change in any of the study parameters, including lung function, need for steroids, and subjective symptom scores, and concluded that further study with better trial design and larger-scale studies are needed.

### ***Vitamin E***

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In a small double-blind RCT of another well know antioxidant, vitamin E, in daily doses of 500 mg for 6 weeks failed to show any demonstrable benefit in lung function, symptom scores, bronchodilator use, or serum IgE levels in atopic adults with mild to moderate asthma.<sup>76</sup>

### ***Magnesium***

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Magnesium has been recognized as useful intravenously for treating acute asthma exacerbations,<sup>77</sup> but data on its oral use for treating chronic asthma in outpatient settings have mostly shown no benefit. A small double-blind RCT study of 17 patients given 400 mg of magnesium a day for 3 weeks after previous exposure to a low magnesium diet showed improvement in asthma symptom scores, but no change in airflow parameters, airflow reactivity to methacholine, or bronchodilator use.<sup>78</sup>

Another well-done double-blind RCT study of 100 asthmatic patients who received supplementation with magnesium (450 mg/d) for 16 weeks showed no beneficial effect in any outcome measurement of asthma control, including airflow or reactivity measurements, symptom scores, or bronchodilator use.<sup>79</sup> A recent double-blind RCT study of 37 children and adolescents using 300 mg of magnesium a day for 2 months demonstrated fewer asthma exacerbations, less salbutamol use, and decreased responsiveness to methacholine challenges and skin test responses to antigens, but had no change in spirometry values.<sup>80</sup>

### ***Fish Oil and Omega-3 Fatty Acids***

Given the known influence of inflammatory mediators on asthma, fish oil supplementation has naturally been a topic of significant interest for treatment and prevention of asthma, because of the known antiinflammatory effects of omega-3 fatty acids present in fish oil. Epidemiology studies have shown that populations (such as Eskimo communities) with diets high in fish have low rates of asthma, and as diets in other communities have become higher in saturated fats, asthma incidence has increased.<sup>81</sup> Two very small double-blind RCTs of only 10 and 16 patients with exercise-induced asthma using fish oil capsules containing 3.2 g of eicosapentaenoic acid and 2.0 g of docohexaenoic acid daily for 3 weeks demonstrated clinical improvement in pulmonary function response to exercise, decreased bronchodilator use, and decreased sputum inflammatory mediators.<sup>82,83</sup> However, a Cochrane Systematic Review in 2002<sup>81</sup> failed to demonstrate any clinical benefit of the use of n-3 marine fatty acids supplementation for asthma. In the comprehensive review, the investigators identified 9 studies that met study inclusion criteria, and found no convincing evidence that supplementation of diet with marine n-3 fatty acids leads to an improvement in asthma symptoms, asthma medication usage, bronchial hyper-reactivity or FEV<sub>1</sub>, nor was there evidence of risk or adverse effects identified. They concluded with 2 interesting caveats: first, that the studies concentrated mainly on supplementation of marine n-3 fatty acids rather than eating more fish per se, and that perhaps there are other elements in the original food source that could have beneficial effects for asthma; second, that much of the interest in n-3 fatty acid supplementation for asthma began in the era when the neutrophil was considered to possibly have an important role in the pathogenesis of asthma, because the most profound antiinflammatory effects of n-3 fatty acids are on neutrophil function and mediator generation. However, eosinophils and mast cells are now believed to be more important effector cells in asthma, and therefore this may explain their relative lack of efficacy, given that n-3 fatty acids lack significant antiinflammatory effect on eosinophils and mast cells *in vitro*.

In an extremely detailed and comprehensive review of omega-3 fatty acids in asthma by the Agency for Healthcare Research and Quality in 2004,<sup>84</sup> the investigators were unable to derive any definite conclusion about benefit because of the paucity of evidence from well-designed, well-conducted, and adequately powered studies, citing limitations caused by missing data, flawed designs, and noncomparable study parameters, but again found no significant evidence of harm. They made reference to an ongoing prospective study at that time looking at the use of omega-3 fatty acids for asthma prevention in children (Childhood Asthma Prevention Study), which was at its conclusion in 2007, that also failed to identify any beneficial protective effect.<sup>85</sup> Another more recent British systematic review in 2006 came to the same conclusions, and recommended a large, randomized, controlled study to effectively answer the question about omega-3 effects on asthma.<sup>86</sup>



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**Summary of Supplements for Asthma**

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Other than some mild improvement in asthma symptom scores for magnesium supplementation that was not confirmed in a well-designed double-blind RCT, none of the supplements demonstrated any benefit for use in chronic asthma.

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**Other Complementary Therapies**

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**Acupuncture**

Acupuncture is a form of therapy derived from TCM involving the stimulation of points on the body with the use of needles for therapeutic or preventative purposes. The points are derived from TCM theory and relate to the meridians, a system that purportedly allows the flow of Qi through the body, blockages of which are believed to cause health problems.<sup>87</sup> Three comprehensive systematic reviews in 2002, 2003, and 2006 evaluated the effect of acupuncture in asthma, each approaching the literature with slightly different criteria and review techniques. Martin and colleagues<sup>88</sup> searched for all RCTs since 1970 that compared acupuncture at real and placebo points and used at least 1 objective measurement of pulmonary function. They took estimates from the 11 trials that met inclusion criteria, and combined estimated standardized mean differences between acupuncture and placebo to estimate the overall effect. The Cochrane Systematic Review<sup>87</sup> was only able to pool data for 2 outcomes (PEFR and global assessment of well-being) in the 12 RCTs involving 350 patients that met their criteria. The systematic review by Passalacqua and colleagues<sup>64</sup> looked at a variety of CAM modalities in asthma, including acupuncture, without doing meta-analysis.

Despite the differences in approach, all 3 reviews arrived at similar conclusions. (1) With minor exceptions, the reviews basically found no significant evidence of efficacy for acupuncture in asthma, whether in lung function parameters, subjective symptom measurements, or with medication usage. (2) As with herbal medications, study quality, sample size, missing information, and heterogeneity in measurements limited data pooling and the ability to draw useful, statistically significant conclusions. (3) Reviewers commented in particular about the challenge unique to acupuncture research in choosing appropriate placebo acupuncture points, noting that studies varied in choosing nonmeridian points versus nonindicated but legitimate acupuncture points for placebo control. The points used in the sham arm of some studies were used for the treatment of asthma in others (according to TCM). Further heterogeneity occurs with needle depth, duration of insertion, choice of laser versus needle, and the choice of either standardized points versus allowing treating providers to individualize and customize points depending on diagnoses made using a TCM nosology quite foreign to western physicians and research methods. They concluded with clear recommendations for larger studies with particular attention to the nature of sham/control points and including a no-treatment control arm in addition to sham groups, as well as the need for studies to include patients with more severe asthma.

**Homeopathy**

Homeopathy, founded by Hahnemann at the beginning of the 1800s, relies on the principle that symptoms of a disease can be cured by the same substances that provoke them when they are ultra diluted. Homeopathic remedies are selected according to symptoms and prepared with a special technique involving repeated dilutions. A recent systematic review<sup>64</sup> identified 3 studies in asthmatic patients conducted with good methodology that showed no or marginal effects. Another well-done, randomized, double-blind, placebo-controlled trial over 12 months in pediatric patients<sup>89</sup> also failed to demonstrate any benefit in terms of peak flow rates, use of medication,

symptom scores, days off school, asthma events, or global assessment of change for homeopathic remedies as prescribed by experienced homeopathic practitioners.

The 2004 Cochrane review<sup>90</sup> identified 6 trials with a total of 556 people. The investigators noted significant methodological flaws with many studies, precluding pooling of results, but were not able to find evidence of benefit.

### **Manual therapy**

Evidence for various forms of manual therapy (chiropractic, osteopathic manipulation, various physical therapy techniques) in asthma is mixed. Recent Cochrane Reviews<sup>91,92</sup> found no significant benefit for chiropractic manipulation or the Alexander physical therapy technique, and noted methodological flaws in many studies limiting informed conclusions. A randomized, single-blind, controlled trial of osteopathic manipulation therapy in 140 pediatric asthma patients showed a statistically significant improvement in PEFs from 7 L per minute to 9 L per minute. However, the validity of the conclusions are potentially hampered by the nonblinded evaluator, and the different osteopathic manipulative therapy (OMT) techniques of different providers. Further study addressing these shortfalls was recommended.

### **Mind-body (relaxation) therapies**

Three comprehensive review studies<sup>93</sup> came to mixed conclusions about the role for mind-body, relaxation, or breathing technique in asthma, with methodological flaws in study design once again posing challenges to deriving valid conclusions. Progressive muscle relaxation, breathing retraining, and yoga appeared to have potential benefits for lung function, self-perceived well-being, and quality of life measurements, with further better designed studies recommended to derive more valid conclusions. A recent British RCT<sup>94</sup> demonstrated improvements in quality of life measurements but there seemed to be no effect on asthma pathophysiology and therefore no change in the need for antiinflammatory medication. Small studies on the use of mental imagery, hypnosis, and biofeedback showed some promising results for these approaches that although clearly safe, also need further research to validate their effectiveness.<sup>95–97</sup>

### **Summary of Other Complementary Therapies in Asthma**

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Mind-body techniques seem to have some benefit for quality of life indicators in asthma; homeopathy seems to have no evidence of benefit and poor quality studies hamper conclusions about acupuncture and manual therapies.

### **COPD**

COPD is a preventable and treatable disease that is frequently associated with smoking, and characterized by chronic airflow limitation that is not fully reversible, is usually progressive, and is associated with abnormal inflammatory response to noxious particles or gases.<sup>98</sup> Common symptoms are chronic and progressive dyspnea and sputum production. In the United States, COPD affects more than 5% of the adult population and is the fourth leading cause of death and the twelfth leading cause of morbidity.<sup>99</sup> Although there is no cure for COPD, smoking cessation is the only therapeutic intervention shown to reduce disease progression. Unsatisfactory treatment outcomes and side effects from conventional drugs, such as steroids and theophylline, contribute to the increasing popularity of CAM and, in particular, herbal medicine.<sup>100</sup> Studies show that between 33% and 41% of COPD patients admit to using some form of CAM<sup>101,102</sup>; the most common types include herbal and nutritional supplements, as well as garlic, acupuncture, and homeopathy. As with asthma, the main source of information on CAM practices are most often relatives, friends, and

advertisements, with only a small number of the patients consulting with their physicians about CAM. This makes it important for physicians to be knowledgeable about the scientific evidence for efficacy and safety of these practices (**Table 4**).

### **Herbals**

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There is a long history of using herbal remedies to treat COPD, particularly in China, India, and other Asian countries. Herbal expectorants, based on extracts from *Hedera helix* (ivy) or *Thymus vulgaris* (thyme) also enjoy considerable popularity in many European countries.<sup>100</sup> However, even more so than with asthma, quality evidenced-based studies on the use of herbal treatments in COPD are lacking. In the first and only comprehensive systematic review of the topic, done in 2006,<sup>100</sup> the investigators reviewed English, Chinese, and German literature, finally identifying 14 eligible RCTs, with placebo-controlled comparisons in 6. As with the asthma literature, the methodological quality was generally low, with problems caused by small sample size, lack of double blinding, use of a placebo control, unclear herbal content, and nonstandardized evaluation tools.

### ***Panax ginseng***

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The roots of slow-growing perennial *Panax* plants have been used in China for more than 2000 years for various ailments. The major active components of ginseng are a diverse group of steroidal saponins, labeled ginsenosides, which may have a variety of actions, including potential antiinflammatory effects that may play a role in asthma. A well-designed double-blind RCT of 92 moderately severe (FEV<sub>1</sub> 50%–65%) COPD patients in Israel demonstrated that 100 mg of ginseng extract capsules twice daily for 3 months resulted in significant improvement in all parameters of pulmonary function testing, including maximum voluntary ventilation, maximum inspiratory volume and V<sub>O<sub>2</sub></sub> max with no observed side effects.<sup>103</sup> The improvement in airflow in major and peripheral airways as well as improvement in exercise capacity parallels previous studies on athletes. This was interpreted by the investigators as indications of positive effects on respiratory muscle strength possibly caused by postulated neurotransmitter-like actions. Another very small Chinese study of 20 patients using a daily intravenous formulation of 3 herbs with *Panax ginseng* as the main ingredient for 14 days also showed improvements in pulmonary function (FEV<sub>1</sub> and vital capacity) as well as 6-minute walk time and Borg symptom scores.<sup>104</sup>

In general, animal studies indicate that ginseng has very few toxic effects for either acute or chronic (up to 2 years) use, but some in vitro studies show that *Panax ginseng* may inhibit the aggregation of platelets, reduce platelet adhesiveness, reduce internationalized normalized ratio (INR), and reduce warfarin concentrations and increase its clearance.

### ***DCBT1234-Lung KR***

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A randomized, double-blind, placebo-controlled clinical study was done in India on 105 patients comparing 6 months of a plant-based formulation of 3 herbs (*Bryonia alba*, *Drosera peltata* [or sundew], and *Cephaelis ipecacuanha* [better known as ipecac]) against the combination of oral salmeterol, theophylline, and bromhexine and both against placebo.<sup>105</sup> Patients treated with DCBT 1234-Lung KR showed statistically significant (95% level) improvement in FEV<sub>1</sub> and PaO<sub>2</sub> compared with salbutamol+theophylline+bromhexine, and equivalent control of symptoms such as dyspnea, wheezing, cough, expectoration, disability, and sleep disturbances, both

Table 4

## Summary of alternative treatments for COPD

| Name                        | Suggested Dose or Treatment Details  | Drug Interactions   | Side Effects  | Scientific Evidence of Efficacy                   |
|-----------------------------|--|---|---|---|
| <i>Panax ginseng</i>        | 200–400 mg/d or 100–200 mg of a standardized ginseng extract (4% ginsenosides) | May inhibit the aggregation of platelets, reduce platelet adhesiveness<br>reduce INR and warfarin concentration | Generally well tolerated  | Equivocal   |
| DCBT1234-lung KR            | Unknown  |   | 2 components ( <i>Bryonia alba</i> and <i>ipecacac</i> ) have potentially serious adverse effects, both rated as unsafe | Equivocal   |
| Nutritional supplementation | Variable   |   | Not noted   | Not effective by good evidence                    |
| Acupuncture                 | Variable points chosen depending on study                                      | N/A   | Rare; generally well tolerated  | Possibly effective for dyspnea symptoms           |
| Osteopathic manipulation    | Various techniques used  | N/A   | One study report worsened air trapping and expiratory flow  | Not effective by limited evidence; may cause harm |

Abbreviations: INR, internationalized normalized ratio; N/A, not applicable.

better than placebo. No mention was made in the article about adverse effects in any of the study arms. Concerns expressed by subsequent letter responses challenged the use of nonstandard allopathic medications as control, pointing out that the combination of oral salmeterol and theophylline poses known cardiovascular risks to COPD patients, and expressed concern about the issue of heavy metal poisoning associated with plant-based Ayurvedic medicines.

*Drosera* species have been used for hundreds of years for respiratory tract problems, and it is a fairly commonly used medicine as a solitary ingredient or as part of combination medications in roughly 200 to 300 registered medications. Testing of individual *Drosera* constituents reveals antiinflammatory, antispasmodic, and antibacterial effects, with minimal adverse effects although safety data are limited. Although purported to have some evidence of antitumor and antiinflammatory effects, *Bryonia* has been rated as unsafe with serious gastrointestinal, renal, and neurologic adverse effects reported. *Ipecac* is well known in the United States from its previously recommended role as an emetic in cases of suspected pediatric poisoning. That recommendation was rescinded several years ago, and there have been reports of myopathies and death with chronic use.<sup>68,70</sup> Although this is a promising and interesting study done with reasonable methodology, further study is clearly needed regarding the efficacy, safety, and adverse effects of the individual herbal ingredients.

### **Other Herbals**

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Improvement in at least 1 measure of pulmonary function have been shown with *Salvia miltiorrhiza*, *Echinacea* and *Hedera helix* leaf extract, but the studies were small, failed to use placebo controls, or had other methodological flaws. A small Japanese RCT<sup>106</sup> using 2.5 mg of the traditional Japanese herbal medicine Hochuekkito (a mixture of 10 raw Japanese herbs, mixed in set proportions) given orally 3 times a day for 6 months showed improvements in several markers of systemic inflammation and serum prealbumin levels in older patients with COPD, but did not address pulmonary function. Most small studies of various TCM herbal preparations for COPD have significant methodological flaws that limit useful interpretation or recommendations.

### **Nutritional Supplementation**

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Although up to one-third of patients with COPD have some degree of malnutrition, often becoming severe in advanced or end-stage disease, it has been unclear whether malnutrition plays a causative role in clinical deterioration or whether it is merely a marker of other processes intrinsic to the disease.<sup>107,108</sup> In a 2005 Cochrane Systematic Review of the topic,<sup>109</sup> the investigators identified 14 studies involving 487 patients meeting review criteria, the majority pertaining to outpatient-based oral supplementation for at least 2 weeks to undernourished patients with COPD. Using meta-analysis, they found no evidence that simple nutritional supplementation confers benefit to patients with COPD in terms of clinical outcomes including measuring effects on anthropometric, functional exercise, pulmonary mechanics, peripheral muscle function, and health-related quality of life derived from validated scales. Triceps skinfold thickness was marginally higher with supplementation than control, but was not associated with any other meaningful health improvements, suggesting that some fat was deposited in the patients receiving nutritional supplementation but this change does not constitute a worthwhile response to therapy. However, it is worth noting that 2 weeks may be a short period of supplementation.

The investigators note that explanations for a poor response to nutritional support have included increased metabolism, diet-induced thermogenesis, tissue hypoxia, the influence of increased levels of soluble tumor necrosis factor- $\alpha$  receptors,

and medications such as corticosteroids, and that further research into combinations of nutrition with anabolic substances may prove worthwhile. However, 3 recent well-done, adequately powered, double-blind, randomized, placebo-controlled trials of an anabolic steroid (nandrolone decanoate)<sup>110</sup> and creatine combined with exercise training<sup>111,112</sup> showed no difference in pulmonary function or functional exercise capacity. A prospective, double-blind, randomized, placebo-controlled trial of megestrol acetate of 128 patients did show a 4-mm decrease in PaCO<sub>2</sub>, as a result of its known stimulatory effect on ventilation, and increased appetite associated with a 3.2-kg weight gain; but the weight was mainly fat and again, there was no benefit on respiratory muscle function or functional exercise tolerance.<sup>113</sup>

Other single placebo-controlled studies showed similar negative results for pomegranate juice, *N*-acetylcysteine, and vitamin E.

### **Manual Medicine**

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The osteopathic medical profession has developed a variety of techniques purported to improve pulmonary function by targeting various aspects of the musculoskeletal, neuronal, and lymphatic components of the pulmonary system.<sup>114,115</sup> Previous literature consisting of small, nonrandomized studies has failed to provide a clear picture as to the efficacy and role of OMT in the treatment of COPD. Researchers at the Kirksville College of Osteopathic Medicine performed a well-designed, double-blind, RCT of a single session of multitechnique OMT versus sham therapy in 35 patients more than 65 years of age, looking for evidence of immediate measurable changes in pulmonary function. They did find statistically significant evidence of pulmonary function change, but in the wrong direction: OMT-treated patients had worsening of residual volume, indicating more air trapping, and a decrease in forced expiratory flow. The investigators concluded that further study looking at the effect of individual techniques and studying longer-term pulmonary function responses to OMT will be important to understand if COPD should be a contraindication to the use of this therapy.

### **Acupuncture**

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Several small single-blind RCTs of between 4 and 10 weeks of acupressure and acupuncture have been done in patients with COPD, some with, some without placebo/sham controls.<sup>116–118</sup> Taking into account significant variations in technique, choice of outcome measurements, and methodological flaws in randomization and blinding of evaluators, all studies showed improvement in subjective symptoms of dyspnea, with 2 studies showing improvements in either FEV<sub>1</sub> or 6-minute walk distance. No report of adverse effects was made, and acupuncture was generally well tolerated. Acupuncture shows promise at least in improving subjective symptoms of dyspnea in COPD, but better designed, larger trials are clearly needed before solid recommendations can be made.

### **Summary of CAM Therapies for COPD**

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Acupuncture may play a role in improving walking distance and subjective symptoms of dyspnea, although better studies are needed. Otherwise there is little evidence to support herbal therapy, and fairly good evidence that nutritional supplements are ineffective and osteopathic manipulation is potentially harmful until more extensive research is available.

## **SUMMARY**

The self-medication phenomenon in upper respiratory tract infections, rhinosinusitis, asthma, and COPD are significant and will continue to increase. Current level of

evidence is poor because of the small number of good quality studies, small sample size, short duration, and variation in the composition of the herbal interventions or therapies. The current review points to several potential therapies that could be effective either alone, or as adjunct to conventional therapies.

### ***Caveats and Cautions***

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One of the positive motivations for using CAM is perceived safety. However, there are risks with the use of herbal remedies including drug interactions, inconsistent dosing, contamination, and natural toxicity.<sup>119</sup> These risks are compounded by the tendency of patients to report neither their use of herbal treatments nor suspected adverse reactions of the herbal therapies to their physicians, compared with conventional over-the-counter medications, and because herbal therapy users tend to self-medicate or take the advice of a friend or relative, they are unlikely to consult any practitioner at all on the use of herbal products.<sup>120,121</sup> Blanc and colleagues<sup>122</sup> raise the concern that patients' use of alternative treatments may delay appropriate use of conventional medicines and thus, increase the risk for life-threatening complications.

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