Overview. The prevalence of asthma in the U.S. population is 9%, and 62% of these individuals have “allergic” asthma (i.e., show evidence for atopy). In patients with allergic asthma, the same allergens that trigger allergies (e.g., pollen, dust mites) can also induce asthma symptoms and exacerbations.

There are three treatment options for patients with allergic asthma: 1) allergen avoidance, 2) pharmacotherapy (e.g., inhaled corticosteroids), and 3) immunotherapy. Despite available effective treatments, many patients with asthma do not have their condition under control—a problem that disproportionately affects racial and ethnic minorities. Allergen-specific immunotherapy (IT) is recommended for patients whose allergic asthma cannot be adequately controlled by allergen avoidance and medication. However, studies suggest that the clinical benefits of IT and its potential to reduce asthma symptoms long-term may justify even broader use to improve asthma outcomes.

There are two main forms of IT: subcutaneous IT (i.e., allergy shots) and sublingual IT (i.e., allergen placement under tongue). In 2013, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review on subcutaneous and sublingual IT for treatment of allergic rhinoconjunctivitis and asthma. Overall, high quality evidence is strong that both subcutaneous and sublingual IT are effective and safe for the treatment of asthma, although there is insufficient evidence to favor one form of IT over another. The magnitude of the effect is hard to judge because the systematic review reported effects qualitatively rather than as changes in symptom scores. There is increasing interest in sublingual forms of IT as an alternative treatment to subcutaneous IT due to more convenient administration (does not require injections or office visits), potentially improved safety (reduced risk of anaphylaxis), and shorter time to achieve effect. In addition, despite its broad use in Europe, Asian, and Latin America, sublingual IT in the US was only recently approved by the FDA. In May 2014, the FDA approved the first three allergen tablets for sublingual administration (two are for grass pollens and one is for ragweed). However, even prior to the FDA approval, U.S. physicians had been increasingly prescribing sublingual IT “off-label” (i.e., they prescribe FDA-approved allergen extracts for oral use instead of their labeled use for injections). AHRQ and the American Academy of Allergy, Asthma and Immunology (AAAAI) have both called for head-to-head trials comparing subcutaneous and sublingual IT for treatment of asthma.
Patient-Centeredness. Sublingual IT is gaining traction in the U.S. due in part to its more patient-centered approach – the oral treatment can be administered by patients and does not require injections. There are other potential benefits to sublingual immunotherapy as well – the treatment may have improved safety (reduced risk of anaphylaxis) compared to allergy shots, and may take a shorter time to achieve effect.4

Impact (Burden) of the Condition on the Health of Individuals and Populations. The prevalence of asthma in the U.S. population is 9%, and 62% of these individuals have “allergic” asthma. Asthma is not only a common chronic disease, but carries significant health and economic consequences. Asthma costs the U.S. $56 billion every year and the economic burden is growing – care utilization due to asthma has grown 15% in the last decade.5 Asthma disrupts day-to-day life – 1 in 2 children miss school because of their asthma, 1 in 3 adults miss work because of their asthma, and 3 in 5 people with asthma limit their physical activity.6 And, there are significant racial/ethnic and socioeconomic disparities in care and outcomes. African Americans and Hispanic/Latino children have a lower likelihood than white children to be prescribed, or to follow, courses of asthma treatment.7 In addition, African Americans are 2 to 3 times more likely to die from asthma than any other population.8

Ongoing Evidence Gap. Current clinical guidelines (published in 2011) recommend the use of immunotherapy for the treatment of allergic asthma in both adults and children whose symptoms are not controlled by medication or avoidance measures (e.g., environmental controls), or those who experience adverse effects of medication or wish to reduce long-term use of medication.9 At the time of guidelines publication, no allergen extracts for sublingual IT had been approved in the U.S. Since the focus of the guidelines is on practice in the U.S., they therefore largely pertain to the use of subcutaneous immunotherapy. (Note: Given the FDA’s recent approval of three allergen extract tablets for sublingual IT use, there may be forthcoming changes to these guidelines.)

AHRQ’s comparative effectiveness review (2013) examines the comparative efficacy, effectiveness, and safety of subcutaneous and sublingual therapies for treatment of allergic rhinoconjunctivitis and asthma.10 Authors included 142 RCTs in the review. 74 studies examined subcutaneous IT, 60 studies examined sublingual IT, and 8 studies compared the two forms of IT. Despite these 8 studies comparing subcutaneous and sublingual, there is low grade evidence to support one treatment over another due to bias (e.g., incomplete reporting of missing data, unmasked interventions) in these studies. In addition, all eight studies were conducted outside the U.S. and just four studies designated asthma the primary diagnosis (the others designated rhinitis or rhinoconjunctivitis).

The review states there is sufficient evidence to support the effectiveness and safety of both subcutaneous and sublingual immunotherapy for treatment of allergic rhinitis and asthma, although there is insufficient evidence to favor one form of IT over another. The AHRQ review calls for head-to-head studies comparing the two forms of immunotherapy. There is also a need for head-to-head studies on multi- vs. single-allergen regimens. Most studies in the review were single-allergen regimens (e.g., pollen extract only). Multiple allergen regimens are
commonly used in the U.S., and there are a lack of studies directly comparing the two regimens head-to-head. Although outside the purview of PCORI, there is also a need for studies to document whether immunotherapy modifies the course of allergic disease. Because immunotherapy targets the root cause of allergic asthma by building tolerance to allergens, it is possible that the treatment may prevent or modify the progression of allergic asthma, particularly in children.

There are two relevant Cochrane systematic reviews that corroborate the findings of AHRQ’s review. One review including 88 trials (2010) examined the impact of subcutaneous immunotherapy on asthma and found that the treatment reduces asthma symptoms, the need for medications, and the risk of severe asthma attacks after future exposure to the allergen.\textsuperscript{11} However, there is risk for local (e.g., rash) or systemic (e.g., anaphylaxis) effects. Another review looked at the effectiveness of sublingual immunotherapy, but only within the context of allergic rhinitis.\textsuperscript{12} The review (an update to a review from 2003) included 60 trials and found a significant reduction in symptom and medication use among patients.

**Ongoing research.** There are currently no registered trials in clinicaltrials.gov comparing immunotherapy options for treatment of allergies and/or asthma (using search terms “subcutaneous” and “sublingual” and “immunotherapy”). One study (which was suspended due to lack of recruitment) compared the sublingual and subcutaneous IT in children with mild asthma (2009). Other related trials in clinicaltrials.gov (n=10) mostly pertain to immunological outcomes or long-term effects of immunotherapy, or examine the safety and efficacy of one form of immunotherapy for a single allergen.

**Likelihood of Implementation in Practice.** The AAAAI has reinforced the need for head-to-head trials comparing subcutaneous and sublingual IT, indicating strong interest among clinicians. While subcutaneous IT is used worldwide and studies indicate the treatment has the potential to reduce costs and utilization, it remains underutilized for asthma.\textsuperscript{13} 14 There is growing interest among the clinical community in sublingual IT because despite its proven efficacy and widespread use across Europe (45% of immunotherapy in Europe was administered as sublingual IT in 2009), the FDA only recently (2014) approved three allergen extract.\textsuperscript{15} 16 And, even before the recent FDA approval, U.S. practitioners had been increasingly prescribing sublingual IT off-label.\textsuperscript{17} Given the interest from clinicians, and recent traction with the FDA, it is likely that sublingual administration of IT will gain favor in the U.S. A large head-to-head trial comparing sublingual and subcutaneous IT has good potential to influence practice and policy in the U.S.

The AHRQ review (published before the FDA approval of the allergen tablets) noted that due to differing standardization of potency in the Europe and the U.S., doses have been difficult to translate between countries. In addition, because there were no approved extracts for sublingual IT until last year, there is little standardized information on the preparation of tablets (the approved extracts are only for grass pollen and ragweed). A large U.S. study would also shed light on questions around dosing and allergen extract preparation.
**Durability of Information.** Based on the literature and recent FDA approval of sublingual IT, the use of these treatments is likely to remain relevant for years to come.

**Potential Research Questions.** Per AHRQ’s comparative effectiveness review and conversations with the AAAAI, there is a need for studies to fill the following evidence gaps:

- What is the comparative effectiveness of sublingual IT and subcutaneous IT on asthma outcomes?
  
  - What is the effectiveness of treatment in specific subpopulations (e.g., patients with severe asthma, rural vs. urban patients, pediatric populations)?
- What is the comparative effectiveness of single-allergen versus multiple-allergen therapy for desensitization and treatment of asthma?

**Conclusion.** Subcutaneous and sublingual immunotherapies have been shown to improve asthma outcomes, and are recommended for patients whose asthma cannot be controlled by other methods (i.e., medication and allergen avoidance). Sublingual is recognized for being easier to administer without a doctor’s visit and more patient-centered than subcutaneous. Therefore, the treatment is particularly relevant to populations at risk for asthma disparities. Given the long-term clinical benefits of immunotherapy and its potential to alter the course of allergic asthma, even broader use of immunotherapy could be justified. While both treatment options have been proven to be safe and effective, there is not enough evidence to support one treatment over another. Each treatment requires very different administration and resources (in-office injections by providers vs. patient-administered oral tablets), important for considering patient-centered outcomes. Beyond implications for patient-centered asthma care, additional evidence on sublingual and subcutaneous therapies has high potential to influence asthma practice and policy in the U.S. With the recent FDA approval of the first sublingual treatments, the technique is only beginning to gain favor in this country – a trend that is likely to continue. A large comparative effectiveness trial of immunotherapy options can help determine if one treatment is superior to the other, but may also support the use of immunotherapy as a key clinical strategy to curb persistent disparities in asthma.
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