

Anticholinergic Bronchodilator Therapy of Asthma—Ageless



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Few therapies have appeared in our pharmacopeia for centuries and remained relevant. Anticholinergic bronchodilator therapy of asthma is one such therapy. Against a background of questionable and even harmful treatments offered to breathless patients, anticholinergic bronchodilators were documented as the first effective inhaled therapy in Western medicine.¹ The discovery of anticholinergic botanicals was not made by European physicians or scientists. For centuries in several countries and cultures, the smoke of burning *Datura stramonium* leaves had been described as an effective anti-asthma therapy. Its introduction to Western medicine was attributed by Salter,² in his treatise on asthma, as an import from India during the British Raj. A certain General Gent was stationed in Madras, India, and received treatment for his asthma with the local Ayurvedic medication. He described his relief in glowing terms and, in short order, the practice of smoking anticholinergic bronchodilators became a recognized part of the formulary for up-to-date physicians of the 19th and early 20th centuries. The effective alkaloid, atropine, was later identified as responsible for the benefits (and side effects) of the popular treatment strategy. Eventually, these simple anticholinergic botanical preparations gave way to the more rapidly effective adrenergic agents, and, by the mid to late 20th century, the ubiquitous albuterol had become the quick-relief bronchodilator of choice. It would be a mistake, however, to think of anticholinergic bronchodilators as having disappeared early in the 20th century. Indeed, atropine-containing asthma cigarettes remained available for purchase in North America into the 1960s and 1970s.^{3,4} Literature concerning their use does not appear in allergy, asthma, or pulmonary journals. Instead, emergency department physicians documented their care of hallucinating teens and young adults who had smoked or ingested atropine-containing cigarettes for recreational purposes.^{5,6} Atropine, although an effective

bronchodilator, is readily absorbed across lipid membranes to produce both CNS and other systemic side effects.

Anticholinergic bronchodilator therapy enjoyed a renaissance at the end of the 20th century with the introduction of quaternary anticholinergic bronchodilators such as ipratropium and oxitropium. The former soon became widely employed in respiratory medicine, but less for its use in asthma than for its use as a foundational bronchodilator in patients with chronic obstructive pulmonary disease (COPD). Early COPD guidelines recommended ipratropium and similar short-acting anticholinergic bronchodilators for their efficacy and their apparent safety.⁷ Their use in asthma was more limited. As compared with inhaled beta-2 agonists, inhaled ipratropium produced less bronchodilator benefit and acted more slowly.⁸ However, when the 2 were combined, their combined bronchodilator efficacy was greater than either agent alone. This strategy was employed somewhat when managing ambulatory patients with difficult-to-control disease, but the greatest use of this combination approach was in the emergency department, a strategy that persists today. Early studies showed that combining nebulized anticholinergic bronchodilators with nebulized beta-2 agonist bronchodilators can produce greater benefit than either agent alone.⁹ The strategy appeared effective in both children and adults with acute exacerbations, and at least 1 study suggested a decreased likelihood of relapse when children received such a combination therapy in the emergency department.¹⁰

The next step forward in anticholinergic bronchodilator therapy was the development of the once daily agent tiotropium. The efficacy of tiotropium and subsequent long-acting antimuscarinics (LAMAs) in COPD have made once daily LAMAs the foundational bronchodilators in most COPD guidelines. Their reintroduction as once daily agents in asthma has been a more recent development. Kerstjens et al¹¹ were able to show that, in patients whose asthma was poorly controlled despite high-dose inhaled corticosteroid and long-acting beta₂ agonist (ICS/LABA), the addition of tiotropium in its soft mist inhaler formulation not only increased peak forced expiratory volume in 1 second but increased time to first exacerbation. Asthma guidelines now include LAMA agents as potential adjunctive treatments when asthma is severe and is not completely controlled by high-dose ICS/LABA. As we tackle the problem of severe asthma, the use of LAMA agents seems likely to grow, and such triple therapy might be considered an essential step before the introduction of expensive biologic therapy for patients who fail to be controlled with this strategy. Open triple therapy is not without its pitfalls. Increasing the number of drugs and devices tends to impair adherence and persistence with prescribed medication. One recent review of patient behavior after the introduction of tiotropium added to ICS/LABA in an open triple fashion (2 separate devices) found that, in 6 months, almost half of the patients had forgotten their ICS/LABA controller and were

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relying solely on anticholinergic monotherapy, a losing strategy in difficult asthma.¹² However, several closed triple therapies (1 device) are becoming available that will address the complexity leading to this nonadherence issue.¹³

Despite our centuries-old experience of anticholinergic therapy in asthma, many questions remain about their use, some of them fundamental. Of importance to clinicians in the era of personalized medicine: is there a phenotype or patient characteristic that would identify those most likely to benefit from the anticholinergic modality? One early suggestion concerning anticholinergic bronchodilators was that they were more effective in older patients.¹⁴ If this is true, it may be true only in a relative sense. Adrenergic receptor sensitivity may decline with age, leaving anticholinergic bronchodilators more effective in a relative sense, but not in an absolute sense. Still, this issue challenges the clinician developing a therapeutic strategy for his or her patient with difficult-to-manage asthma. Is it older patients who show better response and greater improvement with the introduction of agents such as tiotropium? In this issue of *JACI: In Practice*, Doherty et al¹⁵ offer an answer to this question. Analyzing the results of 4 studies in adults with difficult-to-control asthma, they could find no clear relationship between the benefit from added inhaled tiotropium and age. That is, they could find no evidence that older patients were more likely to show benefit than younger patients (or vice versa). Studies in pediatric asthma showing benefit when tiotropium was added to ICS/LABA would have hinted at this outcome. The review by Doherty et al also looked at issues of safety, an occasional concern raised over the past several years. They found no age-related evidence of adverse outcomes. As noted, the analysis was limited to just 4 studies of tiotropium add-on therapy. As additional data become available concerning LAMAs in asthma as part of a triple combination, we will no doubt see more extensive analyses to determine if there is a patient demographic or characteristic that might predict greater responsiveness to this treatment regimen.

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