Long-acting medications for chronic obstructive pulmonary disease

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ABSTRACT

This article explores the role of anticholinergic medications for the treatment of chronic obstructive pulmonary disease (COPD). It provides an overview of COPD and outlines the current long-activing anti-muscarinic bronchodilators available. It also looks at issues such as side-effects, adherence, and how these treatments compare with other long-acting drug therapies for COPD.

Key Words: Chronic obstructive pulmonary disease (COPD) • anticholinergic medications • long acting anti-muscarinic bronchodilators

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Chronic obstructive pulmonary disease (COPD) is a progressive and irreversible decline in lung function, with reduced airflow and an inability to supply oxygen to match the demands of exercise. This inadequate oxygen supply is largely due to gas trapped within the damaged alveoli and dynamic hyperinflation as a result of mechanical deterioration of the respiratory muscles. This failure to satisfy oxygen demands combines with chronic inflammation to produce a wide range of comorbidities, including: cardiac disease, obesity and metabolic syndrome—all of which contribute to the patient's individual burden and a poor quality of life (Evans and Morgan, 2014).

COPD is regarded as a long-latency disease, with symptoms developing a number of years after first exposure to particular causative agents. The most important of these is smoking, but others include occupational exposures to fumes, chemicals and dusts, as well as genetic susceptibility and environmental pollution (Health and Safety Executive, 2014).

The prevalence of COPD has been estimated at 900 000 diagnosed cases in England and Wales, but allowing for under-diagnosis the true prevalence is probably closer to 1.5 million (National Institute for Health and Care Excellence, 2004), with a consequential mortality of between 25 000 and 30 000 deaths each year (Health and Safety Executive, 2014). The average annual cost to the NHS for each patient is estimated at £819, of which 54% is due to inpatient hospitalisation, 18% for drug and other treatments and 16% for GP and specialist visits.

Breathing is controlled by the respiratory muscles that are regulated by the vagus nerve and the parasympathetic nervous system, which is mediated through the neurotransmitter acetylcholine (ACh). The parasympathetic nervous system is sometimes described as the 'rest and repose' system and controls physiological functions—including digestion and respiration. It is opposed by the 'fight or flight' activities of the sympathetic nervous system

which acts via the neurotransmitter, adrenaline.

ACh released at nerve junctions stimulates specific receptors—one type are called muscarinic receptors, the stimulation of which constricts airway smooth muscles, increases mucus secretion and the dilation of airway blood vessels (Matera et al, 2014). Parasympathetic activity is increased in patients with COPD, and is an important target for manipulation to reverse the factors that cause airway constriction and obstruction (Gross and Skorodin, 1984).

A number of pharmaceutical agents have been developed over the years to counteract the imbalance in nervous activity that contribute to the development and progression of COPD. An important development was the synthesis of compounds known as the long-acting muscarinic antagonists (LAMA). These include compounds of aclidinium, tiotropium, and glycopyrronium—and more recently umeclidinium (*Table 1*). These are now regarded as the front-line therapies for persistent COPD. LAMA work by blocking the muscarinic receptors, specifically the M3 type and so dilate the bronchial muscles, reduce airway spasm and lessen mucus secretion. This aids air flow and lessens congestion. They also influence the inflammatory cells that are largely responsible for the inflammation, oedema and cellular degradation observed in emphysema (Matera et al, 2014).

After inhalation, these medications take around 20 minutes to act—with three-to-four hours for stabilisation. Due to their long action, they only need to be taken once, perhaps twice, a day. These are preferred over similar short-acting drugs that may have a quicker but shorter duration of action. Trials have shown LAMA improve lung function as measured by spirometry, prevent exacerbations, and reduce dyspnoea or shortness of breath. Overall, they improve health-related quality of life, lessen (non-fatal) serious adverse events and reduce hospitalisation over other available medication (Keating, 2012).

Recent assessments of annual maintenance costs for prescribing aclidinium, glycopyrronium and tiotropium shows annual maintenance costs ranging from £330 to £426 (Lancashire Medicines Management Group, 2014), while umeclidinium is possibly less expensive, with estimated annual saving of £73 over tiotropium and £13 over aclidinium (Scottish Medicines Consortium, 2014). Due to their ability to reduce exacerbations, they have a good cost-benefit status, by reducing inpatient hospitalisation and GP and specialist visits.

Table 1. Long-acting anti-muscarinic bronchodilators for COPD (www.medicines.org.uk)

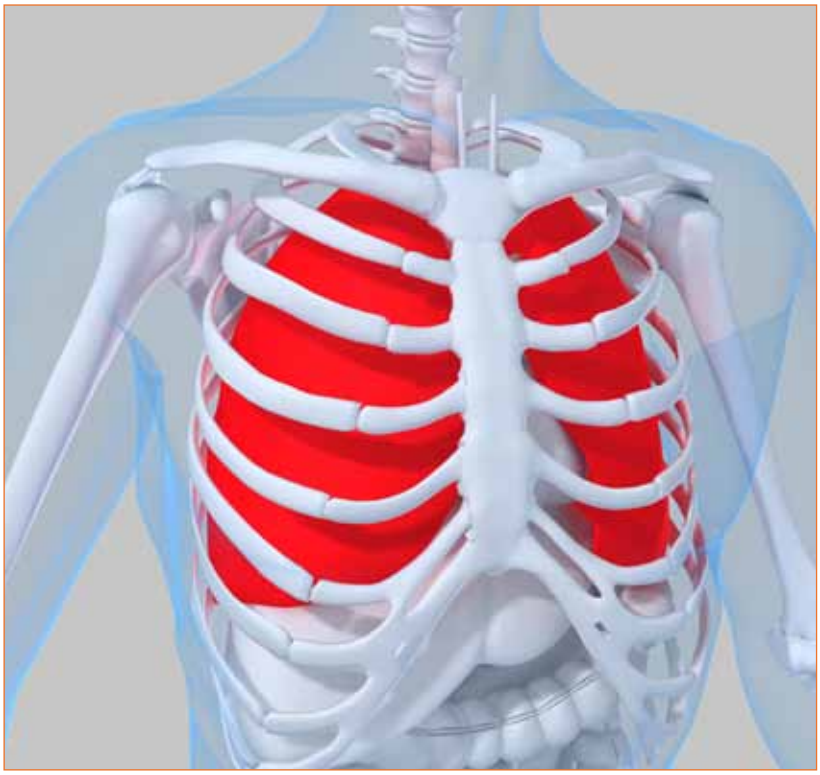
Chemical	Trade name	Description
Ipratropium bromide	Atrovent	250 micrograms/1ml nebuliser solution; inhaler; three-to-four times daily
Aclidinum bromide	Eklira Genuair	322 micrograms inhalation powder; two times daily
Tiotropium bromide	Spiriva Respimat	2.5 microgram per puff; two puffs daily solution for inhalation
Glycopyrronium bromide	Seebri Breezhaler	44 micrograms inhalation powder; hard capsules; once daily
Umeclidinium bromide	Incruse	55 micrograms; dry powder inhaler; once daily

Side-effects

Although the LAMA drugs are generally well-tolerated, there are reports of side-effects including headache, a mild cough and dry mouth. More seriously, but less common, are eye pain, blurry vision or the eyes becoming red, with rare reports of closed-angle glaucoma. There may also be problems urinating, especially in men with an enlarged prostate. In the early clinical trials of LAMA, there were concerns about possible associations with cardiovascular morbidity and mortality, but more recent investigations have largely alleviated these fears (Matera et al, 2014).

Adherence

The efficacy of any drug treatment is largely dependent on patient adherence. Lack of compliance to drug therapy is common in COPD patients, given the high frequency of comorbidities, advanced age and presence of complex medical treatments. The patient's adherence is strongly related to dosing frequency



(Toy et al, 2011). With LAMA having a long duration and once-daily dosing, they are thought to improve adherence to therapy.

Comparative therapy

There are other long-acting drug therapies for COPD and these are activating agents for the sympathetic nervous activity that dilate the lung muscles and increase heart rate. The long-acting β_2-agonists (LABA)—such as formoterol, indacaterol and salmeterol—are a widely used group of drugs that elicit a greater peak bronchodilation over LAMA, but with a shorter duration (usually 12 hours) requiring more dosages. However, trials show LAMA improve long-term lung function to a greater extent. Current guidelines do not distinguish between LAMA and LABA and suggest that the choice between different classes of bronchodilators depends on availability and patient response in terms of symptom relief and side-effects (Global Initiative for Chronic Obstructive Pulmonary Disease, 2014).

Conclusion

Although LAMA are a relatively new type of drug therapy, with new varieties being released, they have some shortcomings as they are still not truly selective muscarinic receptor antagonist. Trials have indicated that LAMA are suitable for maintenance therapy for COPD, but may work better in combination with other therapy, such as long-acting β_2-agonists (Kew et al, 2014), or an inhaled corticosteroid in more complex cases (or for those unresponsive to LAMA monotherapy) (Gershon et al, 2014). BJHCM

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