Information for Parents and Young People on New and Emerging Treatments in Asthma

Asthma continues to be a very common condition that causes a lot of distress to children and their families. For some it is a troublesome condition that can interfere with day-to-day activities such as sports and exercise but for others it can be a very serious condition affecting health, well-being and even risk of serious harm or death.

There are an increasing number of treatments available, and researchers and the pharmaceutical industry continue to look for new treatments. Some new treatments are drugs that are very similar or in the same class of drugs that already exist, for example, new inhaled corticosteroid drugs. Some of these are being developed to make a class of drug work more effectively, or to make them easier to take (e.g. once a day versus twice a day) or are believed to have less side effects. Other new drugs have ways of working that means they are different to any of the drugs we have already. Researchers and drug companies continue to work together to try to find new and better drugs to treat asthma and some of these may become available in the near future.

At present, there are no treatments on the horizon that would be seen as a potential 'cure'. Asthma is a complex condition and is likely caused by a number of different factors. Some people, who have relatives with asthma or other allergic conditions, may have inherited a tendency to asthma. In addition, there are lots of different 'triggers' that can cause swelling in the breathing tubes, for example, pollen or certain animal furs. Also, it is clear now that there are different patterns or 'phenotypes' of illness with some asthmatics starting early in childhood, some later, some starting with infection driven wheeze and others being much more allergic. Understanding these patterns better over recent years has led researchers to consider asthma as not one single condition but a group of conditions that have some common features.

It is unlikely that a single cure will ever emerge for asthma, but improvements may see some types of asthma getting better treatments as developments lead to successful new drugs.

When considering new drugs, we must always consider these in the context of current management strategies. A key reminder of some important approaches before considering new treatments:

- **Drug delivery**: using inhalers correctly is crucial in getting the drugs to the airways where they are needed. Good techniques with spacers for those using 'squirty' (pressurised metered dose inhalers) and with sucking in correctly for those using dry-powder devices is crucial, especially in asthma attacks and in the use of inhaled corticosteroids. Children need support in taking inhalers well and this is one of the most important things a parent can do.
- **Personalised acute asthma plan (PAAP):** knowing how to manage acute symptoms and an asthma attack is vital for all asthmatics. Asthma attacks can be very scary for children and their families, but a PAAP can help you manage an attack in a calm and safe way. Remaining calm and safe with a stepwise plan for treatment works well and can really help children and parents feel they can manage even severe attacks well.
- **Inhaled corticosteroids:** even with the arrival of several new treatments in the last decade, inhaled corticosteroids used every day remain the best preventative treatment. New treatments in recent years are being used in addition to inhaled corticosteroids to give even better asthma control.

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New approaches to well-known treatments

New approaches to Beta 2 Agonists

Beta-2-agonists are drugs that attach to specific small proteins that sit on the outside walls of cells. These are called receptors. By attaching to these receptors, the drug stimulates the receptor to act. Such drugs are called 'agonists'. Beta-2-receptors are found on many cells including the cells that control the muscles of the airways. Beta-2-agonists cause these muscles to relax, so opening up the airways and making it easier to breath.

There are two main classes of drugs in use that are beta-2-agonists: Long-acting beta-2-agonists (LABAs) and short acting beta-2-agonists (SABAs). The reliever inhalers used in asthma uses (such as ***salbutamol*** and ***terbutaline)*** are SABAs

Beta-2 polymorphisms

Research over the last decade has led to a greater understanding of the beta-2 receptor protein. This protein can be very variable from one person to the next with some beta-2-receptor proteins working better than others. A person's genes decide which beta-2-receptor protein they have, and this variability is called '*polymorphic*'**.** Researchers have discovered some people's genes mean they make a beta-2-receptor protein which doesn't respond as well to beta-2-agonist medicines. This is known to be associated with more difficult to treat asthma and may help us understand why some people respond to some treatments better than others.

We cannot yet offer gene testing for beta-2-agonist polymorphisms in routine practice, but many doctors now talk about ***personalised medicines*** coming in the future in which the drugs recommended are very tailored to the individual, including their genetic codes.

New combined inhaled corticosteroid/LABA inhalers

Beclomethasone/formoterol (Fostair)

Fostair is a pressurised inhaler device (or 'squirty' device) that is a combination inhaler with an inhaled corticosteroid (beclomethasone dipropionate or BDP) and a long-acting beta-2 agonist (LABA) (formoterol fumarate). Each metered dose contains 100 micrograms of BDP and 6 micrograms of formoterol. These two drugs have been on the market for some time, in fact beclomethasone is one of the very first inhaled corticosteroid drugs to be used in asthma back in the 1970s. However, the BDP particles in Fostair are smaller than standard beclomethasone inhalers and are therefore more potent. 100 micrograms of Fostair is equivalent to 250 micrograms of standard beclomethasone.

This combination of drugs is aimed at people with asthma not adequately controlled with relievers and inhaled corticosteroids alone, who need to use a LABA. It is an alternative to Seretide pressurised inhaler (fluticasone propionate/salmeterol) and Symbicort dry powder inhaler (budesonide/formoterol).

It is currently licensed for adults (>18 years) and can be used both as a ***maintenance*** day to day preventer and also as an emergency ***relieve***r drug. This is called ***maintenance and reliever treatments (***MART).

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It is given 1 puff twice a day, but an additional 6 puffs can be given during the day as needed as a reliever for symptoms (the dose equivalent of standard BDP for 8 puffs in a day is 2000 micrograms).

Some children's and young people's specialist clinics are now using Fostair inhalers for older teenagers as ***maintenance and reliever treatments***. Fostair is a potent inhaled steroid and may have a higher chance of causing serious steroid side effects. It should only be used off licence in those younger than 18 years with careful advice and monitoring.

Fluticasone furoate/vilanterol (Relvar Ellipta)

Relvar Ellipta is a combination dry powder inhaler containing the inhaled corticosteroid fluticasone furoate and the long-acting beta-2 agonist (LABA) vilanterol. Two strengths of inhaler exist, one with a dose of 92 micrograms of fluticasone and 22 micrograms of vilanterol and the other with a dose of 184 micrograms of fluticasone and 22 micrograms of vilanterol. These are strong inhalers that are thought to be equivalent to Seretide 250micrograms twice a day and 500 micrograms twice a day, respectively. Its advantage is that it is a once-a-day inhaler. There is less data available yet on its side effects, but it has been licenced in 2015 for adults and adolescents aged 12 years and over.

In the specialist children's clinic we use this inhaler in teenagers with severe asthma only who may struggle to remember their twice daily treatments.

New targeted treatments

Monoclonal antibodies

An antibody is a protein that is made by some of the cells of the immune system (e.g. lymphocytes) and is designed primarily to recognise and bind to 'bugs' such as bacteria and viruses. In binding to them they create a signal to other immune cells that can then attach the bug. However, sometimes antibodies can be involved in attacking our own bodies or over-reacting to something. For example, antibody E (or immunoglobulin E also known as IgE for short) is part of the overreaction that occurs in some allergic diseases, including asthma.

A monoclonal antibody is an antibody that is very specific in the protein it binds to. Drug that are manufactured monoclonal antibodies are designed to specifically bind to a protein and in doing so stopping that protein from working.

They are generally a long-term treatment given by injection every 2 or 4 weeks and are intended as an 'add-on' to more standard treatments, including inhaled corticosteroids.

Omalizumab

Omalizumab is a monoclonal antibody treatment that reduces the action of IgE (immunoglobulin E).
It was released in 2013 and is now well established in specialist children's asthma clinics, led by paediatricians with special training in asthma.

Mepolizumab

Mepolizumab is a new treatment that was approved by NICE (National Institute for Clinical and Health Excellence) in January 2017. This treatment is now available for children aged 6 years and above.

The airway inflammation that occurs in asthma is caused by many different inflammatory proteins that cause the airway to become swollen, red and 'twitchy'. Mepolizumab is a specific antibody that binds to a chemical called ***Inetrleukin-5.*** This chemical is one of the messenger chemicals (also called cytokines) that draws ***eosinophils*** into the airways. Eosinophils are one of the key cells involved in allergic asthma.

Mepolizumab is currently licenced for adults and children over 6 years old with the most severe asthma when other treatments have not worked well. The person should have 4 or more asthma attacks in the last year needing oral prednisolone or be on continuous oral prednisolone for over 6 months and most importantly have a blood eosinophil count of more than 300 cells/microlitre in the previous 12 months. It is an expensive drug currently costing £840 per injection and so the use of this is very strictly governed and only those patients who fulfil the above criteria can be given this treatment.

Benralizumab

Benralizumab is a monoclonal antibody being developed by AstraZeneca Pharmaceuticals.

It is designed specifically to bind to the interleukin-5 (IL-5) receptor and thus reduce the effect of IL-5. IL-5 is a key chemical messenger that draws asthma inflammatory cells into the airways.

Currently Benralizumab is only licensed for adults (>18 years).

Dupilimab

Dupilimab is a monoclonal antibody developed by and licensed for severe asthma in those 12 years and over from December 2021. It acts against interleukin 13 This chemical is one of the messenger chemicals (also called cytokines) that draws ***eosinophils*** into the airways. Eosinophils are one of the key cells involved in allergic asthma.

Dupilimab was initially brought in as a treatment for severe eczema in the UK and many children on this for eczema also have asthma. More recently it has been licensed for asthma treatment.

It is licensed for those who have raised blood eosinophils and/or raised FeNO [fractional exhaled nitric oxide] who are inadequately controlled with high dose ICS [inhaled corticosteroid] plus another medicinal product for maintenance treatment'. This means it is only for those with severe asthma who are overseen by a severe asthma specialist team. For children, if they are eligible for the IL-5 monoclonal antibody mepolizumab, they should have tried that first before trying Dupilimab.
There are currently only a few children with asthma on this drug, but we are gradually gaining experience of this.

Fevipiprant

Fevipiprant is a new drug that is still in development. It is given as a tablet twice a day.

Recent research based at Leicester University has shown that this treatment significantly reduces symptoms, improves lung function and reduces asthma inflammation. Its potential advantage is reducing asthma eosinophilic inflammation by taking a pill instead of inhalers.

This drug is now licenced for >12-year-olds with severe asthma that is not controlled with standard medications. At present it is not in widespread use but over time this may be added to the treatments of those with severe asthma.

Other Treatments

Airsonet laminar airflow device

The Airsonet device was licensed in 2010 and is a temperature-controlled laminar airflow device intended to be used as an add-on to standard treatments in those with asthma affected by airborne allergens, particularly those with severe persistent allergic asthma.

So, what does a temperature controlled laminar airflow device mean?
The device sits by the bedside and sucks air in and filters and cools the air before blowing the air gently over the sleeping head. The cooler air means this will fall over the person whilst asleep. It is designed to reduce the number of allergens being breathed in during sleep. It is designed for those with severe asthma who are poorly controlled despite high doses of inhaled corticosteroids.

Two randomised controlled trials of the use of Airsonet in severe asthma showed a significant improvement in quality-of-life questions but no significant reduction in the use of asthma medications or the frequency of asthma attacks. For this reason, many specialist clinics do not favour the Airsonet.

Bronchial thermoplasty

Bronchial thermoplasty is a relatively new treatment that is starting to be used on adults with severe asthma. One of the key features of asthma is wheeze due to severe 'twitchy' airways in which airways narrow due to both inflammation and also due to small fibres of muscle that surround airways contracting. All people have a small amount of muscle, called smooth muscle, that surrounds their bronchial airways. In people with severe asthma the bronchial smooth muscle increases in size (much like the muscles of a body builder who use their biceps to repeatedly lift weights) and this makes the airways narrow even more when an asthma attack occurs.

The treatment is delivered under anaesthesia or sedation as it requires a catheter to be inserted via a bronchoscope (airway camera) into the lungs and delivers pulses of energy circumferentially to the main segments of the airways. This damages the muscles and causes them to shrink. It is usually done three times with at least 3 weeks between treatments.

There is a theoretical risk of developing permanent narrowing (bronchial stenosis) of an airway with this treatment. Also, this treatment has not been tried in children, whose airways are still developing. For young people with severe asthma who transition to an adult specialist clinic, this may be one of the treatments available when you are an adult.