



## Asthma Drugs

Updated: July 7, 2017.

### OVERVIEW

Asthma is a respiratory illness marked by recurrent episodes of airway obstruction, an exaggerated bronchoconstriction response to environmental stimuli, and varying degrees of airway inflammation. Asthma is common, affecting at least 5% of the adult population and often arising in childhood. Asthma can also be severe and is a major cause of morbidity and even mortality in children and young adults.

The therapy of asthma consists of various combinations of inhaled and oral medications, with parenteral agents used during severe attacks. The major classes of agents used for asthma include beta adrenergic agonists, xanthine derivatives, corticosteroids, antileukotrienes, monoclonal antibodies, and miscellaneous agents.

Hepatotoxicity is rare with most antiasthma medications but can occur, particularly with the antileukotrienes. Only oral and parenteral antiasthma agents have been linked to drug induced liver disease. The various inhaled agents have not been definitely linked to liver injury and are not discussed in any detail in this website.

Beta adrenergic bronchodilators act by activation of beta-2 adrenergic receptors on smooth muscle of bronchial tissue, causing relaxation and relief of the bronchoconstriction typical of asthma. Two forms of beta agonists are used in therapy of asthma: short acting agents such as albuterol (salbutamol), bitolterol, metaproterenol and terbutaline; and, the long acting beta agonists such as salmeterol and formoterol. None of these agents has been clearly associated with hepatotoxicity when given orally or by inhalation.

Xanthine derivatives include theophylline which is commonly used and has not been associated with hepatotoxicity in usual oral doses.

Antileukotrienes include the leukotriene receptor antagonists montelukast and zafirlukast, and the lipoxygenase inhibitor zileuton. These agents act by inhibiting the actions or synthesis of the leukotrienes which are potent inflammatory signals that are important mediators of inflammation and injury in asthma. All three of these agents have been associated with rare instances of idiosyncratic, clinically apparent liver injury.

A relatively new approach to therapy of asthma is the use of monoclonal antibodies to inflammatory mediators such as IgE or eosinophils. Omalizumab (Xolair, 2003) is a recombinant humanized monoclonal antibody to IgE that acts by preventing the binding of IgE to mast cells and thus blocking the release of inflammatory mediators of the allergic response. Mepolizumab (Nucala, 2015) and reslizumab (Cinqair, 2016) are humanized monoclonal antibodies to IL-5, a cytokine that promotes the production and maturation of eosinophils. The monoclonal antibodies for asthma require parenteral administration and are typically given as an infusion or subcutaneous injection every 4 weeks. They are generally reserved for cases of severe, persistent asthma not responding adequately to conventional therapies. The monoclonal antibodies used for asthma rarely cause serum enzyme elevations and have not been implicated in cases of clinically apparent liver injury.

Miscellaneous agents include cromolyn sodium, which is used by inhaler and has not been definitely linked to cases of clinically apparent liver injury.

The following links are to individual drug records.

- Beta-2 Adrenergic Agonists
  - Albuterol, Bitolterol, Formoterol, Metaproterenol, Pirbuterol, Salbutamol, Salmeterol, Terbutaline
- Leukotriene Receptor Antagonists
  - Montelukast, Zafirlukast
- Monoclonal Antibodies
  - Benralizumab, Mepolizumab, Omalizumab, Reslizumab
- Xanthine Derivatives
  - Theophylline
- Zileuton

## ANNOTATED BIBLIOGRAPHY

References updated: 07 July 2017

Barnes PJ. Pulmonary pharmacology. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1031-65.

*(Textbook of pharmacology and therapeutics).*

Omalizumab (Xolair): an anti-IgE antibody for asthma. Med Lett Drugs Ther 2003; 45 (1163): 67-8. PubMed PMID: 12915804.

*(Concise review of the safety and efficacy of omalizumab in asthma states that common adverse effects include injection site reactions, rash, diarrhea, nausea, vomiting and epistaxis, and that there have been rare episodes of anaphylaxis [0.09%]; no mention of liver injury or ALT elevations).*

Crompton G. A brief history of inhaled asthma therapy over the last fifty years. Prim Care Respir J 2006; 15: 326-31. PubMed PMID: 17092772.

*(The first modern, pressurized, metered dose inhaler for use in asthma was introduced in 1956; initially using short acting beta-agonists [isoprenaline, fenoterol and salbutamol], followed by corticosteroids, long acting beta-agonists [salmeterol and formoterol] and sodium cromoglycate).*

Makino S, Adachi M, Ohta K, Kihara N, Nakajima S, Nishima S, Fukuda T, et al.; Safety of Sustained-Release Theophylline and Injectable Methylxanthines Committee; Asthma Prevention and Management Guidelines Committee. A prospective survey on safety of sustained-release theophylline in treatment of asthma and COPD. Allergol Int 2006; 55: 395-402. PubMed PMID: 17130682.

*(Survey of 66 medical centers for reports of safety of theophylline in 3921 patients with asthma identified 54 adverse reactions [1.4%], including one instance of ALT elevation, not otherwise described).*

van der Wouden JC, Uijen JH, Bernsen RM, Tasche MJ, de Jongste JC, Ducharme F. Inhaled sodium cromoglycate for asthma in children. Cochrane Database Syst Rev 2008; 4: CD002173. PubMed PMID: 18843630.

*(Systematic review of literature on safety and efficacy of sodium cromoglycate for asthma concludes that it is safe, but has little evidence for efficacy; no mention of hepatotoxicity).*

Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma. NIH Publication 08-4051. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>

*(National Heart, Lung, and Blood Institute supported expert panel committee's guidelines to the treatment of asthma which are regularly updated and available online).*

Drugs for asthma and COPD. *Treat Guidel Med Lett* 2013; 11 (132): 75-86. PubMed PMID: 23896773.

*(Concise review of current recommendations for medical therapy of asthma mentions that both montelukast and zafirlukast have been reported to cause life-threatening hepatic injury and that liver tests should be monitored).*

Chalasan N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. *Gastroenterology* 2015; 148: 1340-52. PubMed PMID: 25754159.

*(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, the only antiasthma drug implicated was montelukast [4 cases: 0.5%]).*

Mepolizumab (Nucala) for severe eosinophilic asthma. *Med Lett Drugs Ther* 2016; 58 (1486): 11-2. PubMed PMID: 26761344.

*(Concise summary of the mechanism of action, clinical efficacy, safety and costs of mepolizumab shortly after its approval in the US for eosinophilic asthma; mentions side effects of headache, back pain, fatigue and infusion site reactions, but does not mention ALT elevations or hepatotoxicity).*

Reslizumab (Cinqair) for severe eosinophilic asthma. *Med Lett Drugs Ther* 2016; 58 (1497): 81-2. PubMed PMID: 27305070.

*(Concise summary of the mechanism of action, clinical efficacy, safety and costs of reslizumab shortly after its approval in the US; mentions side effects of oropharyngeal pain, CK elevations and myalgia and serious adverse events of anaphylaxis [0.3%] and malignancy, but does not mention ALT elevations or hepatotoxicity).*