Exhibit 8: Asthma Medications.

FIGURE 3-1. LONG-TERM-CONTROL MEDICATIONS

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Corticosteroids (Glucocorticoids) *Inhaled:* Beclomethasone dipropionate Budesonide Flunisolide Fluticasone propionate Triamcinolone acetonide	*Indications* ▪ Long-term prevention of symptoms; suppression, control, and reversal of inflammation. ▪ Reduce need for oral corticosteroid. *Mechanisms* ▪ **Anti-inflammatory.** Block late reaction to allergen and reduce airway hyperresponsiveness. Inhibit cytokine production, adhesion protein activation, and inflammatory cell migration and activation. ▪ Reverse beta$_2$-receptor down-regulation. Inhibit microvascular leakage.	▪ Cough, dysphonia, oral thrush (candidiasis). ▪ In high doses (see figure 3-5b), systemic effects may occur, although studies are not conclusive, and clinical significance of these effects has not been established (e.g., adrenal suppression, osteoporosis, growth suppression, and skin thinning and easy bruising) (Barnes and Pedersen 1993; Kamada et al. 1996).	▪ Spacer/holding chamber devices and mouth washing after inhalation decrease local side effects and systemic absorption. ▪ Preparations are not absolutely interchangeable on a mcg or per puff basis (see figure 3-5c for estimated clinical comparability). New delivery devices may provide greater delivery to airways, which may affect dose. ▪ The risks of uncontrolled asthma should be weighed against the limited risks of inhaled corticosteroids. The potential but small risk of adverse events is well balanced by their efficacy. (See text.) ▪ Dexamethasone is not included because it is highly absorbed and has long-term suppressive side effects.
Systemic: Methylprednisolone Prednisolone Prednisone	*Indications* ▪ For short-term (3–10 days) "burst": to gain prompt control of inadequately controlled persistent asthma. ▪ For long-term prevention of symptoms in severe persistent asthma: suppression, control, and reversal of inflammation. *Mechanisms* ▪ Same as inhaled.	▪ Short-term use: reversible, abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis of femur. ▪ Long-term use: adrenal axis suppression, growth suppression, dermal thinning, hypertension, diabetes, Cushing's syndrome, cataracts, muscle weakness, and—in rare instances—impaired immune function. ▪ Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, and *Strongyloides*.	Use at lowest effective dose. For long-term use, alternate-day a.m. dosing produces least toxicity. If daily doses are required, one study shows improved efficacy with no increase in adrenal suppression when administered at 3 p.m. rather than in the morning (Beam et al. 1992).

FIGURE 3-1. LONG-TERM-CONTROL MEDICATIONS (CONTINUED)

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Cromolyn Sodium and Nedocromil	*Indications* ▪ Long-term prevention of symptoms; may modify inflammation. ▪ Preventive treatment prior to exposure to exercise or known allergen. *Mechanisms* ▪ **Anti-inflammatory.** Block early and late reaction to allergen. Interfere with chloride channel function. Stabilize mast cell membranes and inhibit activation and release of mediators from eosinophils and epithelial cells. ▪ Inhibit acute response to exercise, cold dry air, and SO_2.	15 to 20 percent of patients complain of an unpleasant taste from nedocromil.	▪ Therapeutic response to cromolyn and nedocromil often occurs within 2 weeks, but a 4- to 6-week trial may be needed to determine maximum benefit. ▪ Dose of cromolyn MDI (1 mg/puff) may be inadequate to affect airway hyperresponsiveness. Nebulizer delivery (20 mg/ampule) may be preferred for some patients ▪ Safety is the primary advantage of these agents.
Long-Acting Beta$_2$-Agonists *Inhaled:* Salmeterol	*Indications* ▪ Long-term prevention of symptoms, especially nocturnal symptoms, added to anti-inflammatory therapy ▪ Prevention of exercise-induced bronchospasm. ▪ *Not to be used to treat acute symptoms or exacerbations.* *Mechanisms* ▪ **Bronchodilation.** Smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction. ▪ In vitro, inhibit mast cell mediator release, decrease vascular permeability, and increase mucociliary clearance. ▪ Compared to short-acting inhaled beta$_2$-agonist, salmeterol (but not formoterol) has slower onset of action (15 to 30 minutes) but longer duration (>12 hours).	▪ Tachycardia, skeletal muscle tremor, hypokalemia, prolongation of QT_c interval in overdose. ▪ A diminished bronchoprotective effect may occur within 1 week of chronic therapy. Clinical significance has not been established. ▪ See text for additional discussion.	▪ Not to be used to treat acute symptoms or exacerbations. ▪ Clinical significance of potentially developing tolerance is uncertain because studies show symptom control and bronchodilation are maintained. ▪ Should not be used in place of anti-inflammatory therapy. ▪ May provide more effective symptom control when added to standard doses of inhaled corticosteriod compared to increasing the corticosteriod dosage.
Oral: Albuterol, sustained-release			▪ *Inhaled long-acting beta$_2$-agonists are preferred because they are longer acting and have fewer side effects than oral sustained-release agents.*

FIGURE 3-1. LONG-TERM-CONTROL MEDICATIONS (CONTINUED)

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Methylxanthines Theophylline, sustained-release tablets and capsules	*Indications* ▪ Long-term control and prevention of symptoms, especially nocturnal symptoms. *Mechanisms* ▪ **Bronchodilation.** Smooth muscle relaxation from phosphodiesterase inhibition and possibly adenosine antagonism ▪ May affect eosinophilic infiltration into bronchial mucosa as well as decrease T-lymphocyte numbers in epithelium. ▪ Increases diaphragm contractility and mucociliary clearance.	▪ Dose-related acute toxicities include tachycardia, nausea and vomiting, tachyarrhythmias (SVT), central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia, and hypokalemia. ▪ Adverse effects at usual therapeutic doses include insomnia, gastric upset, aggravation of ulcer or reflux, increase in hyperactivity in some children, difficulty in urination in elderly males with prostatism.	▪ Maintain steady-state serum concentrations between 5 and 15 mcg/mL. Routine serum concentration monitoring is essential due to significant toxicities, narrow therapeutic range, and individual differences in metabolic clearance. Absorption and metabolism may be affected by numerous factors (see figure 3-5a), which can produce significant changes in steady-state serum theophylline concentrations. ▪ Not generally recommended for exacerbations. There is minimal evidence for added benefit to optimal doses of inhaled beta$_2$-agonists. Serum concentration monitoring is mandatory.
Leukotriene Modifiers			
Zafirlukast tablets	*Indications* ▪ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥12 years of age. *Mechanisms* ▪ **Leukotriene receptor antagonist**; selective competitive inhibitor of LTD4 and LTE4 receptors.	▪ No specific adverse effects to date. As with any new drug, there is possibility of rare hypersensitivity or idiosyncratic reactions that cannot usually be detected in initial premarketing trials. One reported case of reversible hepatitis and hyperbilirubinemia; high concentrations may develop in patients with liver impairment.	▪ Administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. ▪ Inhibits the metabolism of warfarin and increases prothrombin time; it is a competitive inhibitor of the CYP2C9 hepatic microsomal isozymes. (It has not affected elimination of terfenadine, theophylline, or ethinyl estradiol drugs metabolized by the CYP3A4 isozymes.)
Zileuton tablets	*Indications* ▪ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥12 years of age. *Mechanisms* ▪ **5-lipoxygenase inhibitor.**	▪ Elevation of liver enzymes has been reported. Limited case reports of reversible hepatitis and hyperbilirubinemia.	▪ Zileuton is microsomal CYP3A4 enzyme inhibitor that can inhibit the metabolism of terfenadine, warfarin, and theophylline. Doses of these drugs should be monitored accordingly. ▪ Monitor hepatic enzymes (ALT).

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FIGURE 3-2. QUICK-RELIEF MEDICATIONS

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Short-Acting Inhaled Beta$_2$-Agonists Albuterol Bitolterol Pirbuterol Terbutaline	*Indications* ▪ Relief of acute symptoms; quick-relief medication. ▪ Preventive treatment prior to exercise for exercise-induced bronchospasm. *Mechanisms* ▪ **Bronchodilation.** Smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction.	Tachycardia, skeletal muscle tremor, hypokalemia, increased lactic acid, headache, hyperglycemia. Inhaled route, in general, causes few systemic adverse effects. Patients with preexisting cardiovascular disease, especially the elderly, may have adverse cardiovascular reactions with inhaled therapy.	▪ Drugs of choice for acute bronchospasm. Inhaled route has faster onset, fewer adverse effects, and is more effective than systemic routes. The less beta$_2$-selective agents (isoproterenol, metaproterenol, isoetharine, and epinephrine) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses. Albuterol liquid is not recommended. ▪ For patients with mild intermittent asthma, regularly scheduled daily use neither harms nor benefits asthma control (Drazen et al. 1996). Regularly scheduled daily use is not generally recommended. ▪ Increasing use or lack of expected effect indicates inadequate asthma control. >1 canister a month (e.g., albuterol-200 puffs per canister) may indicate overreliance on this drug; ≥2 canisters in 1 month poses additional adverse risks. ▪ For patients frequently using beta$_2$-agonist, anti-inflammatory medication should be initiated or intensified.
Anticholinergics Ipratropium bromide	*Indications* ▪ Relief of acute bronchospasm (see Therapeutic Issues column). *Mechanisms* ▪ **Bronchodilation.** Competitive inhibition of muscarinic cholinergic receptors. ▪ Reduces intrinsic vagal tone to the airways. May block reflex bronchoconstriction secondary to irritants or to reflux esophagitis. ▪ May decrease mucus gland secretion.	Drying of mouth and respiratory secretions, increased wheezing in some individuals, blurred vision if sprayed in eyes.	▪ Reverses only cholinergically mediated bronchospasm; does not modify reaction to antigen. Does not block exercise-induced bronchospasm. ▪ May provide additive effects to beta$_2$-agonist but has slower onset of action. ▪ Is an alternative for patients with intolerance to beta$_2$-agonists. ▪ Treatment of choice for bronchospasm due to beta-blocker medication.

FIGURE 3-2. QUICK-RELIEF MEDICATIONS (CONTINUED)

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Corticosteroids *Systemic:* Methylprednisolone Prednisolone Prednisone	*Indications* ▪ For moderate-to-severe exacerbations to prevent progression of exacerbation, reverse inflammation, speed recovery, and reduce rate of relapse. *Mechanisms* ▪ **Anti-inflammatory.** See figure 3-1.	▪ Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis of femur. ▪ Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, and *Strongyloides*.	▪ Short-term therapy should continue until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3 to 10 days but may require longer. ▪ There is no evidence that tapering the dose following improvement prevents relapse.

FIGURE 3-5d. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS

Medication	Dosage Form	Adult Dose	Child Dose	Comments
Short-Acting Inhaled Beta$_2$-Agonists				
	MDI			
Albuterol Albuterol HFA Bitolterol Pirbuterol Terbutaline	90 mcg/puff, 200 puffs 90 mcg/puff, 200 puffs 370 mcg/puff, 300 puffs 200 mcg/puff, 400 puffs 200 mcg/puff, 300 puffs	■ 2 puffs 5 minutes prior to exercise ■ 2 puffs tid-qid prn	■ 1-2 puffs 5 minutes prior to exercise ■ 2 puffs tid-qid prn	■ An increasing use or lack of expected effect indicates diminished control of asthma. ■ Not generally recommended for long-term treatment. Regular use on a daily basis indicates the need for additional long-term-control therapy. ■ Differences in potency exist so that all products are essentially equipotent on a per puff basis. ■ May double usual dose for mild exacerbations. ■ Nonselective agents (i.e., epinephrine, isoproterenol, metaproterenol) are not recommended due to their potential for excessivecardiac stimulation, especially in high doses.
	DPI			
Albuterol Rotahaler	200 mcg/capsule	1-2 capsules q 4-6 hours as needed and prior to exercise	1 capsule q 4-6 hours as needed and prior to exercise	
	Nebulizer solution			
Albuterol	5 mg/mL (0.5%)	1.25-5 mg (.25-1 cc) in 2-3 cc of saline q 4-8 hours	0.05 mg/kg (min 1.25 mg, max 2.5 mg) in 2-3 cc of saline q 4-6 hours	May mix with cromolyn or ipratropium nebulizer solutions. May double dose for mild exacerbations.
Bitolterol	2 mg/mL (0.2%)	0.5-3.5mg (.25-1 cc) in 2-3 cc of saline q 4-8 hours	Not established	May not mix with other nebulizer solutions.
Anticholinergics				
	MDI			
Ipratropium	18 mcg/puff, 200 puffs	2-3 puffs q 6 hours	1-2 puffs q 6 hours	Evidence is lacking for anticholinergics producing added benefit to beta$_2$-agonists in long-term asthma therapy.
	Nebulizer solution .25 mg/mL (0.025%)	0.25 mg q 6 hours	0.25-0.5 mg q 6 hours	
Systemic Corticosteroids		(Applies to all three systemic corticosteroids)		
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	■ Short course "burst": 40-60 mg/day as single or 2 divided doses for 3-10 days	■ Short course "burst": 1-2 mg/kg/day, maximum 60 mg/day, for 3-10 days	■ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. ■ The burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3-10 days but may require longer. There is no evidence that tapering the dose following improvement prevents relapse.
Prednisolone	5 mg tabs, 5 mg/5 cc, 15 mg/5 cc			
Prednisone	1, 2.5, 5, 10, 20, 25 mg tabs; 5 mg/cc, 5 mg/5 cc			