Three phases constitute the course of drug actions from dose to effect: pharmaceutical, pharmacokinetic and the pharmacodynamic phase.

I. PHARMACEUTICAL PHASE

This phase describes the route by which a drug is made available to the body. The advantages for treatment with inhaled aerosols are as follows:

• Aerosol doses are usually smaller than doses for systemic administration
• Onset of drug action is rapid
• Delivery is targeted to the lungs
• Systemic side effects are often fewer and less severe

Disadvantages to treatment with inhaled aerosols include:

• Variables affecting the delivered dose
• Lack of adequate knowledge on device performance and use among patients and caregivers

II. PHARMACOKINETIC PHASE

This phase describes the time course and disposition of a drug in the body based on its absorption, distribution, metabolism and elimination.

III. PHARMACODYNAMIC PHASE

This phase describes the mechanisms of drug action, by which a drug molecule causes its effects in the body. Drug effects are caused by the combination of a drug with its matching receptor. Pharmacological control of the airway is mediated by receptors found on the smooth muscle, secretory cells, bronchial epithelium, and pulmonary and bronchial blood vessels.

Each class of drug will be described briefly:

A. Adrenergic Bronchodilators

Adrenergic: a drug that stimulates a receptor responding to norepinephrine or epinephrine. The general indication for use is the presence of reversible airflow obstruction. The most common use of these agents is to improve flow rates in asthma (including exercise induced), acute and chronic bronchitis, emphysema, bronchiectasis, cystic fibrosis, and other obstructive airway states.

Adrenergic bronchodilators can stimulate one or more of the following receptors, with the effects described:

• Alpha-receptors: causes vasoconstriction and a vasopressor effect (increased blood pressure)
• Beta1-receptors: causes increased heart rate and myocardial contractility
• Beta2-receptors: relaxes bronchial smooth muscle, stimulates mucociliary activity, and has some inhibitory action on inflammatory mediator release

Adrenergic bronchodilator agents are all adrenergic agonists. The differences among individual agents are due to their receptor preferences and their different pharmacokinetics. These differences determine the optimal clinical application.

There are 3 subgroups: short-acting catecholamines, intermediate-acting noncatecholamine agents and long-acting adrenergic bronchodilators.

Short-acting catecholamines include the older agents such as epinephrine (Adrenaline, MicroNepfrin, Vaponefrin, and racemic epinephrine), isoproterenol (Isuprel), and isoetharine (Bronkosol).

Intermediate-acting noncatecholamines include longer acting (usually 4-6 hours) Beta2 specific agents including: metaproterenol (Alupent), terbutaline (Brethine, Bricanyl, Brethaire), albuterol (Proventil, Ventolin) and pributerol (Maxair). These drugs are more suited to a maintenance schedule.
Long-acting adrenergic bronchodilators are relatively new on the market and have a longer duration of action (about 12 hours). They are excellent for maintenance therapy, but not as well-suited for relief of acute airflow obstruction due to slow onset. The most common is salmeterol (Serevent).

The potential adverse effects of adrenergic bronchodilators include, but are not limited to:

- Tremors
- Headache
- Insomnia
- Nervousness
- Dizziness
- Hypokalemia
- Propellant-induced bronchospasm
- Worsening ventilation-perfusion ratio

B. Anticholinergic Bronchodilators

Anticholinergic: a drug that blocks a receptor for acetylcholine. Produces airway relaxation through blockade of cholinergic-induced bronchoconstriction. This agent is only effective if bronchoconstriction exists due to cholinergic activity.

Ipratropium bromide (Atrovent) is the only agent approved in the US as an inhaled anticholinergic bronchodilator although additional agents are under investigation. Several other anticholinergic agents (antimuscarinics) are used as bronchodilators including ipratropium bromide and albuterol (Combivent) and glycopyrrolate (Robinul).

Side effects of ipratropium bromide include, but are not limited to:

- Cough
- Dry mouth
- Nervousness
- Dizziness
- Headache

C. Mucus Controlling Agents

Two agents are currently approved in the US for oral inhalation that have an effect on mucus. Both agents are mucolytics, though their modes of action differ.

Acetylcystine (Mucomyst) is indicated for the treatment of excessive viscous mucus secretions that may occur in COPD, acute tracheobronchitis, bronchiectasis or TB. It acts by breaking a portion of the disulfide group of the gel bond in mucus. Acetylcystine is effective in lowering viscosity and can be used in direct instillation during bronchoscopy to remove mucus plugs. There are several side effects including: airway irritation and bronchospasm.

Dornase Alfa (Pulmozyme) is indicated in the management of cystic fibrosis to treat purulent mucoid secretions and to reduce the frequency of exacerbations due to respiratory infections. Common side effects include: pharyngitis, laryngitis, and chest pain.

D. Bland Aerosols

Bland aerosols of water and saline have been traditionally used to improve mobilization of secretions in respiratory disease states. They have been found to increase secretion clearance and mucus production and cause productive coughing.

E. Inhaled Corticosteroids

Corticosteroids used in respiratory conditions are all glucocorticoids. There are 2 general formulations; orally inhaled and intranasal aerosol preparations. The primary use of inhaled steroids is for anti-inflammatory maintenance therapy of mild to moderate asthma and for the control of seasonal allergies.
It is important for patients to understand that steroid inhalers will not provide immediate relief, however daily compliance is essential to control inflammation.

The most common steroid inhalers are: dexamethasone sodium phosphate (Decadron Respihaler), beclomethasone dipropionate (Beclovent, Vanceril), triamcinolone acetonide (Azmacort), flunisolide (AeroBid), fluticasone propionate (Flovent) and budesonide (Pulmicort).

The side effects of all steroid inhalers include: adrenal insufficiency, extrapulmonary allergy, acute asthma, oropharyngeal fungal infections, cough, and bronchoconstriction.

All inhaled steroids should be given with a reservoir device and the mouth should be rinsed after use.

F. Mediator Antagonists

Mediator antagonists are a growing class of drugs in the treatment of asthma. The agents in this drug class include: cromolyn sodium (Intal), nedocromil sodium (Tilade), Zafirlukast (Accolate), zileuton (Zyflo), and montelukast (Singulaire). The last 2 are administered orally, but are classified as bronchoactive drugs. All of these are indicated for the prophylactic treatment of asthma.

The main side effects with any of the mediator antagonists in inappropriate use. They are of no use in acute airway obstruction of asthma. Other side effects include: cough, headache, nausea, vomiting, wheezing, and dry mouth.

G. Anti-infective Agents

Anti-infective agents available in aerosol form include pentamidine isethionate, ribavirin, and tobramycin. In addition a number of antibiotics can be aerosolized.

Pentamidine is used in the treatment of opportunistic pneumonia caused by *Pneumocystis carinii* (PCP). Possible side effects include, but are not limited to: cough, bronchial irritation, bronchospasm, wheezing, fatigue, rash, chest pain, and shortness of breath.

Ribavirin is an antiviral agent used in the treatment of respiratory syncytial virus (RSV) infection. The cost effectiveness is still debated due to the fact that the disease is usually self-limiting. Adverse effects include: skin rash, eyelid erythema, and conjunctivitis.

Aerosolized antibiotics have been used in a variety of pulmonary infections. The most experience clinically is with cystic fibrosis. The aerosolization of antibiotics by Small Volume Nebulizer can require a higher than usual flow rate, such as 10-12 lpm, due to differing viscosities.

Aerosol Drug Delivery Systems

Effective aerosol delivery systems require a device that quickly delivers effective and sufficient drug to the site of action with minimal waste at a low cost. Aerosol generators used clinically include metered dose inhalers, dry powder inhalers, and small and large volume jet nebulizers.

I. Metered Dose Inhalers

Metered dose inhalers are the most commonly prescribed method of aerosol delivery in the US. Properly used, MDIs are at least as effective as other nebulizers for drug delivery. The successful administration of drugs by MDI is highly technique dependent. Due to this factor it is important for the clinician to spend ample time with the patient for instruction of MDI use.

Advantages to MDIs include: convenience, inexpensive, portable, no drug preparation is required, and the drug is difficult to contaminate. The disadvantages include: patient coordination and activation is required, a high percentage of pharyngeal deposition is possible, potential abuse, difficulty in delivering high doses, and most units use ozone-depleting chlorofluorocarbons (CFC).

II. Dry Powder Inhalers
A dry powder inhaler is a breath-actuated metered dosing system. In terms of both drug deposition and drug response, they are at least as effective as MDIs. Proper technique is essential. The patient must have a high inspiratory flow to produce a respirable powder.

Advantages to DPIs include: breath activation, breath-hold not required, can provide accurate dose counts, and do not contain CFC. Disadvantages include: high inspiratory flow is required, usually single dose, can result in pharyngeal deposition, not all medications are available, and difficulty in delivering high doses.

III. Small Volume Nebulizers

Small volume nebulizers are powered by high pressure air or oxygen, as provided by a compressor, gas cylinder, or 50psi wall outlet. Nebulizer design, gas source, and medication characteristics all affect SVN performance. Variations in aerosol output and particle size, in turn, effect where the delivered drug will deposit and what affect it will have.

Advantages include: minimal patient coordination is required, high doses are possible, and no CFC release. Disadvantages include: expensive, wasteful, drug preparation required, possible contamination, not all medications are available, pressurized gas source is required, and length of treatment time.

IV. Large Volume Nebulizers

Large volume nebulizers are particularly useful when traditional dosing strategies are ineffective in treating bronchospasm. To avoid giving SVN treatments 15 minutes apart, the large volume nebulizer can be adapted to an IV infusion pump to drip premixed bronchodilator solutions into the reservoir.

Advantages and disadvantages are the same as for SVN.