Commonly Used Drugs – Uses, Side Effects, Bioavailability & Approaches to Improve it

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Contents

Preface

Pharmacology is the science of medicine used in animals and humans. Many prescribed drugs are dispensed by pharmacists on a daily basis, and this is considered one of the most dangerous and important activities practiced by pharmacists. Comprehensive knowledge and critical understanding of the pharmacology principles which include the pharmacokinetics and pharmacodynamics of drugs is the solid basis for a safe and effective therapeutic practice.

The focus of this book is on providing comprehensive, authoritative, and readable chapters on classes of commonly used drugs for medical and pharmacy students, nurses, junior doctors, pharmacists and other allied professionals in the health sciences.

This book is a collaborative effort by the editor and some of his colleagues and graduate students as coauthors. The book is mainly devoted on describing the pharmacology, pharmacokinetics, uses, side effects and ways to improve the bioavailability for some of the most commonly used drugs.

The first chapter introduces a comprehensive overview on the definition of drugs, approaches of drugs classification and some important aspects of drugs design and development, drug effectiveness and safety, and drug errors.

The second chapter describes the three antibiotic classes, their mechanism of action, clinical uses, side effects, and their resistance by different bacteria. These described antibiotics include vancomycin, penicillins, cephalosporins, carbapenems tetracyclines, aminoglycosides, macrolides, chloramphenicol, fluoroquinolones and sulfonamides.

The third chapter discusses the current used medicines for treating pain. These medications include the non-steroidal anti-inflammatories (NSAIDs), acetaminophen and opiates and their combination.

The fourth chapter describes a number of drugs used to lower lipid levels in the blood such as statins, their adverse effects and methods to improve their bioavailability.

The fifth chapter is devoted to the description of the pathogenesis and types of diabetes and the current used drugs to treat this disease. In addition, a detailed description of the pharmacokinetic properties, mechanism of action, side effects of known anti-hyperglycemic agents is presented.

The sixth chapter describes the two different classes of anti-hemorrhagic agents (hemostatic agents): the first class includes systemic drugs such as tranexamic acid, ω-aminocaproic acid, anti-inhibitor coagulant complex-heat treated, anti-hemophilic factor, factor IX, carbazochrome, fibrinogen concentrate, oprelvekin and phylloquinone, and the

second class of hemostatic agent is the local acting agents such as cellulose, collagen, gelatin, thrombin and thrombin combination products.

The seventh chapter is devoted to osteoporosis (a progressive bone disease) and the various therapies available for treating this disease such as bisphosphonates, raloxifene, calcitonin, teriparatide and denosumab.

The last chapter is devoted to the description of two different autoimmune diseases; multiple sclerosis (MS) and psoriasis. Up to date there is no known cure for MS and psoriasis. The available treatments approved by the FDA are mainly considered symptom relieving drugs and their major therapeutic action is only to slow the disease progression, and they lack the ability to eliminate the disease completely. A great devotion in this chapter was given to discuss several aspects regarding fumarate acid esters including; pharmacokinetics, mode of action, recommendations and specifically their potential as an effective treatment for psoriasis and MS.

I want to express my sincere gratitude to all coauthors for their great efforts and cooperation. It has been a pleasure for me to be in the center of composing this nice piece of pharmacology book. I hope that this book will provide a succinct review of pharmacology with over 750 references. It is especially helpful to undergraduate and graduate students preparing for variety types of examinations.

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Editor

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Chapter 1

Drug Overview

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Abstract

A drug is a chemical substance with known biological effects on humans or other animals. In the pharmacology field, a drug is defined as a chemical substance used in the treatment, cure, prevention, or diagnosis of disease or used to otherwise enhance physical or mental well-being. Drugs usually affect either normal or abnormal physiological processes. Drugs may be used for a limited duration, or on a regular basis for chronic disorders. The way drugs are classified or grouped are confusing. Therefore, a new approach of drugs classification is presented in this chapter along with general information on drugs which includes definition, drugs and diseases types, drugs administration, drugs interactions and drug names. In addition, the chapter describes some important aspects of drugs design and development, drug effectiveness and safety, and drug errors.

Keywords: Drugs, Disease, Drug classification, Drug administration, OTC drugs, Prescription drugs, Drug interactions, Drug safety

Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ADME	Absorption, Distribution, Metabolism and Excretion
AIDS	Acquired Immune Deficiency Syndrome
API	Active Pharmaceutical Ingredients
BCS	Biopharmaceutical Classification System
BP	Blood Pressure

BTC	Behind-the-Counter
CNS	Central Nervous System
CoA	Coenzyme A
COMT	Catechol O-Methyltransfarase
Cox-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
DDT	Dichlorodiphenyltrichloroethane
DMARDs	Disease- Modifying Antirheumatic Drugs
DNA	Deoxyribonucleic Acid
DPP-IV	Dipeptidyl Peptidase-IV
FDA	Food and Drug Administration
GERD	Gastroesophageal Reflux Disease
GIT	Gastrointestinal Tract
HCl	Hydrochloric Acid
HMG-CoA	3-Hydroxy-3-Methylglutaryl-Coenzyme A
I.V	Intravenous Injection
IM	Intramuscular Injection
INR	*International Normalized Ratio*
IRB	Institutional Research Board
K_{cal}	Kilocalorie
LSD	Lysergic Acid Diethylamide
MAO	Monoamine Oxidases
MAOIs	Monoamino Oxidase Inhibitors
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
OMAs	Organic Medicinal Agents
OTC	Over-the-Counter
POM	Prescription Only Medicines
R&D	Research and Development
RNA	Deoxyribonucleic acid
R_x	Medical Prescriptions
SAM	S-Adenosylmethionine
SAR	Structure Activity Relationships
Sc	Subcutaneous
SNRI	Serotonin Nonselective Reuptake Inhibitor
SSRIs	Selective Serotonin Reuptake Inhibitors
T_3	Triiodothyronine
T_4	Thyroxine
TCA	Tricyclic Antidepressant
TNF	Tumor Necrosis Factor

Drugs Definition

A drug is a chemical substance that has known biological effects on humans or other animals, used in the treatment, cure, mitigation, prevention, or diagnosis of disease or used to

enhance physical or mental well-being. Drugs may be used for a limited duration, or on a regular basis for chronic disorders. Drugs are generally taken to cure and/or relieve any symptoms of an illness or medical condition, or may be used as prophylactic medicines. A drug usually interacts with either normal or abnormal physiological process in a biological system, and produces a desired and positive biological action. If the drug's effect helps the body, the drug is called a medicine, whereas, if its effect causes harm to the body, the drug is classified as a poison [1-3]. The drugs can treat different types of diseases such as infectious diseases, non-infectious diseases, and non-diseases (alleviation of pain, prevention of pregnancy and anesthesia).

Disease Classification

There are three various ways of expressing human ill-health: disease, illness and sickness. Disease is abnormal pathophysiological conditions affects either part or all or the body organisms and associated with a group of signs, symptoms and laboratory findings linked by a common pathophysiologic sequence.

Disease may be caused due to external sources, such as infectious diseases such as bacteria (pneumonia, salmonella), viruses (common cold, AIDS), fungi (thrush, athletes foot) and parasites (malaria) or it may be caused due to internal dysfunctions, such as autoimmune diseases or non-infectious diseases such as disorders of the human body caused by genetic malfunction, environmental factors, stress, old age etc. (e.g., diabetes, heart disease, cancer, hemophilia, asthma, mental illness, stomach ulcers, arthritis). Diseases are most likely affect people physically, and/or emotionally.

Diseases could be acute (short e.g., common cold, respiratory infections) or chronic (lasts for a long time, above six months e.g., diabetes, asthma, arthritis, cancer). Illness is a condition of being unhealthy in the body or mind or it is the subjective state of the individual who feels aware of not being well. The ill individual may or may not be suffering from disease (illness can include lethargy, depression, anorexia, sleepiness, hyperalgesia and inability to concentrate). Sickness is the social role assumed by an individual suffering from an illness.

Other terms for ill-health are syndrome and conditions; when the signs and symptoms have not yet clearly been placed in a common pathophysiologic sequence the disease is referred to as a syndrome. Diseases of a chronic nature are sometimes called conditions, especially if they are present since birth [4-5]. Thus; a disease is a condition of impaired health resulting from a disturbance in the structure or function of the body.

Diseases may be classified into the following major categories:

- *Infectious diseases*: also known as transmissible or communicable diseases. They are caused by microorganisms, viruses, rickettsia, bacteria, fungi, protozoa and worms. They are contagious illnesses that can be transmitted between people or animals in a variety of ways. All communicable diseases are transmitted *via* some form of infectious pathogen. A communicable disease that passes through sexual contact is

called a sexually transmitted disease. Antibiotics, antivirals, antifungals, antiprotozoal and anthelminthic agents are the drugs used to treat infectious diseases.

- *Non-communicable diseases*: non-infectious and non-transmissible. They are not mainly caused by an acute infection and result in long-term health consequences and often create a need for long-term treatment and care. They are chronic and considered as the number one cause of death and disability in the world. These include chronic lung disease, autoimmune disease, heart disease, stroke, cancers, asthma, diabetes, chronic kidney disease, osteoporosis, Alzheimer's disease, injuries and mental health disorders and more.
- *Allergic diseases*: are caused by antigens and foreign substances.
- *Metabolic disorders*: are caused by defects in the body's ability to carry out normal reactions, these may be hereditary, deficiency, and congenital defects.
- *Cancer:* is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. The majority of cancers are due to environmental factors and the remaining are due to inherited genetics.
- *Toxic diseases*: are caused by the consumption of substances, which are harmful to the human body (caused by poisons).
- *Psychosomatic and mental diseases*: psychosomatic disorders are diseases which involve both mind (psyche) and body (soma). These may include affective emotional instability, behavioral dysregulation, and/or cognitive dysfunction or impairment. These include major depression, generalized anxiety disorder, schizophrenia, and attention deficit hyperactivity disorder (ADHD). These diseases affected the ability of a person to work or study and harm his life including interpersonal relationships.
- *Miscellaneous diseases*: Among this class are foodborne illness or food poisoning, airborne diseases, lifestyle diseases (any disease that appears to increase in frequency as countries become more industrialized and people live longer, especially if the risk factors include behavioral choices like a sedentary lifestyle or a diet high in unhealthful foods such as refined carbohydrates, trans fats, or alcoholic beverages) and organic diseases (caused by a physical or physiological change to some tissue or organ of the body, excluding infections and mental disorders).

The general classification of diseases which is most widely used, is that based on pathogenesis or disease mechanisms. Most diseases can be assigned in the following classification:

(i) Congenital diseases: also referred as birth defects; the conditions existing at birth and often before birth, involve defects in or damage to a developing fetus. They may be genetic (inherited or sporadic mutations, inheritance of abnormal genes from the parents) and non-genetic (environmental or accidental). The causes also include fetal alcohol exposure, toxic substances (drugs and/or environmental toxin during pregnancy), infections, lack of nutrients (folic acid), radiation and physical restraint [5]. Congenital anomalies and preterm birth are important causes of childhood death, chronic illness, and disability in many countries.

(ii) Acquired diseases: the medical condition which develops after birth. For example, inflammatory, hemodynamic, growth disorders, injury and disordered repair, disordered immunity, metabolic and degenerative disorders [5].

Drugs Classification

There are different ways to group or classify drugs; therefore, different classification systems for therapeutic agents exist. A drug may be classified by its chemical structure; by the way it is used to treat a particular condition, by its source or by its mechanism of action. Each drug can be classified into one or more drug classes [3, 6].

Drug can be classified by the following ways:

1. By its pharmacological effect; drugs are classified by their biological effect they have, e.g., anti-inflammatory, analgesics, antiviral, anticancer, antianxiety, anti-depressants, antipsychotics, antihypertensive, antibacterial agents, antiarrhythmic, diuretics and others [7-9].
2. By its chemical structure; drugs are grouped together by their chemical structures based on a common skeleton they have. Some examples include sulfonamides, sulfonylurea, tricyclic antidepressants, β-lactams (penicillins), barbiturates, opiates, steroids, catechol amines, aminoglycosides and others. All drugs of a certain chemical group have the same uses, or act on the same site of action [9].
3. By its target system; drugs in this class are classified according to a certain target or target organ system in the body where they affect. Examples for such class include drugs acting on the cardiovascular system, drugs acting on the nervous system, drugs acting on the gastrointestinal system and drugs acting on the musculoskeletal system [9].
4. By its site of action; drugs are classified according to the drug targets (receptors, enzymes, cell lipids, pieces of DNA or RNA and carbohydrates) where they interact. Most of drugs interact with enzymes or receptors to give their biological action and others interact with other drug targets such as, drugs inhibit the enzyme acetylcholinesterases. This classification is specific as most of drugs targets have been identified. The drugs in this group have a common mechanism of action [9].
5. By its mechanism of action; there are a difference between actions of drugs and their effects. Drugs are classified by a specific biochemical interaction through which a drug substance produces its pharmacological effect. Drugs are divided into six classes according to their biochemical mechanism of action: (i) signal-transduction systems, (ii) other components of plasmatic membranes, (iii) intracellularly, (iv) a gene therapy, (v) extracellularly and (vi) invasive agents [9-11]. A mechanism of action usually includes the specific molecular targets to which the drug binds or interacts. For example; the mechanism of action of non-steroidal anti-informatory (NSAIDs) drugs is by inhibiting cyclooxygenase enzyme and thus stopping the production of prostaglandins and thromboxane and as a result reducing the pain and inflammation. One major problem of pharmacology is that there is no such a drug

which produces only a single effect. The primary effect is the desired therapeutic effect. Secondary effects are all other effects beside the desired effect which may be either beneficial or harmful. Drugs are chosen to exploit differences between normal metabolic processes and any abnormalities which may be present. Since the differences may not be great, drugs may be nonspecific in action and alter normal functions as well as the undesirable ones which lead to unwanted side effects. The mechanisms of action of some drugs are still unknown. Many drugs have multiple mechanisms of action thus; it is sometimes difficult to agree on how to classify a particular drug.

6. By its physicochemical properties; this classification is also know the biopharmaceutical classification system (BCS). It is the measures of permeability, solubility and dissolution of the drugs. The system is designed mainly for oral drug delivery as most of the drugs are administered orally. BCS is a tool in a drug product development used by the industry. The primary purpose of the BCS is to help in qualifying drug products for a waiver of *in vivo* bioequivalence studies. The aim of the BCS is the measurement of the permeability and solubility of the drug *in vitro* and thus prediction of its performance *in vivo*. The information will help in the drug's formulation. The BCS places a given active pharmaceutical ingredients (API) in one of four categories depending on its permeability and solubility [12]:

Class I: high permeability, high solubility; a drug substance is considered "highly soluble" when the highest dose strength is soluble in less than 250 ml water over a pH range of 1–7.5 and 37 °C. A drug substance is considered "highly permeable" when the extent of the absorption (parent drug plus metabolites) is more than 90% of the administered dose. Those compounds are well absorbed and their absorption rate is usually higher than their excretion. Examples include metoprolol, amiloride, chloroquine, cyclophosphamide, diazepam, digoxin, doxycycline, fluconazole and etc.

Class II: high Permeability, low Solubility; drug's absorption in this class is generally slower than those in Class 1. The dissolution-rate of these drugs is limited. However, specific techniques may be considered to enhance their dissolution rate. The bioavailability of those products is limited. Examples for this class include glibenclamide, bicalutamide, ezetimibe, carbamazepine, dapsone, ibuprofen, nifedipine, sulfamethoxazole, trimethoprim and etc.

Class III: Low Permeability, High Solubility; drugs in this class are quite soluble and generally have rapid dissolution rates; however, their absorption is limited due to their low permeation. The formulation method to be used should change the permeability or gastro-intestinal duration time and thus enhance intestinal absorption. Examples include cimetidine, abacavir, acetaminophen, acyclovir, allopurinol, atenolol, captopril, codeine phosphate, metformin, promethazine, sodium cloxacillin, ibuprofen and etc.

Class IV: Low Permeability, Low Solubility; drugs in this class have significant problems due to their low solubility and low permeability. Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected. Techniques can be considered regarding selection of excipients designed to enhance their dissolution rates and absorption. Examples include hydrochlorothiazide, furosemide, ritonavir, acetazolamide and etc.

7. By its source or origin; drugs can be classified according to their origin:

(i) *Natural compounds*: materials obtained from either plant or animal, such as vitamins, hormones, amino acids, antibiotics, alkaloids and glycoside. Natural products (secondary metabolites) have been the most successful source of potential drug leads.
(ii) *Synthesis compounds*: they are chemically produced in a laboratory, either pure synthesis or synthesis of organic compounds whose structures are closely related to those of naturally occurring compounds.
(iii) *Semi-synthesis compounds*: some compounds either cannot be purely synthesized or cannot be isolated from natural sources in low cost. Therefore, the natural intermediate of such drugs could be used for the synthesis of the desired product such as semisynthetic penicillins [13].

8. By its activity: drug activity can be classified as structurally non-specific drugs or structurally specific drugs. The actions of structurally non-specific drugs result from accumulation of a drug in some vital part of a cell with lipid characteristics such as general anesthetics, hypnotics, some bactericidal and insecticides. The structurally non-specific drug depends on physical properties like solubility, partition coefficients and vapor pressure and not on the presence or absence of some chemical groups [14]. Structurally specific drug is dependent upon the interaction of the drug with a cellular receptor. It is dependent upon factors such as the presence or absence of certain functional groups, intramolecular distance, and shape of the molecules. The drug activity is not easily correlated with any physical property and small changes in the structure often lead to changes in activity.
9. By its route of administration: route of administration is the path by which a drug or other substance is taken into the body. Route of administration are generally classified by the location at which the drug is applied or where the target of action is. Each route of administration has specific purposes, advantages, and disadvantages [15-17]. Drugs are introduced into the body by several routes: *(a) Gastrointestinal/enteral:* administration through the gastrointestinal tract (GIT) is termed enteral or enteric administration (meaning 'through the intestines'). Usually includes oral and rectal administration. Sublingual (under the tongue) and buccal are sometime classified as enteral. Enteral administration can be used for systemic administration such as tablets and capsules, as well as local (topical), such as enema. Many drugs can be administered orally as liquids, capsules, tablets, or chewable tablets. The oral route is the most often used and most convenient because it is the safest and least expensive. Some drugs are placed under the tongue (taken sublingually) or between the gums and teeth (buccal). Nitroglycerin (used to treat angina) is given sublingually, has a rapid absorption and an immediate effect. Many drugs that are administered orally can also be administered rectally as a suppository. A suppository is prescribed for people who cannot swallow (pediatrics, elderly). Other routes of administration are used when the oral route cannot be used. For example, when a person cannot take anything by mouth or a drug must be administered rapidly or in a precise or very high dose, or a drug is poorly or erratically absorbed from the digestive tract. *b) Central nervous system:* this includes epidural (injection or infusion into the epidural space), intracerebral (into the cerebrum) direct injection into the brain (e.g., treatment of brain malignancies and

intracerebroventricular (into the cerebral ventricles) and *(c) Other locations:* this includes; intravenous, intramuscular, intravaginal, intrauterine, epicutaneous or topical (application to the skin). *Topical:* local effect, substance is applied directly where its action is desired to a specific location. Examples, epicutaneous, inhalational, enema, ophthalmic drugs/ eye drops (onto the conjunctiva), and otic drugs (ear drops). *Enteral:* administration involves any part of the GIT. The desired effect is systemic; drug is given via the digestive tract. The drug may be introduced orally by mouth or by gastric feeding tube, duodenal feeding tube, or gastrostomy. *Parenteral:* desired effect is systemic; substance is given by routes other than the digestive tract. Examples: intravenous, intra-arterial, intra-muscular, intracerebral, intracerebroventricular and subcutaneous (hypodermoclysis).

10. By its safety during pregnancy: many drugs are used in pregnancies. The most commonly used drugs include antiemetics, antacids, antihistamines, analgesics, antimicrobials, diuretics, hypnotics, tranquilizers, and social and illicit drugs. Medications taken by the pregnant woman can cross the placenta and enter the developing baby's bloodstream. A medicine's effect on the unborn baby depends on the medication and the trimester in which the medicine is taken. Drugs that cross the placenta may have a direct toxic effect or a teratogenic effect. The food and drug administration (FDA) classifies drugs into 5 categories (A, B, C, D and X, Table 1) based on the potential for producing birth defects or safety for use during pregnancy. Drugs that fall into either class A or B are considered safe and are routinely used [18-19].

Category A: these drugs have been tested and found to be safe during pregnancy. Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote. Category A includes drugs such as folic acid, vitamin B6, and some thyroid medicines in prescribed doses.

Category B: these drugs are frequently used during pregnancy and do not appear to cause major birth defects or other problems. Animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, and animal-reproduction studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters). Category B includes some antibiotics, acetaminophen, aspartame, famotidine, prednisone, insulin, and ibuprofen. Pregnant women should not take ibuprofen during the last three months of pregnancy.

Category C: no studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. It is wise to avoid taking the medications during pregnancy. Drugs should be given only if the potential benefit justifies the potential risk to the fetus. Always the pregnant woman should consult the doctor about taking any medications, whether prescription or over-the-counter.

Category D: there is a positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-

threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Category X: studies in animals or humans have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Table 1. Classification of some drugs [19]

Pharmaceutical agent	**Category**	**Pharmaceutical agent**	**Category**
Acetaminophen/Paracetamol	B	Tetracycline	D
Acetylsalicylic acid/Aspirin	D	Triamcinolone (skin)	C
Amoxicillin	B	Chloramphenicol	X
Amoxicillin with clavulanic acid	B	Sulfonamide	X
Cefotaxime	B	Misoprostol	X
Diclofenac	C	Finasteride	X
Isotretinoin	X	Methimazole	X
Leflunomide	X	Valproic Acid	X
Loperamide	B	Metronidazole	X
Paroxetine	D	Warfarine	X
Phenytoin	D	Lithium	X
Rifampicin	C	Alcohol	X
Thalidomide	X	Theophylline	C

As mentioned previously, drugs can be classified according to various criteria including chemical structure or pharmacological action or origin. Since there is uncertainty in the relationship between chemical structure and pharmacological activity, it would be unwisely to classify all drugs on the basis of their chemical structures or origin. Therefore, it is advantageous to classify them according to their medicinal use. Using this classification we may divide drugs into the following main groups [20]:

- Chemotherapeutic agents: those drugs which are used to fight pathogenic, used to cure infectious diseases and cancer such as sulphonamides, antibiotics, antimalarial agents, antivirals, anticancer agents and etc.
- Pharmacodynamic agents: drugs that act on the various physiological functions of the body, used in non-infectious diseases such as cholinergic, adrenergic, hallucinogenic and sedatives.
- Miscellaneous agents: such as narcotic analgesics and local anesthetics.

Drugs are classified into different groups according to their chemical characteristics, structure and how they are used to treat specific disease. There are about eighty such broad categories of drugs under therapeutic classification, they are: [7-8, 13, 21-24].

Analgesics: agents that relieve pain without causing loss of consciousness. Examples include acetaminophen, ibuprofen and aspirin.

Anesthetics: produce lack of feeling either local or general depending upon the type and way of administration. Examples include lidocaine and procaine.

Antacids: neutralize acid such as magnesium hydroxide, aluminum hydroxide and calcium carbonate.

Anthelmintics: used to treat worm infections such as albendazole, mebendazole, triclabendazole, levamisole, aminoacetonitrile, flubendazole and tiabendazole.

Antianemics: prevent or cure anemia or increase the number of red blood cells or the amount of hemoglobin in the blood, deficiencies of which characterize the disorder known as anemia. Examples of this class are ferrous sulfate, folic acid and vitamin B12.

Antianginals: prevent or relieve angina attacks, used in the treatment of angina pectoris, a symptom of ischemic heart disease. Examples include nitroglycerin, isosorbide dinitrate, isosorbide mononitrate), acebutolol, oxprenolol, verapamil, amlodipine, nifedipine and Diltiazem.

Antianxiety agents: relieve anxiety and muscle tension such as chlordiazepoxide, valium, alprazolam, clonazepam, oxazepam, clorazepate, rromazepam and afobazole.

Antiarrhythmics: control cardiac arrhythmias such as lidocaine, propranolol, quinidine, procainamide, phenytoin, atenolol, amiodarone and verapamil.

Antibiotics: destroy or inhibit growth of microorganisms; agents target the bacterial cell wall e.g., penicillins and cephalosporins or cell membrane e.g., polymyxins, those targets protein synthesis e.g., macrolides, lincosamides, tetracyclines, aminoglycosides, those interferes with essential bacterial enzymes e.g., rifamycins, lipiarmycins, quinolones, and sulfonamides. Others antibiotics include cyclic lipopeptides (such as daptomycin), glycylcyclines (such as tigycycline), oxazolidinones (such as linezolid) and lipiarmycins (such as fidaxomicin).

Anticholinergics: block parasympathetic nerve impulses; decrease oral and respiratory secretions such as atropine, trihexyphenidyl, benzatropine, ipratropium bromide and bupropion.

Anticoagulants: prevent or delay blood clotting such as heparin, warfarin, dabigatran, rivaroxaban and apixaban.

Anticonvulsants: prevent or relieve convulsions/seizures such as phenytoin, ethosuximide, carbamazepine, valproic acid, eslicarbazepine acetate, pregabalin, vigabatrin, felbamate and stiripentol.

Antidepressants: prevent or relieve symptoms of depression; *tricyclic antidepressant* such as imipramine, *monoamino oxidase inhibitors* (MAOIs) such as phenelzine and isocarboxazid, and *selective serotonin re-uptake inhibitors* (SSRIs) such as fluoxetine and fluvoxamine.

Antidiabetics: used to manage diabetes.

Antidiarrheal agents: prevent or relieve diarrhea; inhibit peristalsis and reduce fecal volume. Examples include methylcellulose, bismuth subsalicylate, electrolyte and bulking agents such as fibers.

Antidotes: counteract poisons and their effects. Examples include naloxone: antidote of opioids, flumazenil: antidote of benzodiazepines, *N*-Acetyl cysteine: antidote of paracetamol, deferoxamine: antidote of iron, ethanol or fomepizole: antidote of methanol and ethylene glycol.

Antidysrhythmics: control and prevent cardiac dysrhythmias

Antiemetics: prevent or relieve nausea and vomiting. Examples include trimethobenzamide, dimenhydrinate, metoclopramide, promethazine and dronabinol.

Antiflatulents: relieve gas and bloating in GI tract. Examples include simethicone, lactase, beano, marmite, epazote and asafetida.

Antifungals: kill or inhibit growth of fungi. Examples include amphotericin B, candicidin, natamycin, nystatin, econazole, ketoconazole, tioconazole, fluconazole, terbinafine, benzoic acid, flucytosine and griseofulvin.

Antigout agents: inhibit production of uric acid. Examples include colchicine, allopurinol, benzbromarone, febuxostat, sulfinpyrazone and Probenecid.

Antihistamines: act to prevent the action of histamine (allergies). Examples include fexofenadine, diphenhydramine, brompheniramine, cyproheptadine, loratadine and bromodiphenhydramine.

Antihyperlipidemic agents: used to lower abnormally high blood levels of fatty substances (lipids). Examples include atorvastatin, gemfibrozil, lovastatin, niacin and *simvastatin*.

Antihypertensive agents: prevent or control high blood pressure. Examples include clonidine, methyldopa, metoprolol, enalapril and nifedipine.

Anti-impotence agents: used to treat erectile dysfunction. Examples for such class include sildenafil; Viagra, tadalafil; Cialis, vardenafil, prostaglandin E_1, papaverine and phentolamine.

Anti-infective agents: kill and inhibit growth of bacteria.

Anti-inflammatory agents: prevent inflammation. Examples include ibuprofen, naproxen and aspirin.

Antimanic agents: used for treatment of manic episode of manic-depressive and bipolar disorder. Examples for such class include lithium, haloperidol, clonazepam and lorazepam.

Antimigraine agents: cause vasoconstriction in large intracranial arteries. Examples include 2-bromo-lysergic acid, amidrine, cafergot, ergotamine, iprazochrome, lasmiditan, methysergide, migraleve, oxetorone, telcagepant, treximet and antimigraine.

Antineoplastic agents: prevent the replication of neoplastic cells; used to treat tumors. Examples include busulfan and cyclophosphamide.

AntiParkinsonian agents: used for palliative relief of major symptoms of Parkinson disease. Examples include L-dopa, ropinirole, amantadine, deprenyl and apomorphine.

Antiprotozoal agents: destroy protozoa. Examples include metronidazole, furazolidone, eflornithine, melarsoprol, ornidazole, paromomycin, pentamidine, pyrimethamine and tinidazole.

Antipsychotic agents: used to treat psychotic disorders. Examples include amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, chlorpromazine, flupentixol, haloperidol, levomepromazine, pericyazine, perphenazine, pimozide, sulpiride, trifluoperazine and zuclopenthixol.

Antipyretics: reduce fever. Among the examples included in this class are paracetamol and aspirin.

Antiretroviral agents: used to manage HIV infections. This class includes maraviroc, enfuvirtide, zidovudine, abacavir, lamivudine, emtricitabine, ritonavir, elvitegravir and nevirapine.

Antispasmodics: control hyper motility in IBS. Examples include anisotropine, atropine, cindinium, hyoscyamine, dicycloverine, mebeverine, donnatal, metaxalone, methocarbamol, chlorzoxazone, dantrolene and baclofen.

Antituberculosis agents: used in treatment of tuberculosis; inhibit growth of mycobacteria. Among examples included in this class are isoniazid, ethambutol, rifabutin, rifapentine, pyrazinamide, rifampin, streptomycin, kanamycin, ciprofloxacin and thioridazine.

Antitumor necrosis factor agents: slow and halt the destruction of joints by disrupting the activity of tumor necrosis factor (TNF). Examples include etanercept, infliximab, adalimumab, golimumab and certolizumab pegol.

Antitussive agents: prevent or relieve cough. This class includes codeine, dextromethorphan, guaifenesin and benzonatate.

Antiulcer agents: used in treatment of active duodenal ulcer and for pathological hyper secretory; controls stomach acid. Examples include cimetidine, ranitidine, nizatidine and famotidine.

Antivirals: combat a specific viral disease such as herpes. Examples include acyclovir, zanamivir, penciclovir, oseltamivir, Zidovudine and famciclovir.

Bone resorption inhibitors: treat and prevent *osteoporosis*. Examples include alendronate, risedronate, ibandronate, zoledronic acid, raloxifene, denosumab and teriparatide.

Bronchodilators: dilate the bronchi. This class includes albuterol, isoproterenol, salbutamol, salmeterol, formoterol, ipratropium, theophylline and tiotropium.

Cardiac glycosides: exert a positive inotropic effect on the heart; increase strength and force of contractions and slow heart rate. Examples include digitalis preps; digoxin and digitoxin.

Contraceptives: device, method or agent that prevents conception. Examples include intrauterine device, progestogens and estrogens.

Corticosteroids: suppress inflammation and modify normal immune response. This class includes cortisol, prednisone, methylprednisolone, triamcinolone acetonide, fluocinonide, betamethasone, dexamethasone and hydrocortisone 17-butyrate.

COX-2 Inhibitors: inhibit cyclooxygenase (COX-2) enzyme found in joints and other areas affected by inflammation. Examples include rofecoxib and celecoxib.

Decongestants: reduce nasal congestion and/or swelling; produce vasoconstriction. Examples for such class are pseudoephedrine, phenylephrine, naphazoline and xylometazoline.

Disease-modifying antirheumatic drugs (DMARDs): may influence the course of disease progression of rheumatoid arthritis. Examples include leflunomide, penicillamine, cyclophosphamide, methotrexate and auranofin.

Diuretics: increase the excretion of urine. Examples include *loop diuretics* such as furosemide, *thiazides diuretics* such as hydrochlorothiazide, *carbonic anhydrase inhibitors* such as acetazolamide and methazolamide, *potassium-sparing diuretics* such as spironolactone and amiloride, *calcium-sparing diuretics* such as thiazide (chlorothiazide and hydrochlorothiazide), *Osmotic diuretic* such as mannitol and *low ceiling diuretic* such as bendroflumethiazide and hydrochlorothiazide.

Electrolytes: treat or prevent electrolyte depletion. They are used to replace fluids and minerals such as sodium and potassium lost due to diarrhea and vomiting. They help preventing or treating the loss of too much body water (dehydration).

Emetic agents: used to induce vomiting. Examples include apomorphine, ipecac syrup, **hydrogen peroxide and xylazine**.

Expectorants: facilitate the removal of secretion from bronco-pulmonary mucous membrane. Examples include guaifenesin, carbocysteine, potassium iodide and potassium guaiacol sulfonate.

Gastric acid-pump inhibitors: suppress gastric acid secretions; also used for gastroesophageal reflux disease (GERD). Examples include pantoprazole, omeprazole, lansoprazole and rabeprazole.

Hemostatic agents: control or stop bleeding. Examples for such class include vitamin K, aminocaproic acid, chitosan, fibrinogen and aluminum sulfate.

Hormone replacement (HRT) agents: treat vasomotor symptoms of menopause. Examples for such agents are Estrogen and progestin derivatives.

Hypnotics: produce sleep or hypnosis; depress CNS. Examples include chloral hydrate, ethchlorvynol, secobarbital, phenobarbital, methaqualone, alprazolam, lorazepam, diazepam, clonazepam and zopiclone.

Hypoglycemics: lower blood glucose level. Examples include Insulin and oral hypoglycemic agents such as *Sulfonylurea* e.g., chlorpropamide, tolbutamide, glipizide, glibenclamide, glimepiride, *α-Glucose inhibitors* e.g., acarbose, *meglitinides* e.g., repaglinide, mitiglinide and nateglinide, *thiazolidinediones* (Glitazones) e.g., rosiglitazone, pioglitazone, lobeglitazone, troglitazone, *biguanides* e.g., metformin; glucophage®, phenformin, buformin, *dipeptidyl peptidase-IV (DPP-IV) inhibitors* e.g., sitagliptin, vildagliptin, saxagliptin, linagliptin, anagliptin, teneligliptin, alogliptin, gemigliptin, dutogliptin, berberine and lupeol.

Immunologic agents: induce immunity and prevent infectious diseases; stimulate body to produce antibodies. Examples for such class are Varicella vaccine, MMR vaccine, DPT vaccine, Hepatitis B vaccine.

Immunosuppressants: treat and prevent rejection of transplanted organs. Examples include glucocorticoids, cytostasis, cyclophosphamide, methotrexate, azathioprine, fluorouracil, antibodies, interferons, infliximab, etanercept, adalimumab, mycophenolic acid, fingolimod, ciclosporin, tacrolimus and sirolimus.

Laxatives: loosen and promote normal bowel elimination; relieve constipation. Examples for such class include bisacodyl, sennosides**,** magnesium hydroxide**; milk of magnesia®**, psyllium, methyl cellulose, polycarbophil calcium, glycerine, sorbitol, lactulose, magnesium sulfate, castor oil, lubiprostone, cisapride and tegaserod.

Leukotriene receptor antagonist blockers: used for treatment and management of asthma. Examples include zafirlukast, zileutin and montelukast.

Lipid-lowering agents: this class includes cholesterol-lowering drugs, *statins* such as atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin, *niacin*, *bile-acid resins*, *fibric acid derivatives* (fibrates), *Cholesterol absorption inhibitors* (ezetimibe) and *omega-3- fatty acids.*

Mucolytic agents: break chemical bonds in mucus, lowering the viscosity. Examples include acetyl cysteine, erdosteine, bromheksin, carbocysteine, guaifenesin and iodinated glycerol.

Muscle relaxants: produce relaxation of skeletal muscle. Examples include diazepam, metaxalone, orphenadrine, chlorzoxazone and methocarbamol,

Neuroleptic: modifies psychotic behavior (Risperdal, Zyprexa, Stelazine)

Ophthalmic anti-infective agents: treat eye infections. Examples include levofloxacin, tobramycin, ciprofloxacin, azithromycin, gatifloxacin, natamycin, moxifloxacin, idoxuridine, chloramphenicol and gentamicin.

Otic preparations: treat ear conditions. Examples include antibiotics, hydrogen peroxide, isopropyl alcohol, glycerin, boric acid, hydrocortisone, ethyl alcohol, acetic acid, aminoglycosides antibiotics, aluminum acetate, triamcinolone and dexamethasone.

Platelet inhibitors: inhibit the ability of platelets to adhere to each other; similar to coagulant. Examples include aspirin, triflusal, clopidogrel, prasugrel, ticagrelor, ticlopidine, vorapaxar, abciximab, tirofiban and dipyridamole.

Selective serotonin reuptake inhibitors (SSRIs): selectively inhibit serotonin reuptake and result in potentiation of serotonergic neurotransmissions. Examples include fluvoxamine, paroxetine, *fluoxetine*; Prozac and sertraline.

Serotonin nonselective reuptake inhibitors (SNRIs): inhibit the reuptake of both serotonin and norepinephrine. Examples for such class are venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran and sibutramine.

Smoking deterrents: used to manage nicotine withdrawal. Examples include bupropion, topiramate, varenicline, nicotine and clonidine.

Thrombolytic agents: dissolve an existing thrombus (clot) when administered soon after their occurrence. Examples include streptokinase, anistreplase, alteplase and urokinase.

Thyroid hormone agents: increase basic metabolic rate (Triiodothyronine; T_3, Thyroxine; T_4)

Vasodilators: produce relaxation of blood vessels; lowers blood pressure. Examples include Iisosorbide dinitrate and nitroglycerin.

Vasopressors: produce contraction of muscles of capillaries and arteries; elevate blood pressure; used to treat allergic reactions (Norepinephrine, Metaraminol)

Weight control agents: used to manage obesity. Examples include a combination of phentermine and topiramate, orlistat, lorcaserin, sibutramine, rimonabant, amphetamine, Phenylpropanolamine, metformin and pramlintide.

Drug Types

There are four types of drugs: 1-medication, 2-recreational, 3-spiritual and 4-nootropic [26-35].

Medication Drugs: A medication or medicine is a drug taken to cure and/or improve any symptoms of an illness or medical condition, or may be used as preventive medicine that has future benefits but does not treat any existing or pre-existing diseases or symptoms. Medications are classified in various ways. One of the key divisions is between traditional small molecule drugs, usually derived from chemical synthesis, and biopharmaceuticals which include recombinant proteins, vaccines, and blood products used therapeutically, gene therapy and cell therapy.

Dispensing of medication is often regulated by governments into three categories:

Over-the-counter (OTC): medications which are available in pharmacies and supermarkets without special restrictions and without a need of prescription. The list of OTC medicines varies from country to country.

Behind-the-counter (BTC): drugs that are dispensed by a pharmacist without a need for a doctor's prescription and are available in pharmacies. They are called pharmacy medicines in the United Kingdom. These medicines are only sold in registered pharmacies, by or under the supervision of a pharmacist. These medications are designated by the letter P on the label. The number of medicines available without a prescription varies from country to country.

Prescription only medicines (POM): these medications must be prescribed by a licensed medical professional, usually a physician and are available in pharmacies or clinics.

Medications are typically produced by pharmaceutical companies and are often patented to give the developer exclusive rights to produce them, but they can also be derived from naturally occurring substance in plants called herbal medicine. Those that are not patented (or their patent has expired) are called generic drugs. Generic drugs can be produced by other companies without restrictions or licenses from the patent holder. A pharmaceutical drug (medicine or medication and officially medicinal product) is any chemical substance formulated or compounded as a single active ingredient or in combination of other pharmacologically active substance, it may be in a separate but packed in a single unit pack as combination product intended for internal, or external or for use in the medical diagnosis, cure, treatment, or prevention of diseases [36-44].

Examples of Important OTC Drugs: in the United States, the FDA classified whether medicines are prescription or nonprescription based on the safety and effectiveness of the drug if used under a physician care or not. The term prescription (Rx) refers to medicines that are safe and effective when used under a doctor's care.

Nonprescription or OTC drugs are medicines that are safe and effective for use without a doctor's prescription. The FDA also has the authority to decide when a prescription drug is safe enough to be sold directly to consumers over the counter.

The regulatory process known as Rx-to-OTC switch is allowing Americans to take a more active role in their health care. As a result of this process, more than 700 products are sold as OTC. There are more than 80 classes of OTC drugs, ranging from allergy medicines to pain relievers to weight loss products [45-47]. OTC medicines vary from country to country.

OTC Drugs for Aches, Pains, and Headaches: OTC pain medicines can help with headache, arthritis pain, sprains, and other minor joint and muscle problems. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen and naproxen (Figure 1) are used as OTC drugs for pain relief. Acetaminophen (Tylenol) and ibuprofen (Advil, Motrin) used to reduce fever in children and adults.

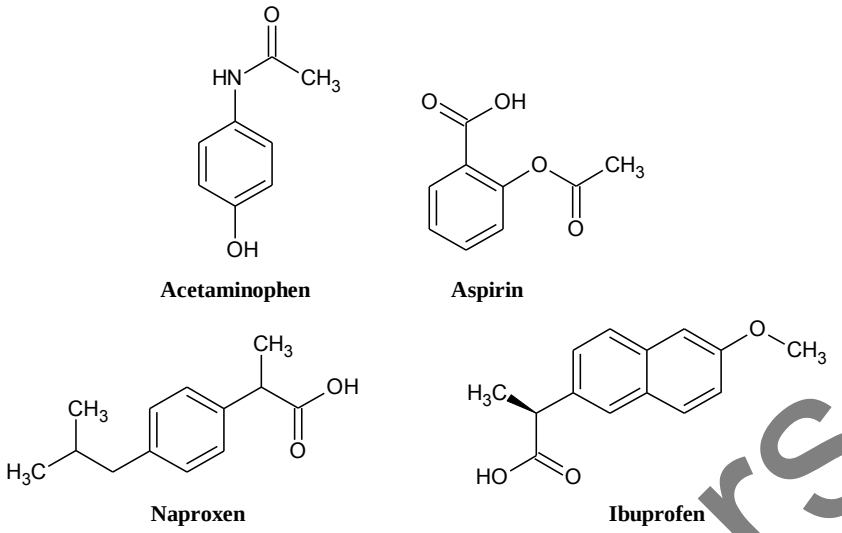


Figure 1. Chemical structures of acetaminophen, aspirin, naproxen and ibuprofen.

OTC Drugs for **Cold, Sore Throat and Cough:** Cold medicines can treat symptoms not the specific cold viruses. Treatment the cold symptoms make the patient feels better, they don't cure the cold, but they can bring relief, lighter symptoms, or maybe even shorten the cold. Using zinc supplements within 24 hours of the start of a cold may reduce the symptoms and duration of the cold. Cough medicines include guaifenesin (Figure 2) which helps break up mucus, menthol throat lozenges which soothe "tickle" in the throat. Liquid cough medicines with dextromethorphan (Figure 2) suppress the cough (Benylin, Delsym, Robitussin DM, and Simply Cough, Vicks, and store brands).

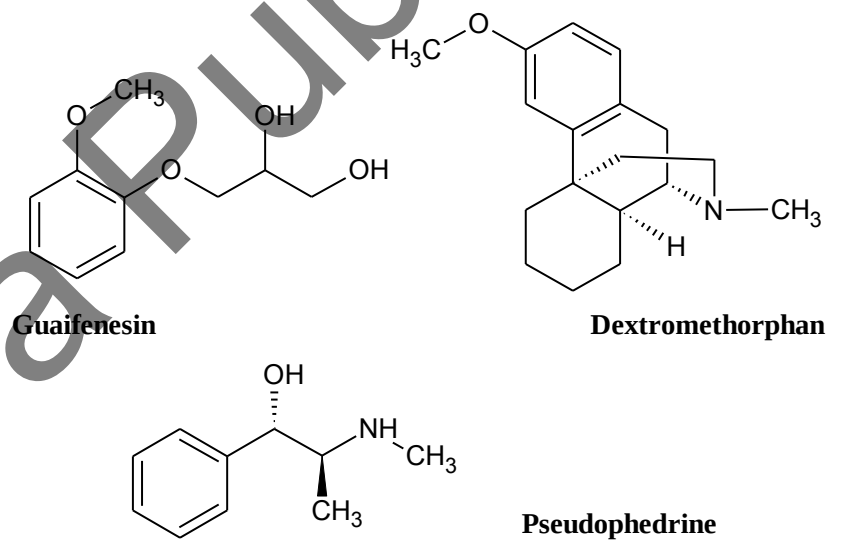
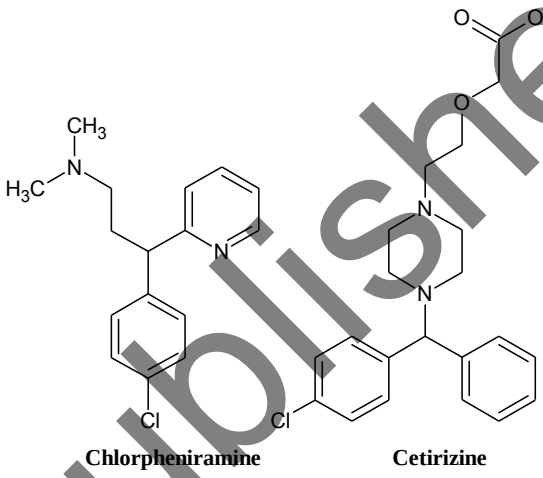


Figure 2. Chemical structures of guaifenesin, dextromethorphan and pseudoephedrine.

Decongestants help clear a runny nose and relieve postnasal drip. Examples of oral decongestants include pseudoephedrine (Figure 2) (Contact Non-Drowsy, Sudafed, and store brands), phenylephrine (Sudafed PE and store brands). Examples of decongestant nasal sprays are oxymetazoline (Afrin, Neo-Synephrine Nighttime, Sinex Spray), phenylephrine (Neo-Synephrine, Sinex Capsules) [45-47].

OTC Drugs for Allergy: In general, there is no cure for allergies, but there are several types of medications available, both OTC and prescription. These medications help ease and treat annoying symptoms like congestion and runny nose. These allergy drugs include antihistamines, decongestants, combination drugs, corticosteroids, and others. For *allergies* antihistamine pills and liquids work well for treating allergy symptoms. Among the Antihistamines that may cause sleepiness are diphenhydramine (Benadryl), chlorpheniramine (Chlor-Trimetron) (Figure 3), brompheniramine (Dimetapp), or clemastine (Tavist). Examples of antihistamines that cause little or no sleepiness are loratadine (Alavert, Claritin, Dimetapp ND), fexofenadine (Allegra), cetirizine (Zyrtec) (Figure 3).



Chlorpheniramine **Cetirizine**

Figure 3. Chemical structures of chlorpheniramine and cetirizine.

OTC Drugs for Diarrhea, Nausea and Vomiting: Diarrhea, vomiting and nausea are common complaints that can result from diseases such as gastrointestinal and inflammatory bowel diseases, conditions such as food allergies, and from usage of antibiotics or other drugs. The fluid and electrolytes lost during diarrhea and vomiting need to be replaced promptly. Anti-diarrhea medicines such as loperamide (Imodium) are effective for terminating diarrhea. Medicines that contain bismuth may be taken for mild diarrhea (Kaopectate, Pepto-Bismol). Rehydration fluids may be used for moderate and severe diarrhea (Enfalyte or Pedialyte). For mild nausea and vomiting, liquids and pills for stomach upset may help (Emetrol; Pepto-Bismol). Rehydration fluids may be used to replace fluids from vomiting (Enfalyte or Pedialyte). Medicines for motion sickness such as dimenhydrinate (Dramamine), meclizine (Bonine, Antivert, Postafen, and Sea Legs) can be effective in nausea and vomiting conditions [45-47].

OTC Drugs for Skin Rashes and Itching: Oral antihistamines may help in itching and allergy conditions. Hydrocortisone cream may help with mild rashes (Cortaid, Cortizone 10). Anti-fungal creams and ointments may help with diaper rashes and rashes caused by yeast (nystatin, miconazole, clotrimazole, and ketoconazole) [45-47].

Top Twenty OTC Medications Sold in US: The following are the top twenty OTC drugs sold in the united states: Advil (ibuprofen), Aleve (naproxen), Cēpacol® antibacterialmulti-protection mouthwash (cetylpyridinium chloride), Children's Dimetapp Cold and Cough (brompheniramine maleate, dextromethorphan HBr, and phenylephrine HCl), Claritin (loratadine), Colace (docusate sodium), Cortaid Maximum Strength (hydrocortisone acetate), Dulcolax (docusate sodium or bisacodyl), Excedrin Extra Strength (acetaminophen, aspirin, caffeine), Gaviscon (aluminum hydroxide, magnesium carbonate), Lotrimin® AF Antifungal (miconazole nitrate, Figure 4), Maalox Antacid (aluminum hydroxide, magnesium carbonate), Midol (ibuprofen), Motrin IB (ibuprofen), Orajel Maximum Strength (benzocaine Figure 4), Pepto-Bismol (bismuth subsalicylate), Rolaids® Multi-Symptom (calcium carbonate, dimethicone or simethicone), Tagamet HB (cimetidine), Tylenol® (acetaminophen) and Zantac75® (ranitidine hydrochloride, Figure 4) [47].

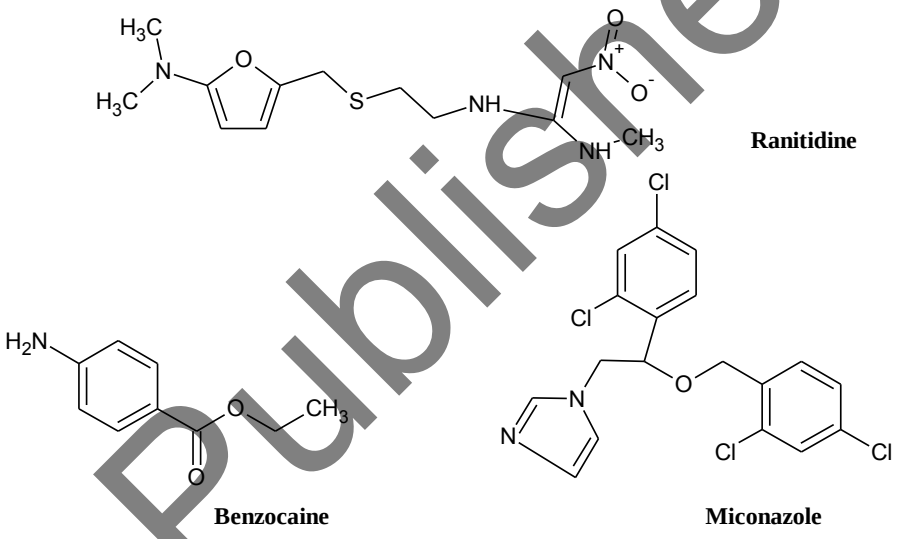


Figure 4. Chemical structures of ranitidine, benzocaine and miconazole.

Drug Administration

Drugs, both medicinal and recreational, can be administered by a number of ways. Many drugs can be administered in a variety of ways rather than just one as the following [48].

Bolus: is the administration of a medication, drug or other compound that is given to raise its concentration in blood to an effective level. The administration can be given intravenously, by intramuscular, intrathecal or subcutaneous injection. An intravenous injection can be more difficult to administer than a subcutaneous or intramuscular injection because inserting a needle or catheter into a vein may be difficult, especially if the person is obese. The

subcutaneous route is used for many protein drugs because such drugs would be destroyed in the digestive tract if they are taken orally.

Inhaled: Inhaled medications can be absorbed quickly, and act both locally and systemically. They are breathed into the lungs as an aerosol or dry powder. This includes smoking a substance. Usually, this method of administration is used to administer drugs that act specifically on the lungs, such as aerosolized antiasthmatic drugs in metered-dose containers (called inhalers) and gases used for general anesthesia.

Injected: They can be as a solution, suspension or emulsion. They are given either intramuscular, or intravenous, or intraperitoneal or intraosseous. Intravenous administration is the best way to deliver a precise dose quickly and in a well-controlled manner throughout the body. The intramuscular route is preferred over the subcutaneous route when larger volumes of a drug are needed.

Insufflation: snorted into the nose. Drugs administered by this route generally work quickly. Some of them irritate the nasal passages.

Orally: The oral route is the most common route of drug administration. It may be in the form of a liquid or solid (tablets, capsules, syrup, emulsions or powders) that is absorbed through the intestines. The advantages of this route are its convenience, cheapest, easy to use, safe and acceptable. While the disadvantages of this route include less amount of a drug reaches the target tissue, some of the drug is destroyed by gastric juices, the drug's absorption is slow, gastric irritation may be caused by the drug, objectionable in taste and discoloration of teeth.

Rectally: Drugs in solid forms such as suppositories or in liquid forms such as enema are given by this route and absorbed by the rectum or colon. This route is mostly used in old patients and pediatrics that have difficulties in swallowing. Drugs may have local or systemic actions after absorption. The advantages of this route are preferred in unconscious or uncooperative patients, avoiding nausea or vomiting can be achieved using this route and drugs are not destroyed by enzymes (avoid hepatic first pass metabolism, drugs given by rectal route have 50% first pass metabolism). While the disadvantages are patients dislike suppositories or may be not acceptable by the patients. Locally acting drugs include glycerin and bisacodyl suppository and systemic acting drugs include indomethacin (anti-inflammatory) and aminophylline (bronchodilator).

Sublingually: drugs are diffused into the blood through tissues under the tongue.

Topically: usually as a cream or ointment. A drug administered in this manner may be given to act locally or systemically.

Vaginally: Some drugs may be administered vaginally to women as a solution, tablet, cream, gel, suppository or ring. The drug is slowly absorbed through the vaginal wall. Suppositories are primarily used to treat vaginal infections. This route is often used to give estrogen to women during menopause to relieve vaginal symptoms such as dryness, soreness and redness.

Recreational Drugs: Recreational drugs are chemical substances that affect the central nervous system (CNS) such as opioids or hallucinogens. They may be used for effects on perception, consciousness, personality and behavior. They are taken for enjoyment, or leisure purposes, rather than for medical reasons. Alcohol, nicotine, and caffeine are the most widely consumed psychotropic drugs worldwide. Some drugs can cause addiction and habituation and all of these drugs have side effects [26-35]. The use of these drugs is incredibly common around the world and it very often leads to disaster and crime.

Spiritual Drugs (Entheogen): Spiritual drugs are chemical substances, typically of plant origin or may be synthesized, that are ingested to produce unordinary state of consciousness for religious or spiritual purposes. These drugs can cause severe damage to mental or physical health. There are a number of drugs that are said to induce spiritual experiences including lysergic acid diethylamide (LSD) (Figure 5), peyote, ayahuasca, psilocybin (magic mushrooms), ecstasy, marijuana, mescaline and etc. [26-35].

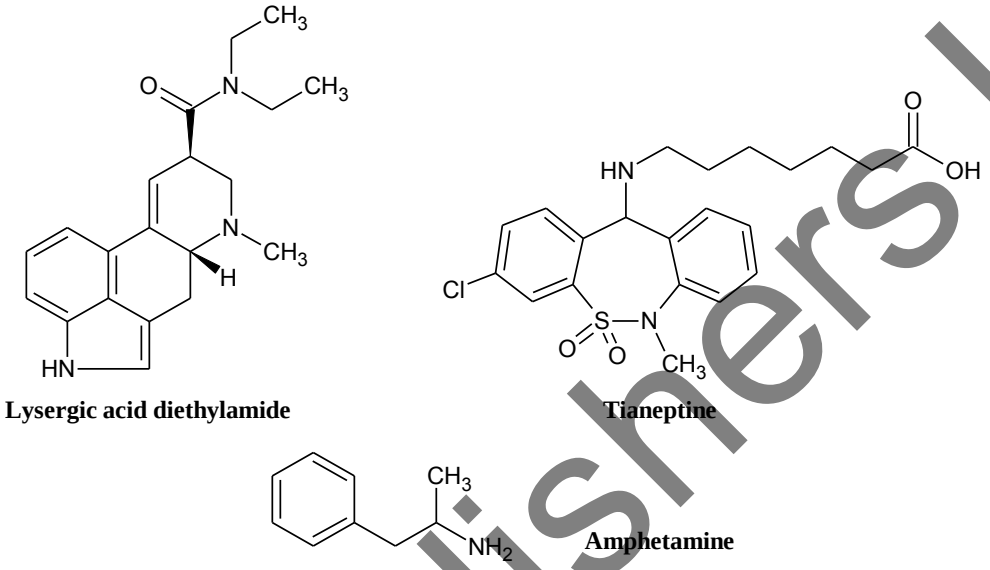


Figure 5. Chemical structures of lysergic acid diethylamide, tianeptine and amphetamine.

Nootropic Drugs: Nootropic drugs also referred to as smart drugs, memory enhancers, neuro enhancers, cognitive enhancers, and intelligence enhancers, are drugs, supplements, nutraceutical, and functional foods that improve one or more aspects of mental function, such as working memory, motivation, and attention. These drugs are used primarily to treat people with cognitive or motor function difficulties attributable to such disorders as Alzheimer's disease, Parkinson's disease, Huntington's disease and ADHD. Examples for such drugs include stimulants (amphetamine, Figure 5), methylphenidate, eugeroics (armodafinil and modafinil), xanthines and nicotine. Certain stimulants will enhance cognition in the general population, but only when used at low (therapeutic) concentrations. Relatively high doses of stimulants will result in cognitive deficits. Other examples are phosphatidylserine, tianeptine (Figure 5), valproate and isoflavones [26-35].

Drug Interactions

A drug interaction occurs when a drug affects the activity of another drug when both are administered together. Drug interactions can result in unwanted side effects, reduce the effectiveness of a medicine or possibly increase the action of a particular medicine or produce a new effect that neither produces on its own. Drug interactions are usually divided into four

groups: antagonism (drug's reduces or blocks the effect of another), synergism (drug's effect is increased), potentiation (drug A boosts the effects of drug B), and interaction with metabolism. There are different risk factors of drug interactions: age (elderly or young), multiple disease, multiple drug therapy, renal and liver impairment, narrow therapeutic index (e.g., Insulin, Lithium, Digoxin, Warfarin, Phenytoin, Theophylline, Phenobarbitone) and enzyme inhibitors or inducers. The outcomes of drug interactions might be loss of therapeutic effect, toxicity, unexpected increase in pharmacological activity, beneficial effects e.g., additive and potentiation (intended) or antagonism (unintended) and chemical or physical interaction (e.g., I.V incompatibility in fluid or syringes mixture). Drug interactions may result from pharmacokinetic interactions (absorption, distribution, metabolism, and excretion) or from interactions at drug receptors. These interactions may occur out of accidental misuse or due to lack of knowledge about the active ingredients involved in the relevant substances.

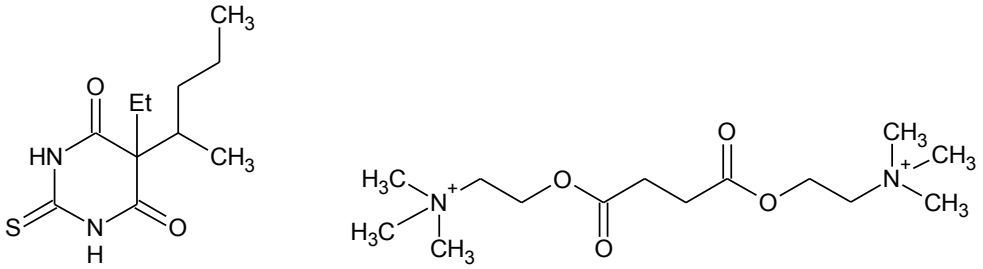
Interactions may also exist between drugs and foods (drug-food interactions), as well as drugs and medicinal plants or herbs (drug-plant interactions). Drug-food interactions can happen with both prescription and OTC medicines. Not all medicines are affected by food, but many medicines can be affected by what we eat and when we eat. An example of a drug-food interaction; patients who take monoamine oxidase inhibitors (antidepressants) should not take food containing tyramine (found in cheese) because hypertensive crisis may occur [49-53].

The pharmacological interactions of drugs are important to know and understand. For example; if a person is taking two drugs and one increases the effect of the other it is possible that an overdose may occur (toxicity occurs). The interaction of the two drugs may also increase the risk of side effects. On the other hand, if the action of a drug is reduced it may reduce or diminish any therapeutic effect because of under dosage. Nevertheless, sometimes the interactions may improve the therapeutic effect. Examples of this include the use of codeine with paracetamol to increase the analgesic effect of the medication. The combination of clavulanic acid with amoxicillin is another example to overcome the bacterial resistance to antibiotics. The interactions that are important are those that have negative effects on patients. The risk that a pharmacological interaction will cause is increased as a function of the number of drugs administered to a patient at the same time.

As mentioned before, it is possible that an interaction will occur between a drug and another substance present in the body (such as food or alcohol). In certain specific situations a drug may even react with itself (hypersensitivity).

In other situations, the interaction does not involve any effect on the drug. In certain cases, the presence of a drug in an individual's blood may affect certain types of laboratory analysis (*analytical interference*).

It is also possible for interactions to occur outside the organism before the administration of a drug. This can occur when two drugs are mixed together. Some classic examples of this type of interaction include thiopentone and suxamethonium (Figure 6) which should not be placed in the same syringe and the same is also true for benzylpenicillin and heparin.



Thiopentone **Suxamethonium**

Figure 6. Chemical structures of thiopentone and suxamethonium.

Drug interactions may be due to various processes such as alterations in the pharmacokinetics of the drug (alterations absorption, distribution, metabolism, and excretion (ADME)) or/and interactions in the pharmacodynamic properties of the drug (co-administration of a receptor antagonist and an agonist for the same receptor). Pharmacodynamics is related to the pharmacological activity of the interacting drugs e.g., synergism, antagonism, altered cellular transport, effect on the receptor site [49-53].

Types of Drug Interactions

As mentioned before, drug interaction is the modification of the effect of one drug (the object drug) by the prior concomitant administration of another (precipitant drug). There are different types of drug interaction: (i) pharmacokinetic interactions, (ii) pharmacodynamic interactions, (iii) drug-nutrient interactions, (iv) drug-disease interactions and (v) pharmaceutical interactions. The outcomes of drug interactions are loss of therapeutic effect, toxicity, unexpected increase in pharmacological activity, beneficial effects such as additive and potentiation (intended) or antagonism (unintended) and chemical or physical interaction such as I.V incompatibility in fluid or syringes mixture. There are essentially two types of drug interactions: pharmacodynamic and pharmacokinetic.

Pharmacokinetic Interactions

Pharmacokinetic interactions involve the effect of a drug on another and the drugs absorption, distribution, metabolism and excretion are the important factors playing roles in such interactions. Pharmacokinetic interactions are those in which one drug results in an alteration (increase or decrease) of the concentration of another drug in the system. Different parameters can be affected by pharmacokinetic interactions, including a drug's bioavailability, volume of distribution, peak level, clearance and half-life. Such changes can lead to changes in drug plasma concentrations and ultimately increase the risk of side effects or diminish the efficacy of one or more drugs. Pharmacokinetic interactions are more complicated and difficult to predict because the interacting drugs often have unrelated actions.

The paragraphs below are a brief summary and some examples of the four pharmacokinetic processes that may be involved individually or collectively in various drug interactions.

Absorption*:* Drug absorption refers to the route or method by which the drug reaches the blood supply (the movement of drugs into the body depends on how the drug is administered). There are three areas in which interactions might occur at the level of drug absorption. One drug may affect the rate and/or extent of absorption of other drugs if it alters GI motility, gastric pH or chemically binds with other drugs to form insoluble, non-absorbable complexes.

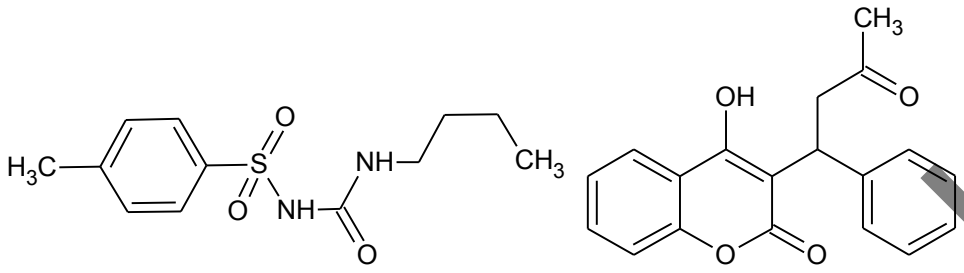
Alteration of GIT absorption can occur as a result of either (1) alteration of pH (such as antacids and H2 antagonists decrease the pH and thus decrease the absorption of Ketoconazole, (2) alteration bacterial flora (e.g., In 10% of patients receive digoxin about 40% or more of the administered dose is metabolized by the intestinal flora). If antibiotics are administered with digoxin, a toxicity might occur as digoxin concentration increases because antibiotics kill a large number of the normal flora of the intestine, (3) formation of drug chelates or complexes (e.g., tetracycline interacts with iron preparations, milk products and antacids. Aluminum or magnesium hydroxides decrease the absorption of tetracycline by 85% due to chelation, (4) drug induced mucosal damage (e.g., antineoplastic agents such as cyclophosphamide, vincristine, procarbazine which inhibit the absorption of several drugs such as digoxin) and (5) altered GIT motility (e.g., metoclopramide (antiemetic), increases the toxicity of cyclosporine because it increases its absorption due to the increase of stomach empting time).

Displaced protein binding (distribution): Distribution is the movement of the drugs around the body. Once the drug is absorbed, it is rapidly distributed around the blood supply, and then slowly distributed to the various tissues and organs. The rate and extent of the drug distribution depends on the blood flow, tissue size, and affinity of the drug to plasma protein (albumin) and tissue components, and permeability of tissue membranes. The most likely bound drugs are capable to displace others. The free drug is increased by displacement by another drug with higher affinity. For example, drugs that are highly bound to plasma protein such as phenytoin, tolbutamide and warfarin (Figure 7) can displace other agents with lower affinity to plasma protein such as aspirin, sulfonamides and phenylbutazone. Warfarin and methotrexate bound to albumin and plasma protein in the blood and they will be unavailable to interact with their targets. When another drug is taken with these medications which have the ability to compete for plasma protein binding (e.g., sulphonamide), a certain percentage of previously bounded drug (warfarin or methotrexate) is released, thus increasing the free form of the drug and consequently its effect.

Altered metabolism: the effect of one drug on the metabolism of the other is well documented. The liver is the major site of drug metabolism but metabolism can occur in other organs such as WBC, skin, lung, and GIT. Cytochrome P450 family is the major metabolizing enzyme in phase I (oxidation process). Therefore, the effect of drugs on the rate of metabolism of others can involve the followings:

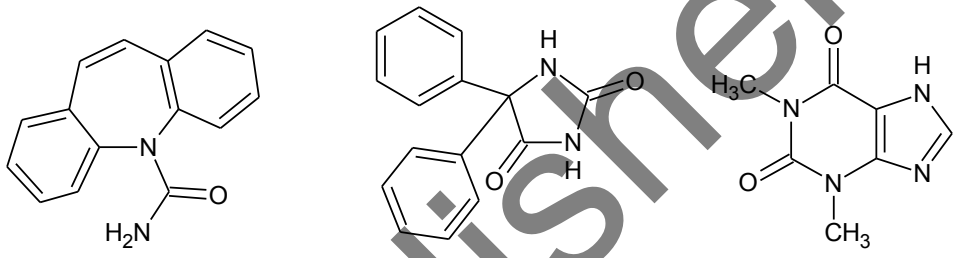
(a) Enzyme induction; a drug may induce the enzyme that is responsible for the metabolism of another drug or even itself such as in the case of carbamazepine (antiepileptic drug, Figure 8) which increases its own metabolism. Phenytoin increases hepatic metabolism of theophylline (Figure 8), leading to a decrease in the latter's concentrations level and

reduces its therapeutic action. Enzyme induction involves protein synthesis. Therefore, it needs time up to 3 weeks to reach a maximal effect.



Tolbutamide **Warfarin**

Figure 7. Chemical structures of tolbutamide and warfarin.



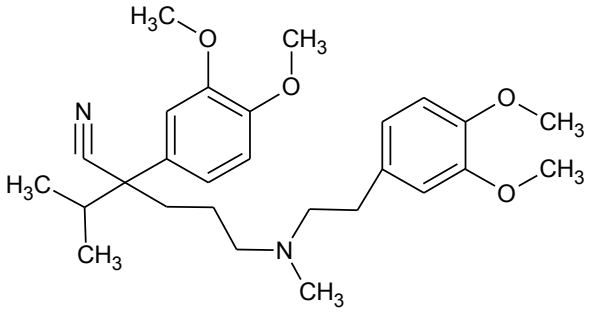
Carbamazepine **Phenytoin** **Theophylline**

Figure 8. Chemical structures of carbamazepine, pheytoin and theophylline.

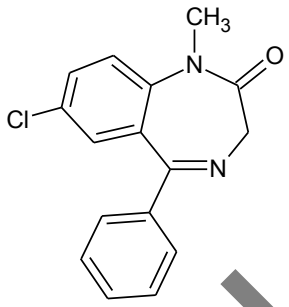
(b) Enzyme inhibition; it is a decrease of the rate of metabolism of a drug by another one. This will lead to an increase of the concentration of the target drug and consequently to an increase of its toxicity. Inhibition of the enzyme may be due to the competition on its binding sites. When an enzyme inducer such as carbamazepine is administered with an inhibitor such as verapamil (Figure 9), the effect of the inhibitor will be predominant. Erythromycin inhibits the metabolism of astemazole and terfenadine, thus increases their serum concentrations and leads to an increase of the life threatening cardio-toxicity. Another example is omeprazole (Figure 9) which inhibits the oxidative metabolism of diazepam (Figure 9).

Excretion: Renal excretion (active tubular secretion); it occurs in the proximal tubules, a portion of renal tubules. The drug combines with a specific protein to pass through the proximal tubules. When a drug has a competitive reactivity to the protein that is responsible for the active transport of another drug this will reduce a drug excretion increasing its concentration and hence its toxicity. For example, probenecid (Figure 10) decreases tubular secretion of methotrexate (Figure 10).

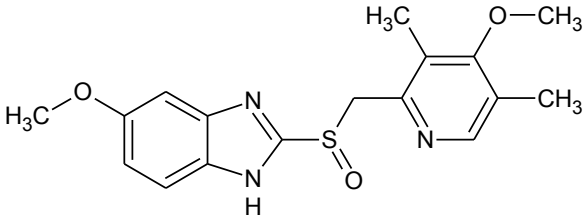
Passive tubular reabsorption; excretion and reabsorption of drugs occur in the tubules by passive diffusion which is regulated by concentration and lipid pharmacodynamics interactions solubility. Ionized drugs are reabsorbed in a lower extent than non-ionized ones. Sodium bicarbonate increases lithium clearance and decreases its action. Antacids increase salicylates clearance and decrease their action [54-58].



Verapamil

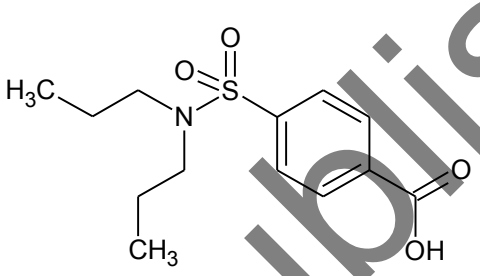


Diazepam

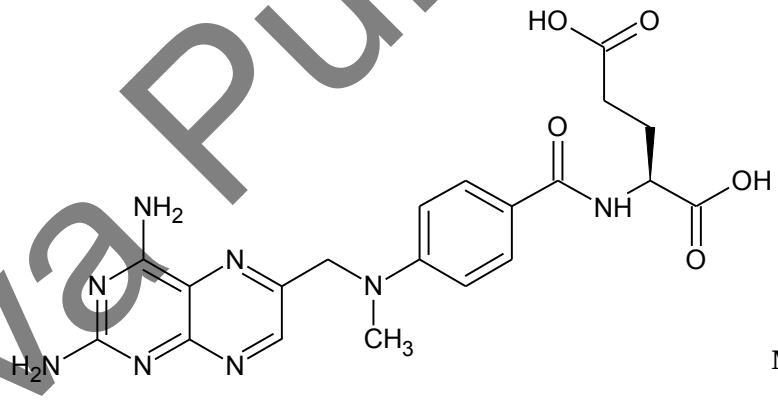


Omeprazole

Figure 9. Chemical structures verapamil, diazepam and omeprazole.



Probenecid



Methotrexate

Figure 10. Chemical structures of probenecid and methotrexate.

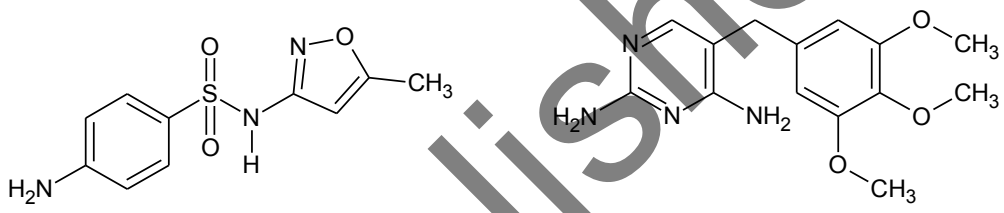
Pharmacodynamic Interactions

Pharmacodynamic interactions are alteration of the dug action without a change in its serum concentration by pharmacokinetic factors. The Pharmacodynamics interactions types are:

A synergism (1+1=3)**:** When the therapeutic or toxic effects of two drugs are greater than the effect of an individual drug, it is called synergism. Drug synergism is of two types: additive effect and potentiation. Propranolol + verapamil is synergistic or additive effect

Additive effect (1+1=2): when the net effect of two drugs used together is equal to the sum of the individual drug effects, the drugs are said to have an additive effect. For example, the combination of a thiazide diuretic and a beta adrenergic blocking drug used for the treatment of hypertension.

Potentiation **(**1+0=2): when the net effect of two drugs used together is greater than the sum of the individual drug effects, the drugs are said to have potentiation effect. For example, the combination of sulfamethoxazole (Figure 11) and trimethoprim (Figure 11) used as antimicrobial agents.



Sulfamethoxazole **Trimethoprim**

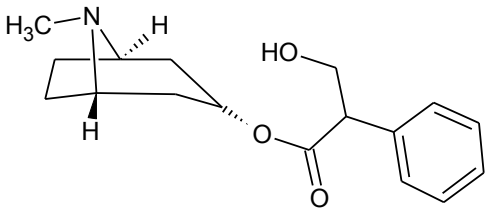
Figure 11. Chemical structures of sulfamethoxazole and trimethoprim.

Antagonism (1+1=0 or 0.5): the effect of one drug can be reduced or abolished by the presence of another drug and this effect is termed drug antagonism. Drug antagonism is of three types- chemical, physiological and pharmacological. Physiological and pharmacological antagonisms involve the interaction of an agonist with an antagonist.

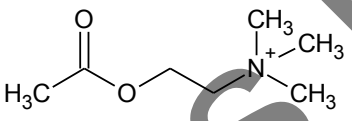
Chemical antagonism; when a drug antagonizes the effect of another drug by simple chemical reaction without activating a receptor. For example, antacid neutralizes the gastric acid. *Physiological antagonism;* when the physiological effect of a drug is antagonized by another drug by acting on two different types of receptors. For example, acetylcholine causes contraction of an intestinal smooth muscle by acting on muscarinic choline-receptors. Whereas this action of acetylcholine is antagonized (that is relaxation of the intestinal smooth muscle) by adrenaline. *Pharmacological antagonism;* when a drug antagonizes the effect of another drug by acting on the same receptor it is called pharmacological antagonism. Pharmacological antagonism is of two types: competitive and noncompetitive.

Competitive antagonism; competitive antagonism is reversible. The inhibitory effect of an antagonist is overcome by using large amount of agonist. Here, both, the agonist and antagonist compete for the same receptor and are able to displace each other at the receptor site. For example, acetylcholine causes contraction of intestinal smooth muscle. Atropine

(Figure 12) blocks the effect of acetylcholine (Figure 12). When a low concentration of an agonist is plotted against the responses, a sigmoid shaped curve will be obtained. The maximum response of the agonist is obtained in the presence of competitive antagonist. The dose-response curve remains parallel but is shifted to the right.



Atropine



Acetylcholine

Figure 12. Chemical structures of atropine and acetylcholine.

Noncompetitive antagonism; the maximum response of an agonist in the presence of antagonist is reduced. The inhibitory effect of a drug is not overcome by using large amount of agonist [48, 54, 57, 59-63].

Drug-Nutrient Interactions

Nutrition can affect the body's response to drugs; conversely, drugs can affect the body's nutrition. Food, beverages, and dietary supplements alter the effects of drugs the person takes. Foods can enhance, delay, or decrease drug absorption. The presence of food in the digestive tract may reduce the absorption of a drug. Often, such interactions can be avoided by taking the drug 1 hour before or 2 hours after eating. Dietary supplements are regulated as foods, not as drugs, so they are not tested comprehensively. However, they may interact with prescription or OTC drugs. People who take dietary supplements should inform their doctors and pharmacists, so that interactions can be avoided. For instance, taking alcohol with metronidazole can cause flushing, headache, palpitations, and nausea and vomiting. Drugs such as terfenadine, cyclosporine and felodipine interact with grapefruit juice. Other food, such as orange juice, coffee, or mineral water, may reduce the absorption and effectiveness of these drugs. Anticoagulants interact with foods containing high concentrations of vitamin K (such as broccoli, brussels sprouts, spinach, and kale).

Such foods may reduce the effectiveness of anticoagulants such as warfarin and increase the risk of clotting. Intake of such foods should be limited, and the amount consumed daily should remain constant. Digoxin interacts with oat meals, the fiber in oat meal and other cereals, when consumed in large amounts, can interfere with the absorption of digoxin. Tetracycline interacts with calcium or foods containing calcium, such as milk and other dairy products. These foods can reduce the absorption of tetracycline which should be taken 1 hour before or 2 hours after meals [64-67].

Drug-Disease Interactions

Sometimes, drugs that are helpful in one disease are harmful in another. Drug-disease interactions can occur in any age group but are common among old people, who tend to have more diseases. For example, some beta-blockers taken for heart disease or high blood pressure can worsen asthma. This interaction makes it hard for people with diabetes to tell when their blood sugar is too low. Some drugs taken to treat a cold may worsen glaucoma. People should tell their doctor all of the diseases they have before the doctor prescribes a new drug [68-72].

Pharmaceutical Interactions

Pharmaceutical interactions occur when two drugs react chemically or physically during administration or absorption so that the amount of drug available for absorption (of one or both drugs) is altered. Pharmaceutical interactions also occur as a result of mixing two or more antagonistic substances and an undesirable product is formed which may affect the safety, efficacy and appearance of pharmaceutical preparation. The types of interactions are: (i) *physical interaction*, examples immiscibility, insolubility, precipitation and liquefaction, (ii**)** *chemical interaction*; (1) tolerated: the chemical interaction can be minimized by changing the order of mixing or mixing the solutions in dilute forms but no alteration is made in the formulation, (2) adjusted: the chemical interaction can be prevented by an addition or substitution of one of the reacting ingredients of a prescription with another of equal therapeutic value [73-76].

Serious loss of potency can occur from incompatibility between an infusion fluid and a drug that is added to it. Similarly, an addition of more than one drug to the same infusion fluid may result in interactions which cause loss of activity. The immediate effect of soluble insulin is reduced if it is drawn up with potassium zinc insulin in the same syringe or drip [73-76].

Examples of pharmaceutical interactions are mixture of thiopentone and suxamethonium (precipitation), mixture of diazepam and infusion fluid (precipitation), mixture of phenytoin and infusion fluid (precipitation), mixture of heparin and hydrocortisone (inactivation of heparin), mixture of kanamycin and hydrocortisone (inactivation of kanamycin) and mixture of carbenicillin and gentamicin (inactivation of gentamicin). Table 2 illustrates some examples of drug interactions.

Table 2. Examples of some important drug interactions

Interaction	Effect	Time to Effect	Recommendations
SSRIs with selegiline or nonselective monoamine oxidase inhibitor	Hypertensive crisis	Soon after initiation	Avoid.
SSRIs with tramadol	Seizures; serotonin syndrome	Any time	Monitor the patient for signs and symptoms of serotonin syndrome

Interaction	Effect	Time to Effect	Recommendations
SSRIs with St. John's wort	Serotonin syndrome	Any time	Avoid
SSRIs with naratriptan, rizatriptan, sumatriptan or zolmitriptan	Serotonin syndrome	Possibly after initial dose	Avoid. monitor the patient for signs and symptoms of serotonin syndrome
Lovastatin with warfarin	Warfarin effects increased	Any time	Monitor INR.
SSRIs with tricyclic antidepressant (TCA)	TCA level increased	Any time	Monitor for anticholinergic excess and consider lower dosage of TCA
Warfarin with ciprofloxacin, clarithromycin, erythromycin, metronidazole	Warfarin effects increased	within 1 week	Use another antibiotic
Warfarin with acetaminophen	Bleeding & INR increased	Any time	Reduce the dose of acetaminophen and monitor INR.
Warfarin with aspirin	Bleeding & INR increased	Any time	Reduce the dose of aspirin to 100/ day and monitor INR.
Warfarin with NSAIDs	Bleeding & INR increased	Any time	Avoid combination or use a cyclooxygenase-2 inhibitor instead of Cox-1 inhibitor and monitor INR.
Fluoroquinolones with sucralfate	Fluoroquinolones absorption decreased	Any time	Space administration by 2 -4 hr.
Carbamazepine with cimetidine, erythromycin, clarithromycin or fluconazole	Carbamazepine levels Increased	within 1 week	Monitor carbamazepine levels
Phenytoin with cimetidine, erythromycin, clarithromycin or fluconazole	Phenytoin levels increased	within 1 week	Monitor phenytoin levels
Phenobarbital with cimetidine, erythromycin, clarithromycin or fluconazole	Phenobarbital levels increased	within 1 week	Monitor phenobarbital levels
Phenytoin with rifampin	Phenytoin levels decreased	within 1 week	Monitor phenytoin levels.
Phenobarbital with rifampin	Phenobarbital levels decreased	within 1 week	Monitor phenobarbital levels.
Carbamazepine with rifampin	Carbamazepine levels decreased	within 1 week	Monitor carbamazepine levels.
Lithium with NSAID or diuretic	Lithium levels increased	Any time	Decrease lithium dosage by 50% and monitor lithium levels
Oral contraceptive with rifampin	Effectiveness of contraception decreased	Any time	Avoid combination or use contraceptive pill with a higher estrogen or use different method of contraception

Table 2. (Continued)

Interaction	Effect	Time to Effect	Recommendations
Oral contraceptive with antibiotics	Effectiveness of contraception decreased	Any time	Avoid combination or use another contraceptive
Oral contraceptive with troglitazone	Effectiveness of contraception decreased	Any time	Avoid combination or use contraceptive pill with a higher estrogen or use different method of contraception
Cisapride with erythromycin, clarithromycin, fluconazole, itraconazole, ketoconazole, nefazodone	Cisapride metabolism inhibited	within 1 week	Avoid. Or use metoclopramide
Cisapride with class IA or class III antiarrhythmic agents, tricyclic antidepressants or phenothiazine	Prolongation of QT interval along with arrhythmias	Any time	Avoid. Or use metoclopramide.
Sildenafil (Viagra) with nitrates	Acute hypotension	Directly after taking sildenafil	Absolute contraindication
Sildenafil with cimetidine, erythromycin, itraconazole or ketoconazole	Sildenafil levels increased	Any time	Initiate sildenafil at a 25-mg dose
HMG-CoA reductase inhibitor with niacin, gemfibrozil, erythromycin or itraconazole	Any time	Rhabdom-yolysis	Avoid combination

Prescription or Nonprescription Drugs

According to laws, drugs are divided into two groups: prescription drugs and nonprescription drugs (OTC). Prescription drugs are used only under medical supervision and dispensed only with a prescription from a licensed medical professional (physician, dentist or veterinarian). Nonprescription drugs are used without medical supervision (such as aspirin) and are sold as OTC. In the United States, the FDA is the government agency that decides which drugs require a prescription and which don't require prescription [77-80].

Dietary supplements do not require the FDA approval before marketing; thus their safety and efficacy standards are different and not the same as prescription or OTC drugs because these products are not classified as drugs. Dietary supplements include medicinal herbs and nutraceutical which given as supplement to the diet. These products may contain vitamins, amino acids, minerals, and herbs or other plant-derived material. They can act in the same way as a drug does in the body and may cause health problems if not used correctly or if taken in large amounts. These products may not claim to treat specific medical conditions because they do not meet the FDA standards for safety and efficacy [77-80].

Drug Names

Drugs have three or more names including a chemical name, brand or trade name (proprietary, given by the pharmaceutical company it is developed by), and generic or common name (nonproprietary or official, scientific name, named for the active ingredient of the medicine). The chemical name is assigned according to rules of nomenclature of chemical compounds. The brand name is always capitalized and is selected by the manufacturer. The generic name refers to a common established name irrespective of its manufacturer. For example, sildenafil is the generic name of a medicine used to treat erectile dysfunction. However, the company that makes sildenafil, Pfizer, sells it under the brand name Viagra. In most cases, a drug bearing a generic name is equivalent to the same drug with a brand name. Some knowledge of drug names can help in understanding drug product labels. The names of medicines can often be confusing, as the same medicine can sometimes be called differently.

The chemical name describes the atomic or molecular structure of the drug. The chemical name is usually too complex and cumbersome for general use. So an official body assigns a generic name to a drug. The generic names for drugs of a particular type (class) usually have the same ending. For example, the names of all beta-blockers, which are used to treat such disorders as high blood pressure, end in "lol" such as metoprolol and propranolol.

The trade name is chosen by the pharmaceutical company that manufactures or distributes the drug. Patented drugs are usually sold under a trade name. Generic versions of trade-name drugs manufactured after expiration of the pharmaceutical company's patent may be sold under the generic name (for example, ibuprofen) or under the manufacturer's own trade name (for example, Advil) [81-84].

Drug Development

Before a drug is tested in human, the drug should be tested in a laboratory and animals to determine how the drug works and to evaluate its safety in humans. Drug Development is the process of bringing a new drug to the market after identification of the lead compound through a drug discovery process. Drug development includes pre-clinical research where the experiments are conducted in microorganisms/animals and clinical trials where studies are carried out on humans. The drug development process may include obtaining an approval from regulatory bodies to market the drug. The drug discovery process begins by focusing on specific diseases and patient needs. Researchers search for biological targets within the body that play a role in a given disease. Targets can be part of the body (such as a protein, receptor, or gene) or foreign (such as a virus or bacteria). Researchers identify, design, and synthesize promising molecules, screening perhaps tens of thousands of compounds, to assess their effect on the relevant biological targets. Molecules that have the desired effect on the target and meet other design criteria become “lead” molecules that go on to the next phase of development.

The structure of the lead compound is usually modified many times to optimize its specificity and selectivity to target site, its potency, efficacy, effect, safety, stability, absorption, pharmacokinetics and pharmacodynamics properties. The structure modification of the lead compound is known as structure activity relationship (SAR). In general, SAR also

overcome the problems associated with certain drugs such as physicochemical properties (solubility, acidity/basicity, reactivity, binding affinity), pharmacokinetics (absorption, distribution, metabolism, excretion), pharmacodynamics (onset of action, duration of action), pharmaceutics (formulation, stability) and pharmacological (effect, side effects, mode of action) in order to have optimum drugs that are suitable for clinical uses. These factors involve what the body does to the drug and what the drug does to the body.

Ideally, when a drug is highly selective for its target site it has minimal or no side effects. The drug should also be highly potent and effective, thus low doses are used in order to minimize the side effects of the drug. The drug should be effective when taken by mouth, absorbed well from the digestive tract, and reasonably stable in body tissues and fluids so that, ideally, one dose a day is adequate.

During a drug development, standard or average doses are determined. However, people respond to drugs differently. Many factors must be considered when doctors determine the dose for a particular person, including age, weight, genetic make-up, and the presence of other disorders, affect drug response. Development of new drugs is a complex and costly process. It takes an average of 10 years and about $950 million to get a new drug from the laboratory to the market. Only one in 1000 compounds which begin laboratory testing will make it to human testing [85-94].

Early development: After a drug that may be useful in treating a disorder is identified or designed, it will undergo extensive study on animals. Early development gathers information about how the drug works, it's effectively, and what toxic effects it produces, including possible effects on reproductive capacity and the health. However, little will be known about the safety, toxicity, pharmacokinetics and metabolism of the drug in humans. The pre-clinical study is the function of drug development to assess all of these parameters prior to human clinical trials. Many drugs are rejected at this stage because they are shown to be too toxic or not effective.

If a drug seems promising after early development, a program describing the clinical study must be approved by an appropriate institutional research board (IRB) and an investigational new drug application is filed with the FDA. If the FDA approves the application, the drug is allowed to be tested in people (a phase called clinical studies) [85-94].

Clinical studies: clinical studies involve three or four steps. These studies occur in several phases and only in volunteers who have given their full consent.

Phase I trials determine safety and dosing usually in healthy volunteers (20 to 80). The investigation in Phase I is to evaluate the safety and tolerability of the drug as well as its pharmacokinetic and pharmacodynamic properties. In phase I, different amounts of the drug are given to a small number of healthy, young, usually male people to determine the dose at which toxicity first appears.

Phase II trials are used to get an initial reading of efficacy and further explore safety in small numbers of sick patients (100 to 500 patient volunteers). In phase-II, safety and tolerability, pharmacokinetic and pharmacodynamic properties, efficiency and dosage to effect relationship are investigated. Phase II evaluates what effect the drug has on the target disorder and what the right dose might be. Different amounts of the drug are given to up to 100 people who have the target disorder to see whether there is any benefit. Just because a drug is effective in animals in early development does not mean it is effective in people.

Phase III trials are large, pivotal trials to determine safety and efficacy in sufficiently large number of patients (up to 1000 or more patient volunteers). In this phase, the drug is

tested in a much larger (often hundreds to thousands, 300-30,000) group of people who have the target disorder to monitor reaction to long term drug use. These people are selected to be as similar as possible to the people who might use the drug in their life. The drug's effectiveness is studied further, and any new side effects are noted. Phase III tests usually compare the new drug to standard drug or to placebo, or both in multicenter and multinational trials. In addition to determining a drug's effectiveness, studies in people focus on the type and frequency of side effects and on factors that make people susceptible to these effects (such as age, sex, other disorders, and the use of other drugs). The overall aim of phase III is risk-benefit evaluation. The outcome of phase III studies is crucial for the decision taking of the regulatory authorities.

Approval: After extensive study and testing, a candidate drug is submitted for regulatory approval. The decision of the regulatory body determines whether or not the drug can be marketed to patients for approved uses. The review process usually takes 6 -24 months or longer. If studies indicate that the drug is effective and safe, a new drug application is filed with the FDA, which reviews all the information and decides whether the drug is sufficiently effective and safe to be marketed. If the FDA approves, the drug becomes available for use. The whole process usually takes about 10 years. On average, only about 5 out of 4,000 drugs studied in the laboratory are studied in people, and only about 1 out of 5 drugs studied in people is approved and prescribed. Overall drug development process on average to bring one drug to market takes 12-15 years. Pre-clinical testing takes 1-3 years, on average 18 months. Clinical research (phase I-III) takes 2-10 years, on average 5 years. The drug development phase is significantly more expensive in terms of time and money than either lead discovery or drug design and many drugs will fail during the wayside. On average, for every 10000 synthesized structures during a drug design, 500 will reach animal testing, 10 will reach phase I clinical trials and only 1 will reach the market place.

Phase IV (post marketing): individuals may respond quite differently to the same medication. Thus, after a new drug is approved, the manufacturers continue monitor the use of the drug and promptly report any additional, previously undetected side effects to the FDA. Usually approved medications have been subjected to extensive testing for safety and efficacy. But even after medications are approved for general use, companies continue to collect product-safety information and monitor the safety profile of all products. In fact, the monitoring increases over time, through the collection of information from ongoing clinical studies, spontaneous adverse-event reports voluntarily reported directly from healthcare providers, and patients using the medicine. The FDA may withdraw approval if new evidence indicates that a drug may cause severe side effects [85-94].

Placebos: Dosage form is made to look exactly like a real drug but do not contain an active ingredient (inactive), usually contains sugar or starch used in research studies. Despite there being no active ingredients, some people who take a placebo feel better. Some others develop side effects. This phenomenon, called the placebo effect. The placebo effect is mainly on symptoms rather than the actual disease.

When a new drug is being developed, investigators conduct studies to compare the effect of the drug with that of a placebo because any drug can have a placebo effect, unrelated to its action. The true drug effect must be distinguished from a placebo effect. Typically, half the study's participants are given the drug, and half are given an identical-looking placebo. Ideally, neither the participants nor the investigators know who received the drug and who received the placebo.

When the study is completed, all changes observed in participants taking the active drug are compared with those in participants taking the placebo. The drug must perform significantly better than the placebo to justify its use [95-96].

Drug Effectiveness and Safety

The main goals of drug development are effectiveness and safety, however, there are three main issues involved in the drug development process: (i) the drug has to be tested to ensure that it is not only safe and effective, but can be administered in a suitable fashion. This step involves preclinical and clinical trials to test toxicity, drug metabolism, stability, formulation, and pharmacological aspects, (ii) there are the various patenting and legal issues and (iii) the drug has to be synthesized in ever-increasing quantities for testing and manufacturing. All drugs can harm as well as help, safety is relative, and this depends upon the dose or quantity of the drug. The difference between the usual effective dose and the dose that causes severe or life-threatening side effects is called the margin of safety. A wide margin of safety is desirable, but when treating a dangerous condition or when there is no other alternatives, a narrow margin of safety must be accepted. The most useful drugs are effective and, for the most part, safe. Penicillin is such a drug. Except for people who are allergic to it, penicillin is nontoxic, even in large doses. On the other hand, barbiturates, which were once commonly used as sleep aids, can interfere with breathing, lower blood pressure, and cause death if taken in excess.

Sometimes it is difficult to design effective drugs with a wide margin of safety and few side effects. Consequently, some drugs must be used even though they have a very narrow margin of safety. For example, warfarin, which is taken to prevent blood clotting, can cause bleeding, but it is used when the need is so great that the risk must be tolerated. Clozapine is another example. This drug often helps people with schizophrenia when all other drugs have proved ineffective. But clozapine has a serious side effect: it can decrease the production of white blood cells, which are needed to protect against infection. Because of this risk, people who take clozapine must have their blood tested frequently as long as they take the drug [97-99].

Drug Errors

Drug errors are mistakes made by doctors, health care practitioners, pharmacists, and patients when drugs are prescribed, given, taken, or stored. Drug errors can make people ill or allow diseases to worsen or even losses their life. Drug mistakes may be caused by the following:

- People become confused and take drugs incorrectly.
- Doctors choose the wrong drug or write a prescription for the wrong dose.
- Pharmacists incorrectly read the prescription and give the wrong drug or dose.
- Health professionals incorrectly read the label of the drug container and give the wrong drug or dose.

- The pharmacist or person incorrectly stores the drug, weakening the drug's strength.
- People use an expired drug.

People should be sure they understand how and when to take a drug when they pick up a prescription. People should keep a written list of all their current drugs and dosages and bring the list to every health care appointment or emergency department visit. If there is any doubt as to which drugs are being used, people are instructed to bring all their drugs to their health care appointments for review [100-103].

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Chapter 2

Antibiotics

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Abstract

Antibiotics are the most active chemotherapeutics among drugs; they exert their therapeutic effect by antagonizing the growth of bacteria. Since 1910 many antibiotics have been developed with different mechanisms of action including: (1) inhibition of bacteria's cell wall synthesis; this class of antibiotics includes vancomycin and β-lactam antibiotics such as penicillins, cephalosporins and carbapenems, (2) inhibition of protein synthesis including tetracyclines, aminoglycosides, macrolides and chloramphenicol and (3) DNA synthesis inhibitors such as fluoroquinolones and sulfonamides that inhibit folic acid synthesis. In this chapter we describe the three antibiotic classes, their mechanism of action, clinical uses, side effects, and their resistance by different bacteria.

Keywords: antibiotics, cell wall synthesis inhibitors, penicillins, β-lactam antibiotics, mechanism of action, cephalosporins, side effects, protein synthesis inhibitors, protein synthesis inhibitors, bacterial resistance

Abbreviations

PBP	Penicillin binding proteins
DHP1	Human renal dehydrogenase 1
I.V	Intravenous
UTI	Urinary tract infection
G.I	Gastrointestinal

AMP	Adenosine monophosphate
STD	Sexually transmitted diseases

History

Infections were the major cause of death during the nineteenth century. The introduction of antibiotics not only helped in the treatment of infections but also have a major role in decreasing mortality and morbidity.

In 1910 Paul Ehrlich developed the first antimicrobial salvarsan for the treatment of syphilis, a disease that was almost incurable back then [1]. In 1932 prontosil, a sulfonamide antibiotic was discovered and since it was cheap, many companies were encouraged to mass produce many derivatives of prontosil [2].

During the second half of the nineteenth century and before the important discovery of Fleming many researchers recorded observations regarding the antibacterial properties of penicillium fungi [2]. In 1929, Alexander Fleming introduced "penicillin" as a compound with antibacterial properties, when he observed that a bacterial growth was terminated by a mold, however, because prontosil was available there was not much interest in penicillin. Till 1941, the purity of extracted penicillin was only 0.3 to 7%, which was not sufficient to be clinically used. In 1945, Dorothy (Crowfoot), Hodgkin and Barbara Low used x-ray crystallography to determine the chemical structure of penicillin and in 1950 penicillin was chemically synthesized [3]. The isolation of 6-aminopenicillanic acid (Figure 1) in 1958 led to the semisynthesis of new penicillins such as ampicillin, methicillin and carbenicillin [3]. Few years later, ticarcillin (1971) and piperacillin (1977) were synthesized and in 1989 the combination of piperacillin- tazobactam was introduced and was widely used because of its high activity against gram positive bacteria [4].

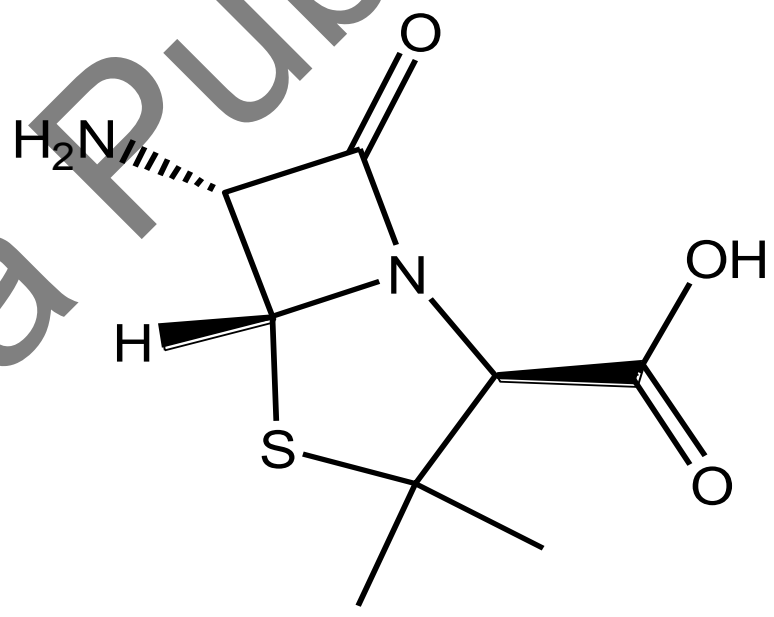


Figure 1. Chemical structure of 6-aminopenicillanic acid.

Selman Waksman, a soil microbiologist, and coworkers isolated the first aminoglycoside streptomycin which was effective against tuberculosis, the main cause of death in the 19th century [5]. In 1953, Newton and Abraham discovered cephalosporin C; its antibacterial activity was low but was not susceptible to hydrolysis by penicillinase. Cephalothin, the first cephalosporin available for clinical use, was introduced in 1964, but it was only available for parenteral use [4]. Lilly Research Laboratories developed cephalexin, which was effective upon oral administration and total synthesis of cephalosporin C was accomplished in 1970. Beecham laboratories discovered β-lactamases inhibitors and Merck developed thienamycin antibiotic which was followed by the discovery of sulfazecin, the monocyclic β-lactam antibiotic, by Takeda Chemical Industries [3].

Cell Wall Synthesis Inhibitors

Penicillin binding proteins (PBP) are bacterial proteins that bind covalently to penicillins and other β-lactam antibiotics. These antibiotics bind and acylate the binding site of PBP leading to inhibition of cell wall synthesis [6].

B – Lactam Antibiotics

β-lactam antibiotics have wide spectrum of activity and low toxicity because the drug targets bacterial cell wall that has no analogues in higher organisms.

Mechanism of Action

The inhibition of cell wall synthesis leads to loss of osmotic support and eventually cell lysis. The last step in cell wall synthesis is the cross linking of peptidoglycans between the carboxyl of D-alanine in one peptidoglycan chain and an amino group in the next chain, this reaction is catalyzed by transpeptidase. The cross linking of the adjacent glycan chains causes the rigidity of the cell wall. Binding of penicillin to the transpeptidase enzyme forms an acyl enzyme complex via the penicillin β-lactam ring cleavage, which leads to transpeptidase enzyme inactivation and eventually cell lysis [7]. Few novel antibacterial drugs were synthesized in the past few years, some of these drugs are inhibitors of peptidoglycan synthesis, such as MurA inhibitors; MurA is an enzyme that catalyses the first step in peptidoglycan synthesis, the natural fosfomycin is an irreversible inhibitor of this enzyme. Inhibitors of MurB, MurC, MurD and MurE were developed as well [8].

Penicillins

Penicillins are the oldest available antibiotics, their bacterial activity is due to the inhibition of cell wall synthesis, despite the development of resistance penicillins remain the

most useful antibiotics today. Natural penicillins have narrow spectrum of activity while the newer penicillins have wide spectrum, they are effective against many gram negative bacteria such as H influenza and E coli. Penicillins are effective in the treatment of nose, throat, lower respiratory tract and genitourinary tract soft tissue infections [9].

Penicillin G (Figure 2) is natural penicillin with narrow spectrum of activity, short half life of 30-60 minutes and easily inactivated by gastric secretions, which makes it mostly used in parenteral administration. Bezathine penicillin is a slow release form of penicillin G and is used for the treatment of early and late stage syphilis as I.M injection [9].

Penicillin V (Figure 3) is natural penicillin that is used orally because of its stability in the gastric secretions.

Synthetic penicillins were developed because of the emergence of resistance due to β-lactamases.

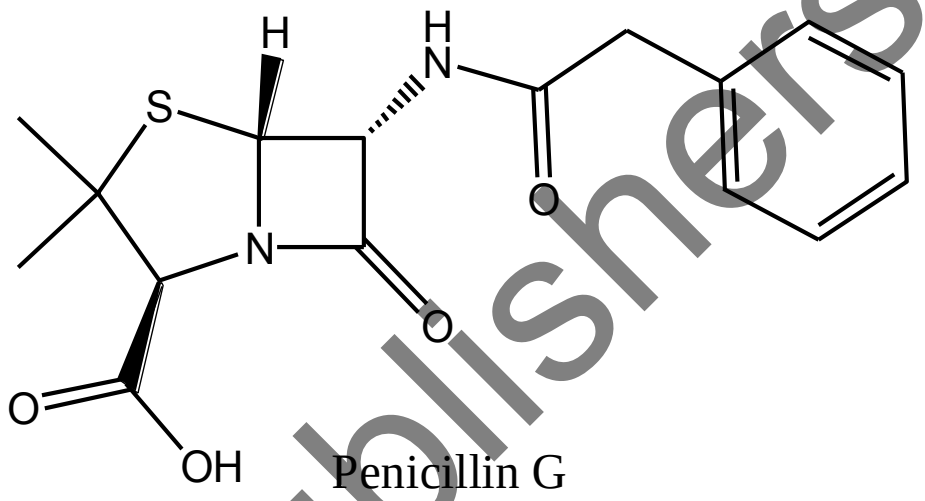


Figure 2. Chemical structure of penicillin G.

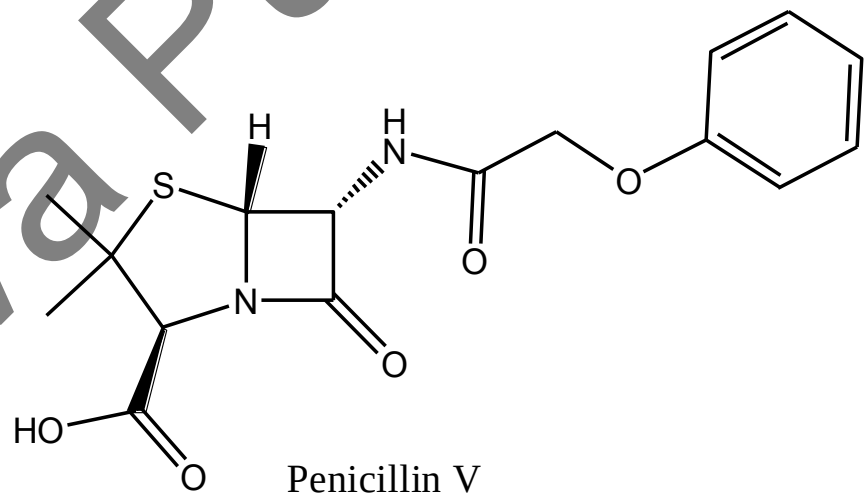


Figure 3. Chemical structure of penicillin V.

Ampicillin (Figure 4) was the first penicillin in this category, developed by the addition of an amino group to benzylpenicillin. Ampicillin is available as oral and parenteral dosage forms and is administered every 6 hours. Amoxicillin (Figure 5) replaced ampicillin because of better absorption when administered orally, bioavailability of 95%, dosing every 8 hours and less G.I side effects. Both ampicillin and amoxicillin are used as prophylaxis before genitourinary and gastrointestinal procedures and prophylaxis against bacterial endocarditis. Further, both penicillins have broader spectrum than the natural penicillins [9]. In the case of chronic bronchitis, H. influenza infections and H. influenza meningitis amoxicillin is the drug of choice [10].

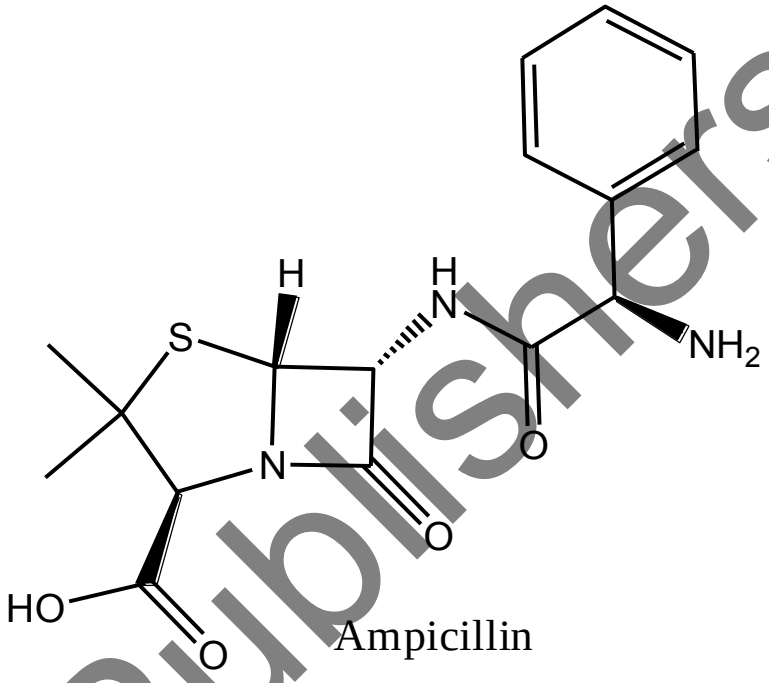


Figure 4. Chemical structure of ampicillin.

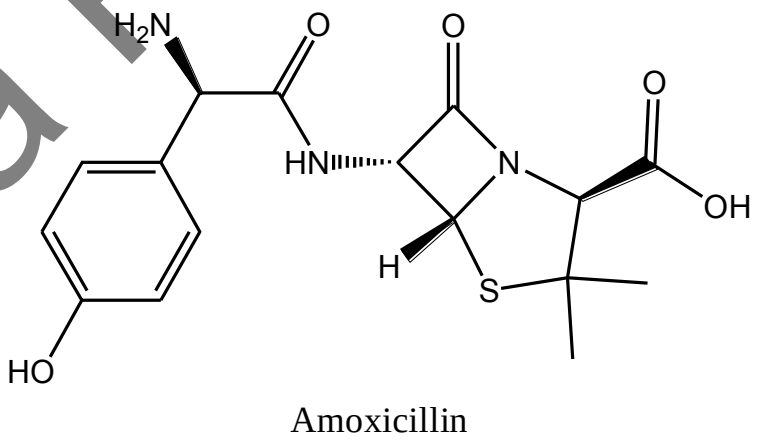


Figure 5. Chemical structure of amoxicillin.

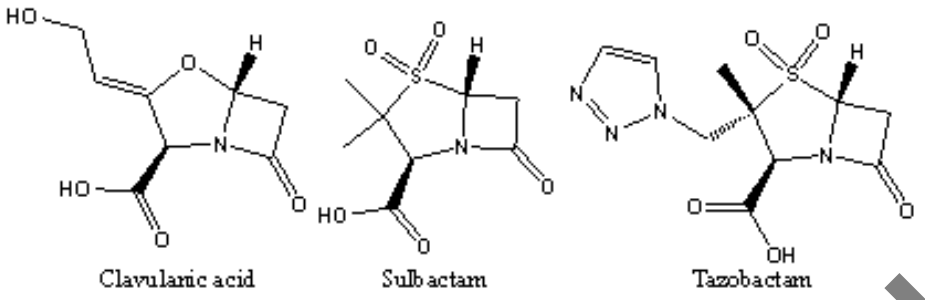


Figure 6. Chemical structure of β-lactamase inhibitors.

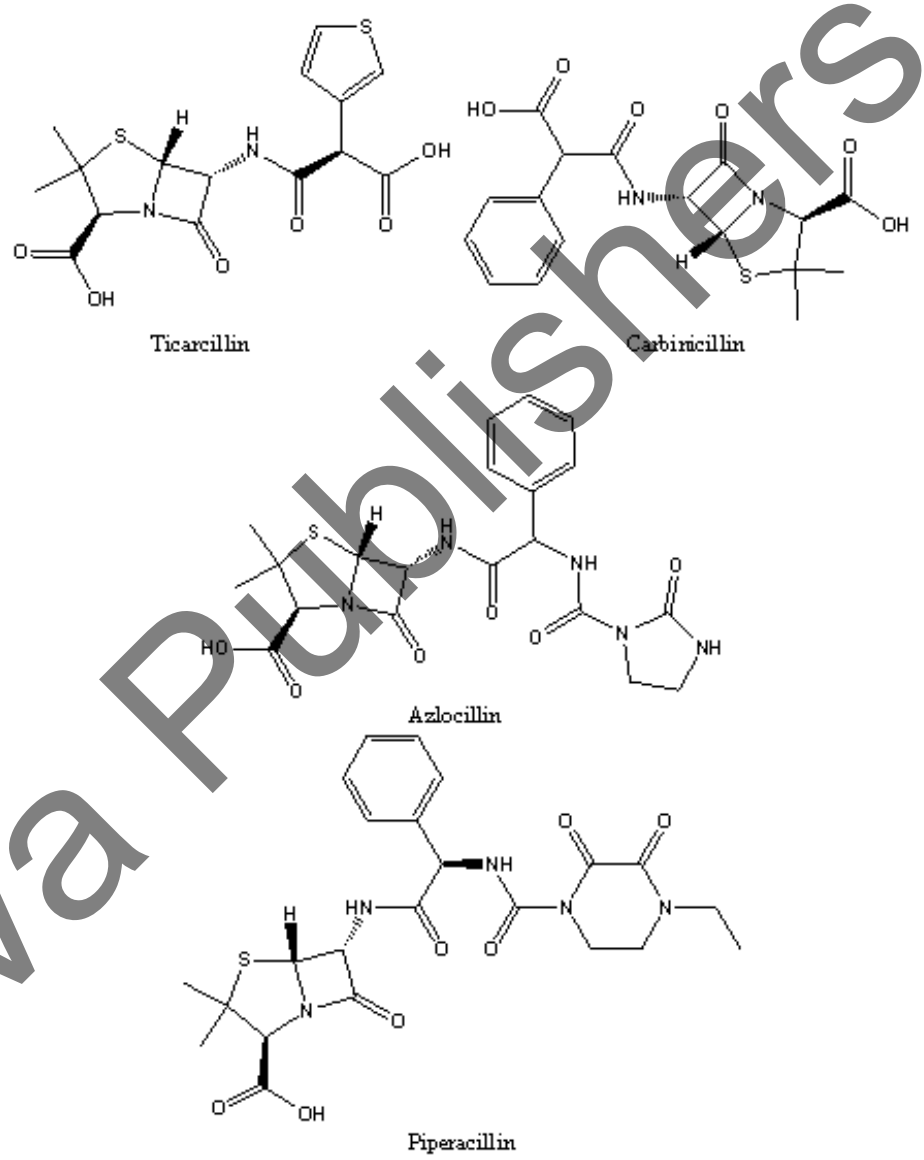


Figure 7. Chemical structures of ticarcillin, carbenicillin, azlocillin and piperacillin.

The development of bacterial β-lactamases caused inactivation and resistance to β-lactam antibiotics. Clavulanic acid, sulbactam and tazobactam (Figure 6) are suicidal inhibitors that bind irreversibly to β-lactamase enzymes. Amoxicillin-clavulanic acid was the first β-lactam-β-lactamase combination introduced into clinical practice [11]. This combination is the only orally available and most widely used in skin and intra-abdominal infections. Ampicillin-sulbactam and piperacillin-tazobactam are available only for intravenous administration [9].

Carboxypenicillins are extended spectrum penicillins such as ticarcillin, carbenicillin, azlocillin and piperacillin (Figure 7), they are used for the treatment of complicated infections [9].

Side Effects of Penicillins

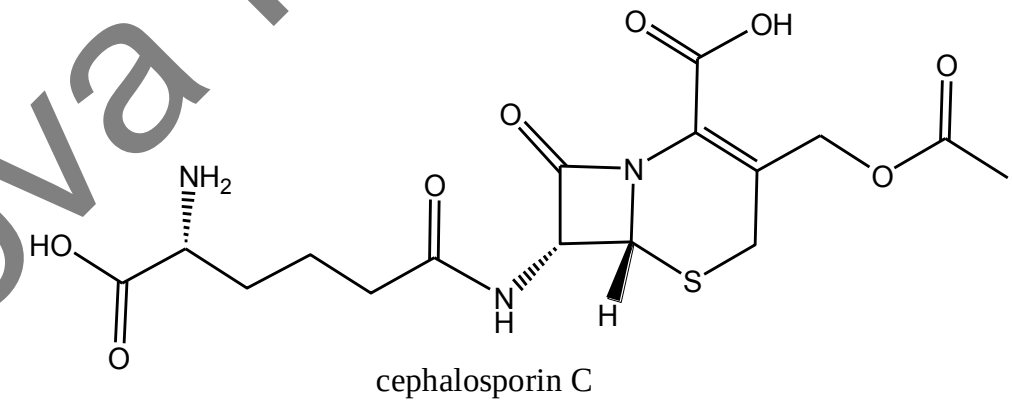
Penicillins are the safest among all antibiotics; they are classified by the FDA as pregnancy category B and are safe for use in breastfeeding women. The most common side effect and allergic symptom is skin rash. In the case of ampicillin G.I side effects are the most common. Candidiasis is common in the use of broad spectrum penicillins. Allergy and hypersensitivity are also common side effects which may cause anaphylaxis [9].

Cephalosporins

Cephalosporins are a large group of β-lactam antibiotics with broad spectrum of activity, compared to older antibiotics cephalosporins have good pharmacokinetic profile and low drug toxicity. Based on their spectrum of activity they are classified into four generations [12].

Semisynthetic cephalosporins are produced by modifications on cephalosporin C molecule (Figure 8). Substitutions on C7 result in providing compounds with more stability against β-lactamases, which caused increase in activity and broader spectrum such as cefuroxime, cefotaxime, ceftriaxone and ceftazidime. Substitutions on C3 yield compounds with longer half life such as in the case of ceftriaxone and ceftazidime [12].

Cephalosporins like other β-lactam drugs bind to the PBP by covalent bond and inactivate transpeptidase enzymes, leading to inhibition of the cell wall synthesis [12].



cephalosporin C

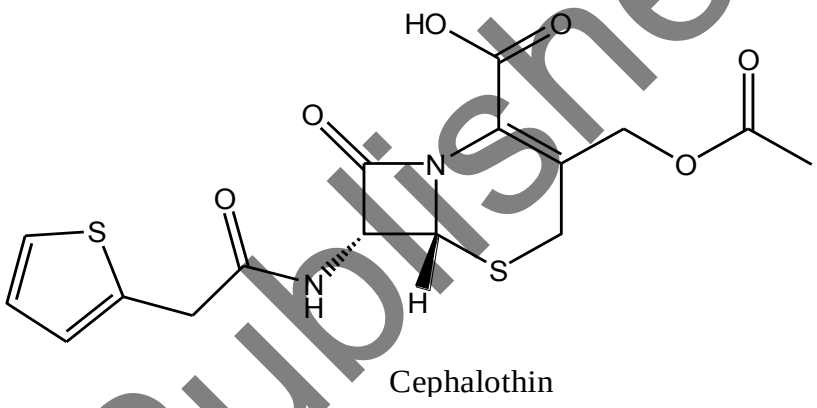
Figure 8. Chemical structure of cephalosporin C.

First Generation Cephalosporins

The first generation cephalosporins were introduced to clinical practice in 1960. Antibiotics of this generation are most active against aerobic gram positive cocci [12]. They include cephalothin (Figure 9), which has a short half life of 0.67 hour [12] and cephaloridine (Figure 10) that causes nephrotoxicity. Both have a broad spectrum of activity but they are susceptible to β-lactamases and ineffective against gram negative bacteria [13]. This generation also includes cephalexin and cefaclor (Figure 11) that are administered orally three to four times daily, they are absorbed in the brush border membrane of the small intestine via a dipeptide transporter, these drugs are best to be administered on empty stomach [12].

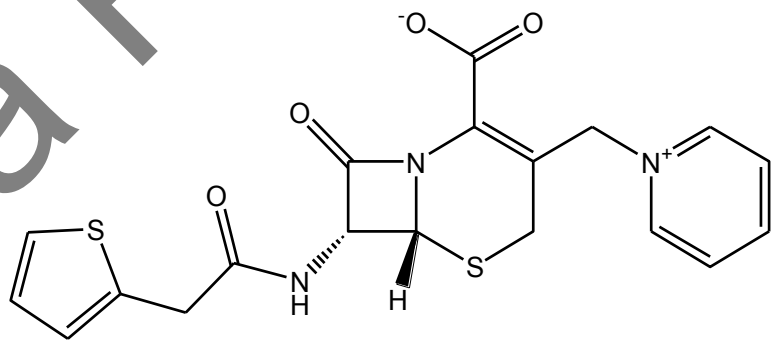
Second Generation Cephalosporins

The second generation cephalosporins are more stable against β-lactamases but not effective against some gram negative bacilli [13]. Cefoxitin and cefotetan (Figure 12) are more active against anaerobic bacteria [12].



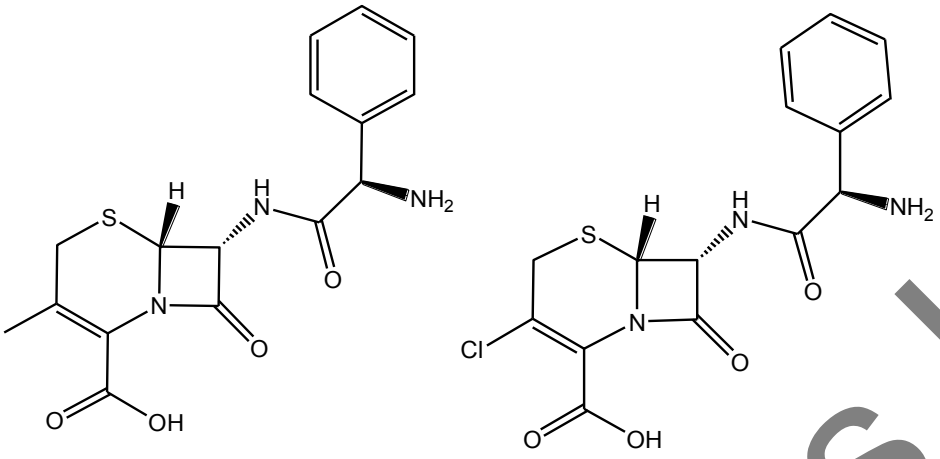
Cephalothin

Figure 9. Chemical structure of cephalothin.



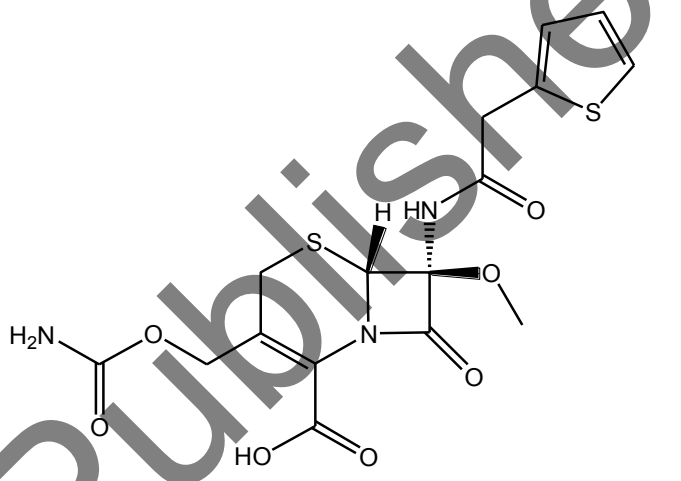
Cephaloridine

Figure 10. Chemical structure of cephaloridine.

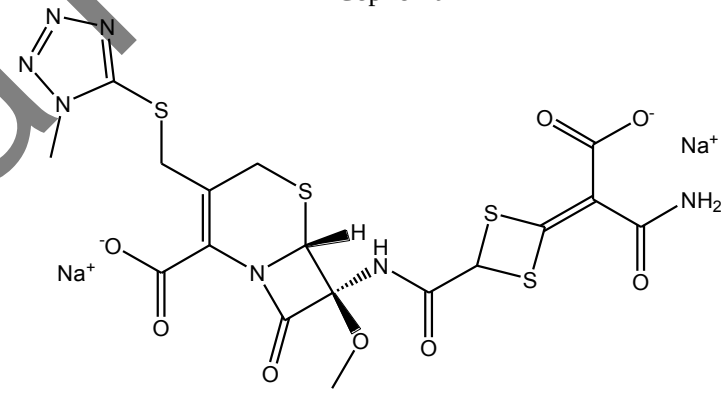


Cephalexin Cephaclor

Figure 11. Chemical structures of cephalexin and cephaclor.



Cephoxitin



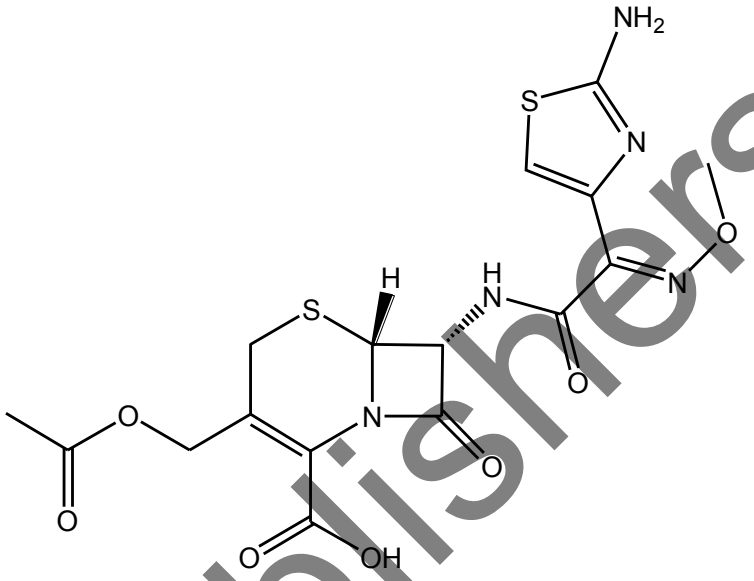
Cephotetan

Figure 12. Chemical structures of cephoxitin and cephotetan second generation cephalosporins.

Third Generation Cephalosporins

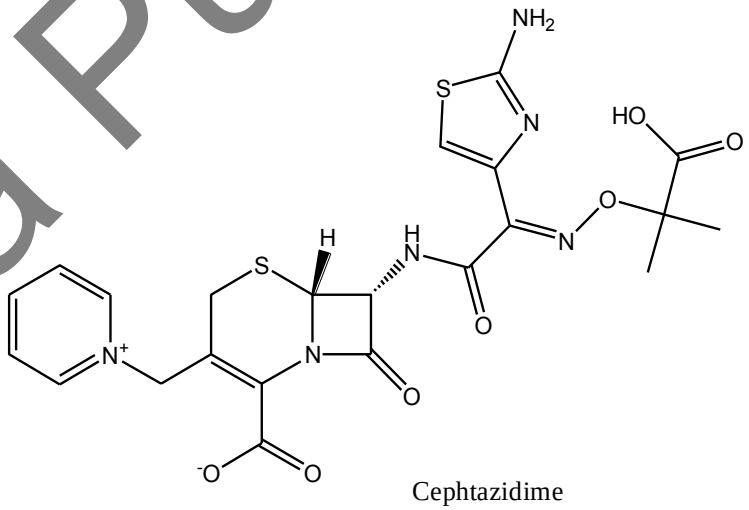
The third generation cephalosporins such as cefotaxime (Figure 13), ceftazidime, cefdinir, cefixime and ceftriaxone are more stable against many β-lactamases and has a broader specrum of activity [14].

Ceftazidime (Figure 14) is highly effective against aerobic gram negative bacteria and most active against pseudomonas aeruginosa [12]. The half life of ceftazidime is 1.9 hours, it is excreted unchanged in the urine [13].



Cefotaxime

Figure 13. Chemical structure of cefotaxime.



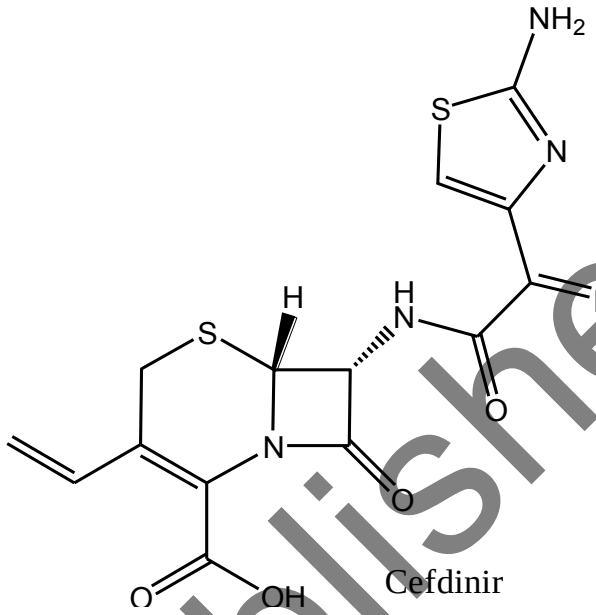
Cephtazidime

Figure 14. Chemical structure of cephtazidime.

Cefdinir (Figure 15) was approved by the FDA in 1997. Diarrhea is the main side effect of cefdinir, it is mainly excreted by kidneys and has a half life of approximately 1.5 hours [15].

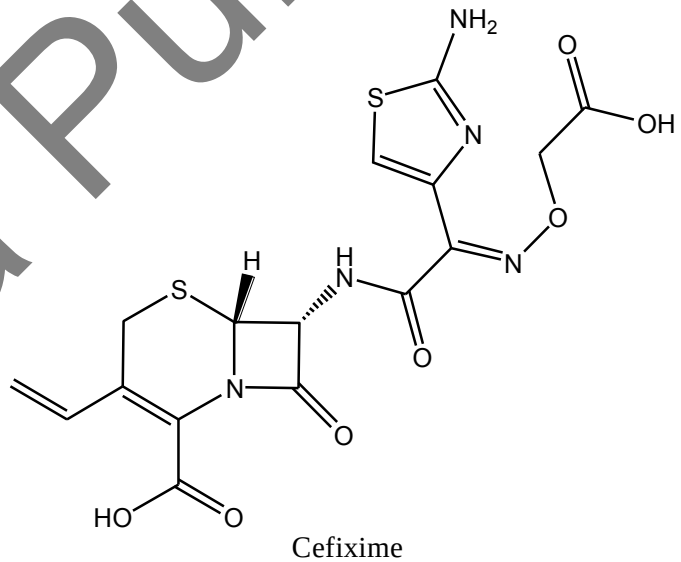
Cefixime (Figure 16) can be administered once daily because it has a half life of three to four hours, which is the longest half life of the orally administered cephalosporins [12].

Ceftriaxone (Figure 17) is administered parenterally and has the longest half life of all β-lactam drugs, it is administered once daily [12].



Cefdinir

Figure 15. Chemical structure of cefdinir.

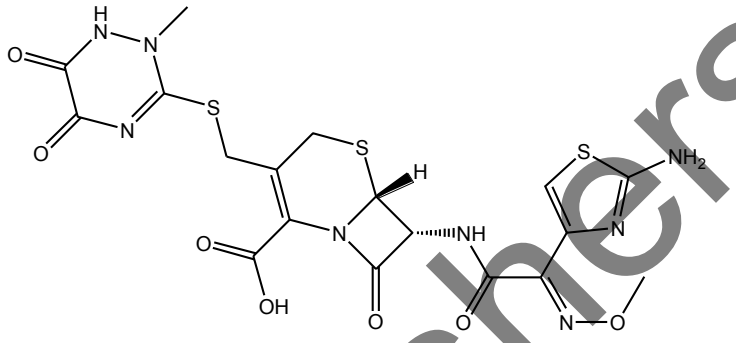


Cefixime

Figure 16. Chemical structure of cefixime.

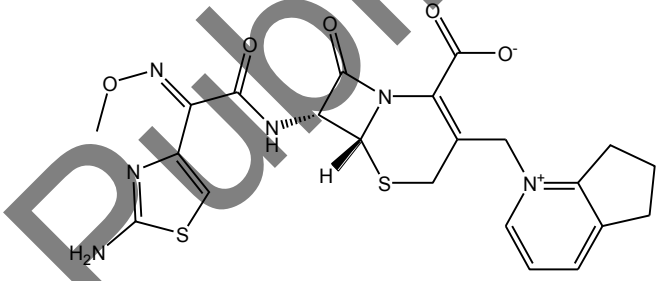
Fourth Generation Cephalosporins

The fourth generation cephalosporins were developed by the addition of a quaternary ammonium group at the C3 position, which makes zwitterionic compounds with the ability to penetrate gram negative bacterial outer membrane [12]. These compounds are parenterally administered and have a broader specrum of activity than the third generation. They are active against both gram positive and gram negative organisms, more effective and have more stability against some β-lactamases. This generation includes cefpirome and cefepime (Figure 18). These antibiotics are given twice daily, and used for the treatment of nosocomial infections specially in intensive care units [14].

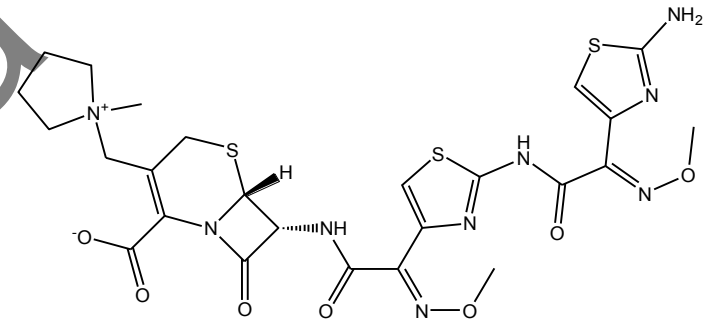


Cefriaxone

Figure 17. Chemical structure of ceftriaxone.



Cefpirome



Cefipime

Figure 18. Chemical structures of cefpirome and cefipime.

Cefpirome has a half life of two hours; it is mainly excreted by the kidneys. The most common side effect is diarrhea, others are rash and nausea. Cefpirome is used for the treatment of respiratory tract infections, complicated urinary tract infections, skin and soft tissue infections, sepsis, bacterial meningitis, fever associated with neutropenia, and combined with metronidazole for intraabdominal infections [14].

Cephalosporins Clinical indications

Second and third generations of cephalosporins are effective in community acquired pneumonia.

For bacterial meningitis, third generation cephalosporins such as ceftriaxone and cefotaxime are drugs of choice. Ceftazidime or cefepime are the initial treatment in a patient with neutropenia and fever. Cephalosporins are also effective in the treatment of gonorrhea, syphilis, surgical prophylaxis and bacterial endocarditis [12].

The excretion of all orally administered cephalosporins is renally, except for cefixime, in which 50% of the dose is excreted in the urine [12].

Adverse Effects of Cephalosporins

Orally administered cephalosporins may cause G.I side effects including nausea, vomiting and diarrhea. Allergic reactions affect 1 to 3% of patients taking cephalosporins. Cephalosporins cause transient, mild increase in hepatic transaminases enzymes in 1 to 7% of patients [12].

The development of bacterial resistance limits the use of cephalosporins, the mechanisms of resistance include synthesis of β-lactamases, alteration in the PBP target and change in the bacterial cell membrane porins [12].

Masking Bitter Taste of Amoxicillin and Cephalexin

Masking bitter taste is crucial for patient compliance especially in pediatric and geriatric patients.

Prodrug approach has been used for masking amoxicillin and cephalexin bitter taste. It is expected that by blocking the free amine group in amoxicillin and cephalexin by a suitable linker the interaction of the antibacterial with bitter taste receptors on the tongue will be blocked.

Based on this theory Karaman's group synthesized cephalexin and amoxicillin prodrugs (Figure 19) [16].

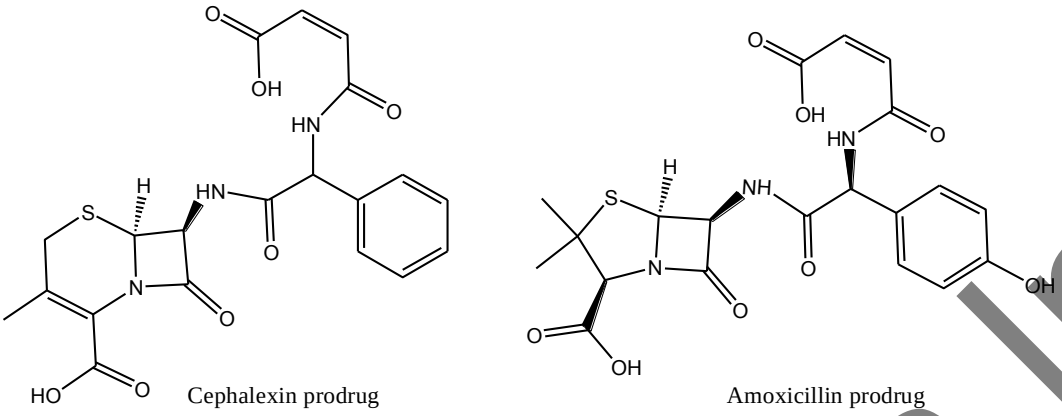


Figure 19. Chemical structures of cephalexin and amoxicillin prodrugs.

Carbapenems

Carbapenems are broad spectrum β-lactam antibiotics; they are stable to almost all β-lactamases. They differ from other β-lactam antibiotics in their nuclear structure, in which the sulfur is replaced by a carbon group and there is an unsaturated bond between carbon 1 and 3 in the thiazolidine moiety (Figure 20) [17].

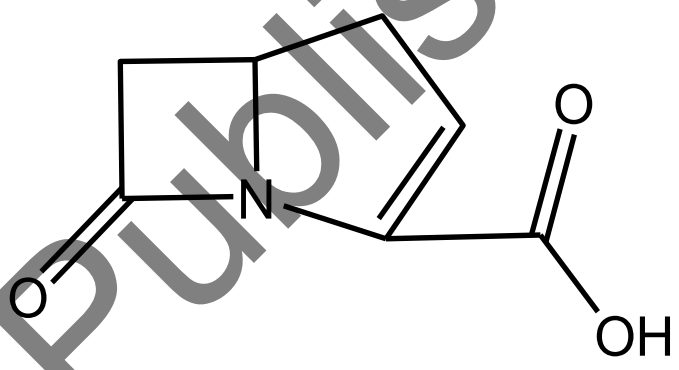
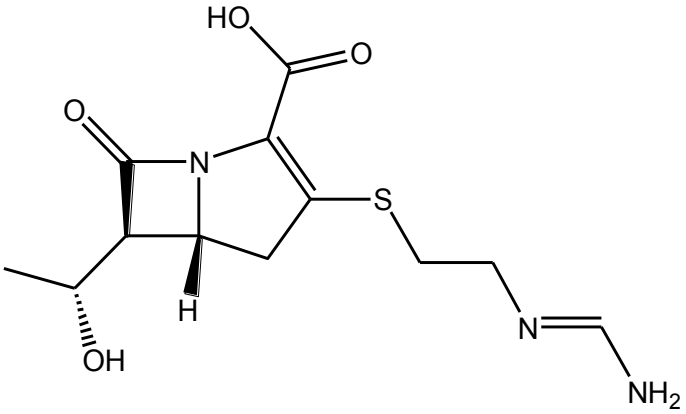


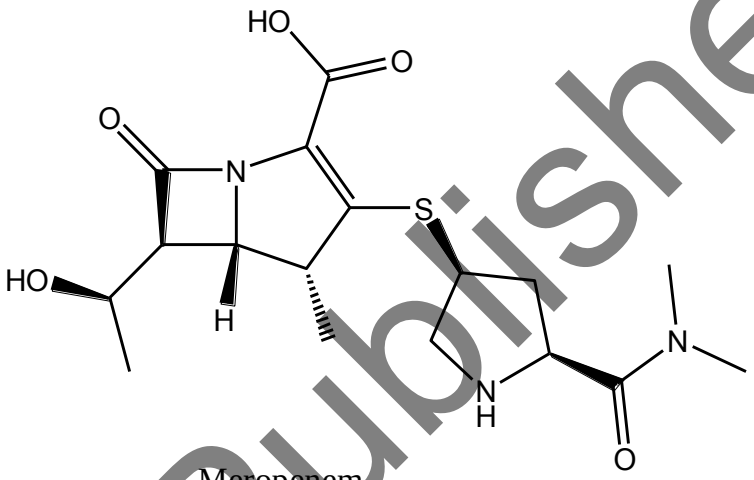
Figure 20. Basic chemical structure of carbapenems.

The first carbapenem introduced into clinical practice was imipenem (Figure 21); it has a broad specrum of activity but was susceptible to hydrolysis by human renal dehydrogenase 1. Then meropenem (Figure 22) was developed, the side chain on the C2 yielded a stable compound to the DHP1 enzyme. Imipenem and meropenem are both administered via I.V injection. Meropenem is more active against gram negative bacteria than imipenem, while the latter is more active against gram positive bacteria. Both are active against lower respiratory tract infections. Meropenem is the only carbapenem that was evaluated in children and is FDA approved to be used in paediatric meningitis. Other carbapenems are ertapenem, panipenem, biapenem, lenapenem and sanfetrinem [17].



Imipenem

Figure 21. Chemical structure of imipenem.



Meropenem

Figure 22. Chemical structure of meropenem.

Vancomycin

This glycopeptide antibiotic (Figure 23) was developed in 1950, the basic structure of this type of antibiotics is seven amino acids, sugars and amino sugars [18]. Vancomycin inhibits cell wall synthesis by forming a complex with peptidoglycan which inhibits transpeptidase [19].

Vancomycin is used for the treatment of infections caused by gram positive bacteria. It is used for staphylococcus epidermis, methicillin resistance staphylococcus aurius (MRSA), endocarditis caused by methicillin resistance staphylococcus aurius and methicillin sensitive staphylococcus aurius and staphylococcus central nervous system infections. However, linezolid and minocycline are pharmacokinetically preferred to vancomycin in gram positive CNS infections [20].

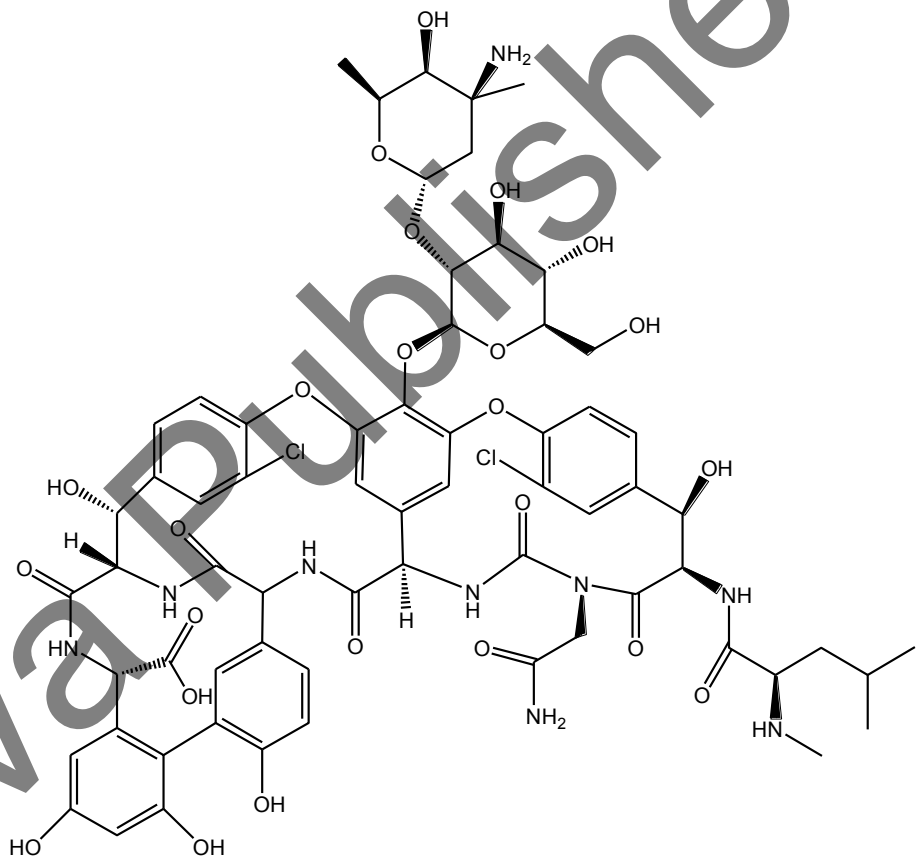
Vancomycin is mainly excreted by glomerular filtration, 90% of the dose is excreted unchanged in the urine, it is available orally and parenterally [20]. Vancomycin mean half life is 6 hours [21].

Excessive use of vancomycin resulted in amplification of vancomycin resistant enterococci. In addition, it caused an increase in staphylococcus resistance, which is caused by the increase in cell wall thickness and a decrease in permeability [20].

Rapid infusion of vancomycin is associated with "red man" or "red neck" syndrome, a nonimmunological reaction which causes pruritus and hypotension.

This side effect can be avoided by a slow administration of the drug. Intravenous administration is also associated with thrombophlebitis at the site of administration. Vancomycin may cause hypersensitivity reactions which includes skin rash and drug fever. Ototoxicity is a major toxicity caused by vancomycin. After ototoxicity the drug must be discontinued, this side effect is reversible [22].

Vancomycin has a poor oral bioavailability caused by the polar nature of the drug. Studies have shown that the use of water in oil in water multiple emulsion incorporating unsaturated fatty acids increased the intestinal absorption [23].



Vancomycin

Figure 23. Chemical structure of vancomycin.

Protein Synthesis Inhibitors

This group of antibiotics targets bacterial ribosome, which composed of 50S and 70S subunits.

Tetracyclines

Tetracylines are lipophilic nonionized molecules composed of a linear fused six membered nucleus (Figure 24). They have a broad spectrum of activity [24].

The first members of tetracyclines are chlortetracycline and oxytertracycline, both were discovered in 1940 [24]. Both have a serum half life range from 6 to 10 hours, they are absorbed in the stomach duodenum and small intestine [25].

Tetracyclines are bacteriostatic to a wide range of gram positive and gram negative bacteria, they inhibit protein synthesis by inhibiting the 30S ribosome [26].

Tetracyclines generally penetrate tissues and body fluids in a well manner. The absorption is decreased by the presence of food, milk and calcium. They penetrate well across sebum which makes tetracycline largely used for acne treatment [24].

Doxycyline and minocycline (Figure 25) are second generation tetracyclines, which have better tissue penetration, longer half life, and large volume of distribution compared to the original tetracylines [26]. These antibiotics can be administered once or twice daily [24]. Doxycycline has a bioavailability of more than 80%, its half life ranges from 12 to 25 hours.

Doxycyline is used for gonorrhea and Chlamydia pelvic infections, Lyme disease, malaria prophylaxis and syphilis. The majority of its dose is absorbed in the duodenum, and it is better taken with food to decrease G.I side effects [26].

Tetracycline Clinical Uses

Tetracyclines generally are used for the treatment of Pasteurella infections, brucellosis, Borrelia recurrentis that cause relapsing fever, early stages of cholera, Mycoplasma pneumoniae infections, rickettsial infections, Shigella dysentery in which a single dose therapy of tetracyclines is effective, Chlyamidia psittaci infections, conjunctivitis, trachoma, L-serotypes of Chlamydia infections, ureteritis caused by Chlamydia or Ureaplasmas, syphilis prophylaxis and chronic bronchitis in which minocycline and doxycycline are preferred [27].

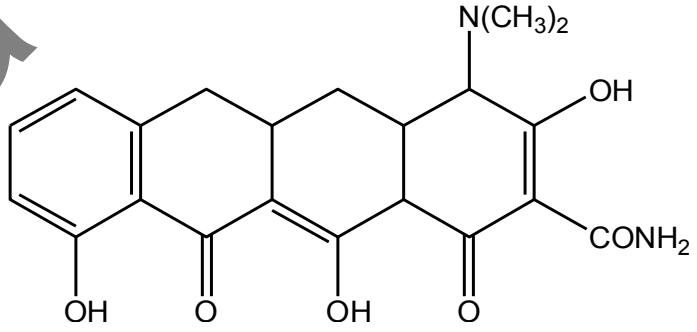


Figure 24. Chemical structure of the minimum tetracycline pharmacophore.

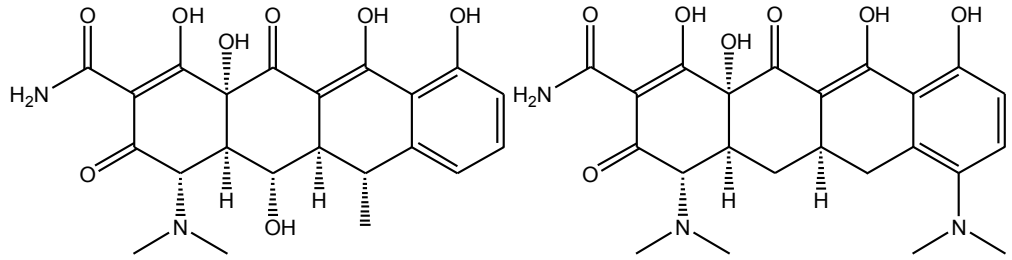


Figure 25. Chemical structures of minocycline and doxycycline.

Minocycline is preferred over doxycycline in the treatment of N. gonorrhea, Bacteroides fragilis, S. aureus gram positive bacterial and staphylococcal skin infections. Minocycline is also preferred for long term low dose treatment of mild to moderately severe acne caused by Corynebacterium acnes, due to its ability to penetrate quite well the lipid layers of the dermis and possess minor side effects [27].

Tetracylines Side Effects

The most common side effects associated with tetracylines are G.I side effects, which include nausea, vomiting, diarrhea and candidiasis. The most tetracycline with G.I side effects is doxycycline. In addition, tetracyclines cause tooth discoloration in adults and children, it can cause this discoloration in developing teeth even during pregnancy [26]. Tetracyclines should not be used for patients less than 8 years old and pregnant women [27].

Resistance to Tetracyclines

The extensive use of tetracycline leads to the development of bacterial resistance, this resistance is caused by:

- Protection of the tetracycline target, ribosome.
- Lowering the amount of tetracycline in the cytoplasm to prevent the tetracycline from reaching the ribosome, this is achieved by decreasing the permeability of the cell envelope and efflux of tetracycline outside the cytoplasm. There are two types of tetracycline efflux pumps tetracycline specific and multidrug resistance efflux pumps.
- Tetracycline inactivation by modifying enzymes [28].

The resistance and its widespread by the mobile tetracycline resistance (tet) genes caused a decrease in the therapeutic effectiveness of tetracyclines [29], and consequently has led to the development of the third generation tetracycline, glycylcylines. Glycylcylines have the same structural features of tetracycline, but they are not substrates for efflux pumps, which makes this generation effective against the resistant organisms [30]. GAR639 a glycylcylines, is an analogue of minocycline that showed in vitro activity against bacterial organisms that are resistant to the old generation tetracyclines [31].

GAR639 is effective against penicillin-resistant Streptococcus pneumonia, vancomycin-resistant enterococci and methicillin-resistant Staphylococcus aureus [29].

Tigycycline (GAR639) which has received FDA approval for the treatment of serious bacterial infections is only available as injectable form administered over 1 hour period, has a long half life of 37 to 67 hours and a large volume of distribution. Oral bioavailability of tigycyline is reported to be limited. The most common side effects of tigycycline are nausea and vomiting [25, 32].

Aminoglycosides

A group of molecules that have a nucleus of amino-cyclitol attached to two or more sugars by a glycoside linkage. They are polar and positively charged which make them insoluble in lipid. This positive charge makes glycosides able to bind to the negatively charged lipopolysaccharides on the bacterial cell wall, but also contributes to the side effects of aminoglycosides [33].

Clinical Uses of Aminoglycosides

Aminoglycosides have a broad spectrum of activity and rapid bactericidal effect. They bind to 30S ribosome and inhibit bacterial protein synthesis. Aminoglycosides generally are used for the treatment of aerobic gram negative bacilli, staphylococci and certain mycobacteria. Streptomycin (Figure 26) is used for tuberculosis. Gentamicin, amikacin and netilmicin (Figure 27) are used for pneumonia, sepsis and meningitis. Neomycin is used for burns, wounds, ulcers and dermatitis [33].

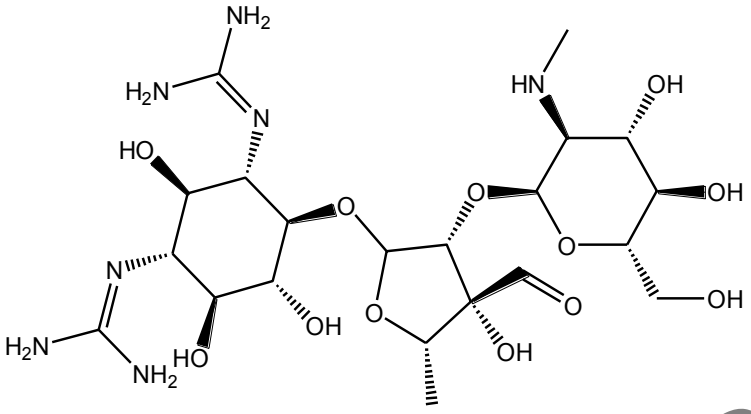
Aminoglycosides are only available for parenteral, intramuscular and intravenous administrations because they are polar compounds [33]. They are excreted unchanged in the urine.

There have been studies to increase aminoglycosides absorption using mixed micellar solutions. It was found that the combinations of bile salts and certain lipids increased the absorption of gentamycin and streptomycin [34].

Aminoglycosides accumulate in the renal tubules which causes nephrotoxicity. Another common side effect is ototoxicity that can be acute, reversible, or chronic and irreversible hearing loss which can be caused by cochlear hair cells degeneration [35].

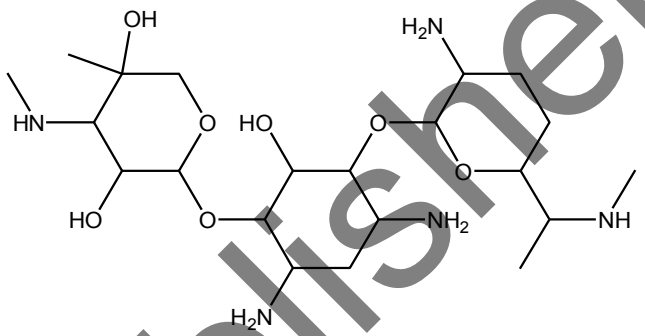
Bacterial Resistance to Aminoglycosides

The widespread therapeutic use of aminoglycosides results in the development of resistance. The most common mechanism of resistance is enzymatic inactivation. There are three types of these enzymes: adenylyl transferase that adds AMP moiety, phosphotransferase that adds a phosphate group to the antibiotic and acetyl transferase that adds acetyl group to one of the amino groups of the aminoglycoside. These modifications reduce the antibiotic affinity to the RNA target and make it unable to prevent protein synthesis. Other mechanisms of resistance are target modification, 16s rRNA methylation and mutations of the ribosome target, and efflux pumps that prevent the antibiotic from reaching the cytoplasm where is the target site [33, 36].

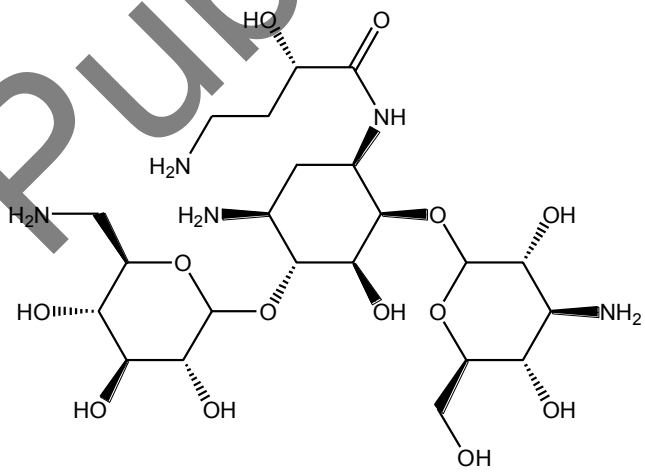


Streptomycin

Figure 26. Chemical structure of streptomycin.

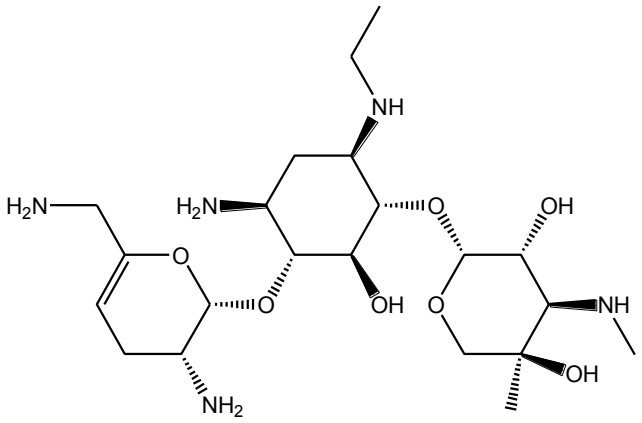


Gentamicin



Amikacin

Figure 27. (Continued).



Netilimicin

Figure 27. Chemical structures of gentamicin, amikacin and netilmicin.

Macrolides

Erythromycin (Figure 28) was the first antibiotic discovered in 1952 among this group. After its discovery many semisynthetic compounds were developed such as clarithromycin, azithromycin and roxithromycin that are all derivatives of erythromycin with better microbiological and pharmacokinetic properties. The general structure of macrolides is a 12 to 16 atoms lactone ring that is attached via a glycosidic linkage to one or more sugars. Macrolides bind to 50S ribosome and inhibit protein synthesis [37].

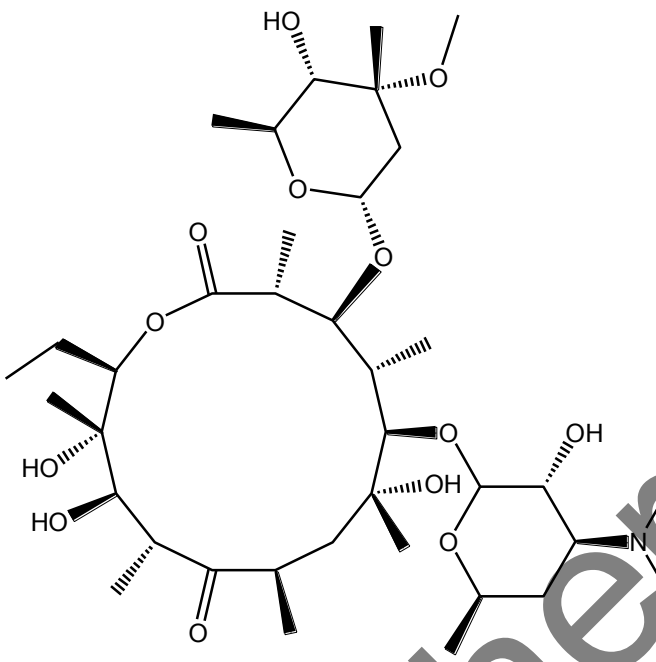
Macrolides are widely used for the treatment of gram positive bacterial infections such as Staphylococcus aureus and Staphylococcus pneumonia.

Erythromycin

Erythromycin (Figure 28) is a 14-membered lactone ring attached to two sugars. It is used for M. pneumonia and Legionella pneumonia infections, diphtheria, pertussis, conjunctivitis and bacillary angiomatosis. Erythromycin is well absorbed from the G.I, excreted primarily in the bile, has a half life of 1.4 hours, inhibits CYP450 enzymes and is available for oral and intravenous administration. The main side effects of erythromycin are nausea, vomiting, diarrhea, abdominal cramps and phlebitis caused by intravenous administration [38].

Clarithromycin

Clarithromycin is a 14-membered lactone ring, a derivative of erythromycin. It has the best absorption from the G.I of all macrolides with 50% bioavailability, administered twice daily and not available for intravenous administration. Clarithromycin is excreted in the urine after extensive hepatic metabolism. It is used for the treatment of upper and lower respiratory tract infections [38]. Clarithromycin is also widely used for H. pylori infections [39].



Erythromycin

Figure 28. Chemical structure of erythromycin.

Clarithromycin is well tolerated in doses less than 2000 mg, but it occasionally causes nausea, diarrhea, abdominal pain, headache and metallic taste. This antibiotic causes drug-drug interactions as a result of inhibiting the CYP450 enzymes [38].

Azithromycin

Azithromycin (Figure 29) is the only 15 membered lactone ring antibiotic of this group. It was developed by the addition of amino group to the erythromycin ring and it has a better gram negative bacterial activity than erythromycin [37]. It is the most active macrolides against H. Influenza and Legionella species. Azithromycin has an oral bioavailability of 37%. It is used as single dose therapy for STDs and short duration of therapy of 3-5 days for skin, soft tissue and some respiratory tract infections because its concentration remains high in these tissues for extended period of time [38]. Azithromycin is excreted unchanged in the feces [40].

Azithromycin side effects are mild to moderate. The primary side effects are gastrointestinal including nausea diarrhea and mild abdominal pain [41].

Resistance to Macrolides

Resistance to macrolides is accomplished by methylation of the adenine in the 23S rRNA, decrease in the drug penetration and enzymatic degradation [41].

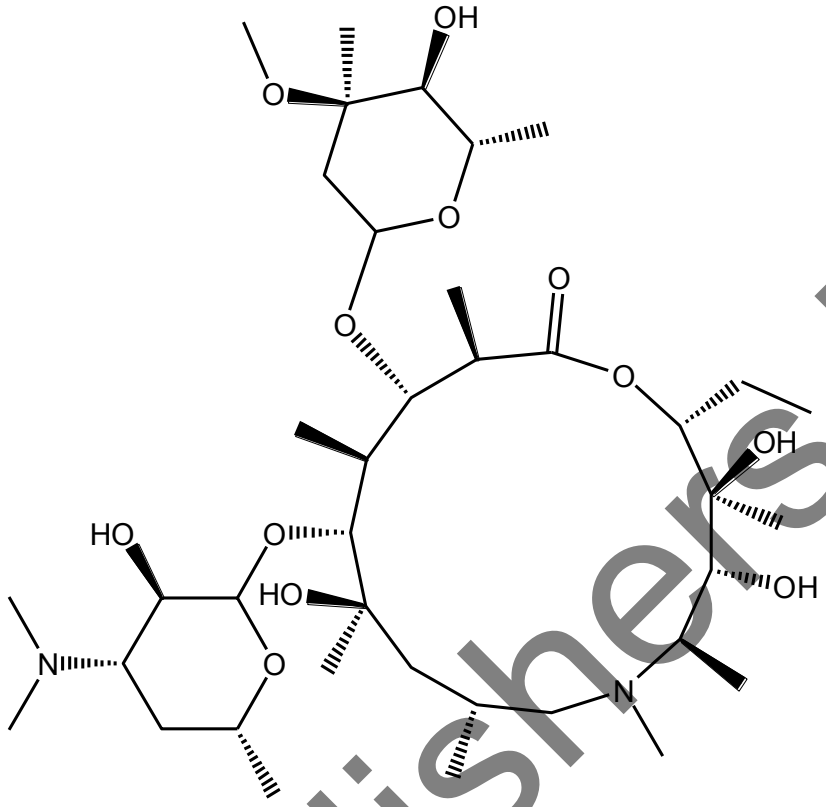


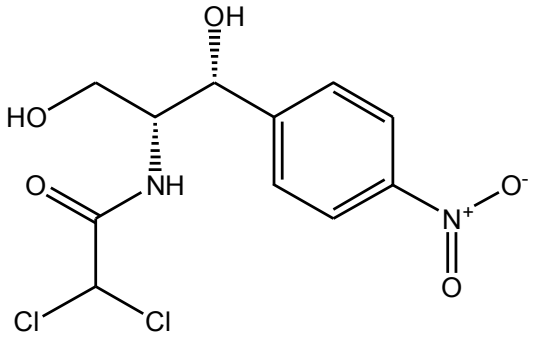
Figure 29. Chemical structure of azithromycin.

Chloramphenicol

Chloramphenicol (Figure 30) was the first broad spectrum antibiotic, it is water insoluble and has extremely bitter taste. The modified forms of chloramphenicol are available for oral and parenteral administration [42]. Chloramphenicol palmitate is available as suspension and capsules for oral administration and chloramphenicol sodium succinate is available for intravenous administration [43]. The bacteriostatic effect of chloramphenicol is a result of protein synthesis inhibition by binding to 50S ribosomal subunit [44].

Because of chloramphenicol toxicity and the availability of safer alternatives chloramphenicol use is limited. It is used only in life-threatening situations.

Chloramphenicol is associated with fatal toxicities including aplastic anemia, that can't be predicted and occurs weeks or months after treatment, and gray baby syndrome in infants and newborns. This syndrome consists of cyanosis, abdominal distention and vasomotor collapse. Another serious toxicity is bone marrow suppression, which is reversible and dose related [43].



Chloramphenicol

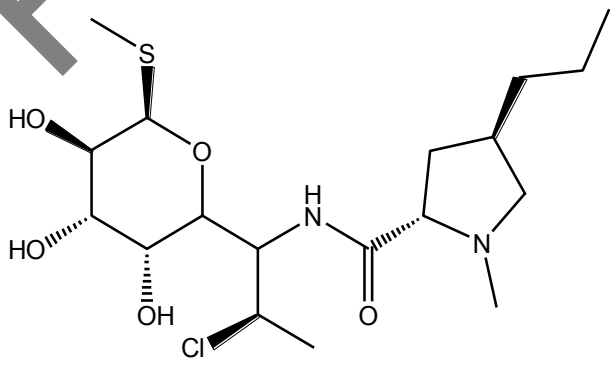
Figure 30. Structure of chloramphenicol.

Clindamycin

Clindamycin was introduced into clinical practice in 1960, derived from lincomycin [43]. Clindamycin (Figure 31) is available orally as capsules as clindamycin hydrochloride and suspension as clindamycin palmitate, It is available as clindamycin phosphate for intramuscular and intravenous administration. It is well absorbed orally and not significantly affected by food [45].

The half life of clindamycin is 2 to 4 hours and it is metabolized in the liver then excreted in the urine and feces [46].

Clindamycin inhibits protein synthesis by binding to 50S ribosomal subunit [47]. It is active against anaerobic gram positive and gram negative bacteria [48]. A common complication of clindamycin that limits its use is C. difficile toxin-mediated pseudomembranous colitis, which can be treated by discontinuation of clindamycin and initiation of vancomycin or metronidazole. Other less serious side effects are nausea, vomiting, flatulence, anorexia, bitter taste, abdominal distention and transient increase in hepatocellular enzymes [47, 48].



Clindamycin

Figure 31. Chemical structure of clindamycin.

DNA Synthesis Inhibitors, Folic Acid Antagonists and Urinary Tract Antiseptics

Fluoroquinolones

Quinolones were derived from quinine. Figure 32 shows the basic chemical structure of fluoroquinolones. Nalidixic acid (Figure 33) was the first fluoroquinolone developed. It has a variable systemic absorption, therefore, its use was limited to urinary tract infections [49]. Later on, norfloxacin was developed by the addition of piperazine group at quinolone's C7 (Figure 34), followed by ciprofloxacin which has a broader spectrum of activity [50].

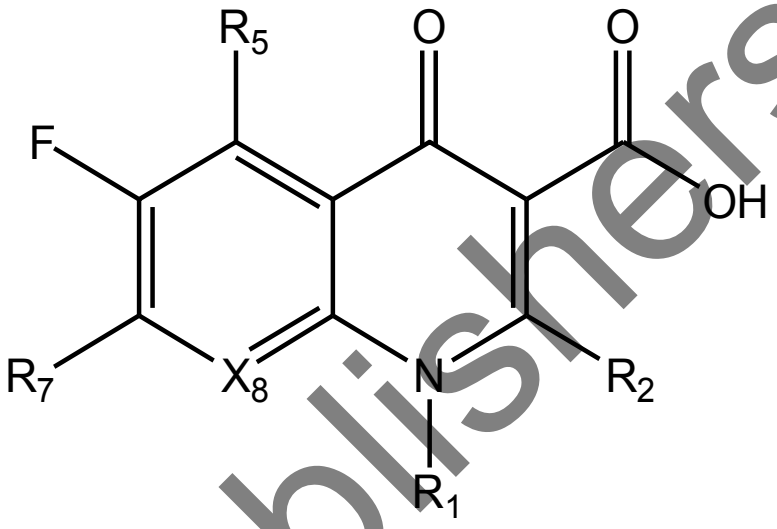
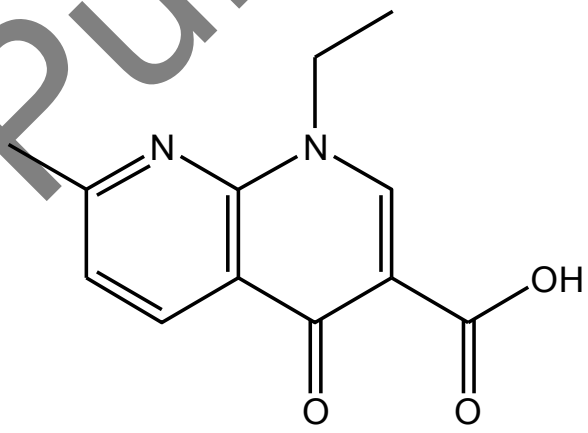
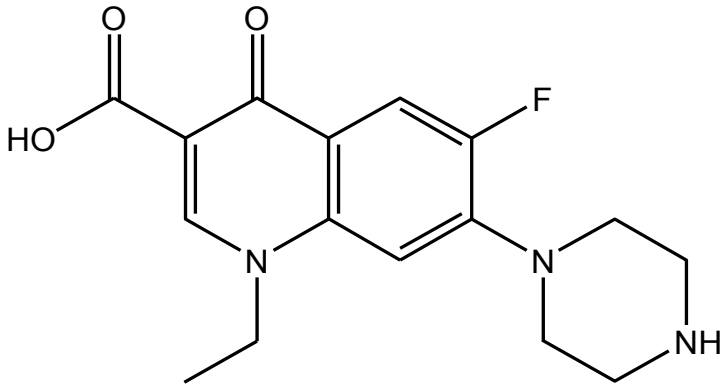


Figure 32. The basic pharmacore of fluoroquinolones.



Nalidixic acid

Figure 33. Chemical structure of nalidixic acid.



Norfloxacin

Figure 34. Chemical structure of norfloxacin.

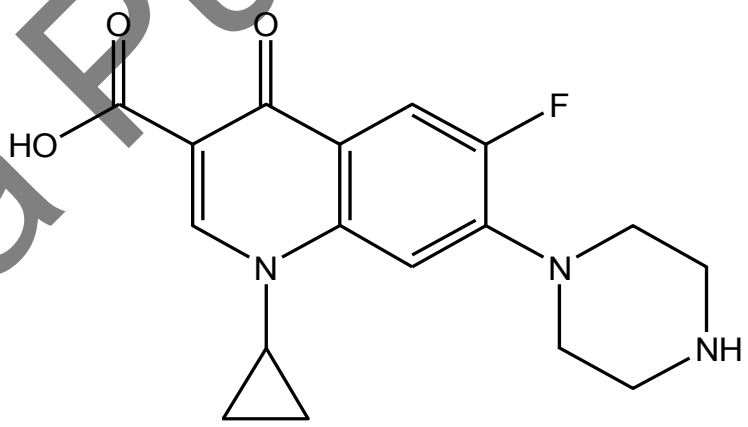
Quinolones interact with two targets, DNA gyrase and topoisomerase IV. They are both essential for bacterial DNA replication, by binding to these targets quinolones disrupt DNA synthesis and cause cell death [51, 52].

Fluoroquinolones Clinical Uses

Fluoroquinolones are very active against enteric gram negative bacilli and cocci, gram negative bacteria, gastrointestinal tract and urinary tract bacterial pathogens, while ofloxacin and ciprofloxacin are preferred for gram positive bacterial infections [53].

Ciprofloxacin

Ciprofloxacin was developed by the addition of cyclopropyl group to the N1 quinolone position (Figure 35), this modification increased the potency of the drug [49]. It has a half life of 3.5 hours, well absorbed and has a bioavailability of 70% [50]. It is used for gram negative bacterial infections and as an anti-pseudomonal agent [49].



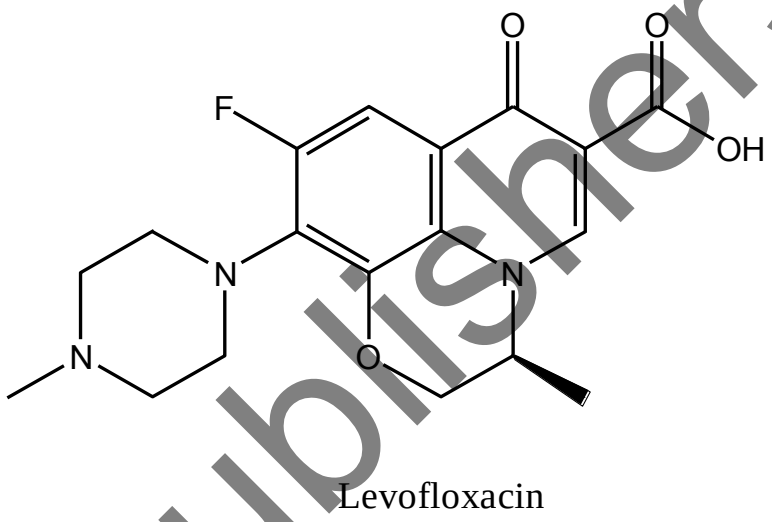
Ciprofloxacin

Figure 35. Chemical structure of ciprofloxacin.

The new fluoroquinolones include clinafloxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, moxifloxacin, sitafloxacin, sparfloxacin and trovafloxacin that are well absorbed after oral administration, have good tissue penetration and their bioavailability ranges from 70% to 99%. They have a longer half life than ciprofloxacin and they are effective in the treatment of respiratory tract infections including community acquired pneumonia, acute exacerbation of chronic bronchitis and acute sinusitis [50].

Levofloxacin

Levofloxacin was developed by the alkylation on position 8 of quinolone (Figure 36). This modification increased the half life of the drug to 7 hours and improved its tissue penetration. Levofloxacin is widely used for respiratory tract infections [49]. The absorption of this drug is rapid and its bioavailability is about 100% [54]. Levofloxacin is mainly eliminated renally and less than 10% of the dose is excreted by metabolism [55].



Levofloxacin

Figure 36. Chemical structure of levofloxacin.

Fluoroquinolones Side Effects

The most common adverse effects of fluoroquinolones are gastrointestinal including nausea, vomiting and diarrhea. Central nervous system adverse effects primarily headache and dizziness, pruritus and skin rash [56, 57]. These side effects are generally mild and reversible. Sparfloxacin and grepafloxacin were withdrawn from the market because of cardiovascular side effects, due to prolongation of the QT interval [50].

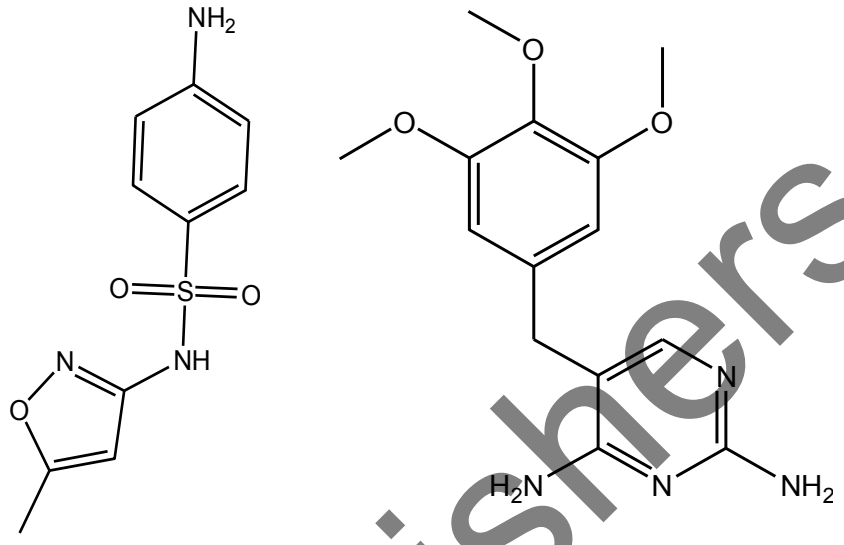
All Fluoroquinolones are contraindicated in paediatric patients because of side effects [50].

Sulfonamides

Sulfonamides are broad spectrum antibiotics that are active against both gram negative and positive bacteria. They inhibit the synthesis of folic acid leading to their bacteriostatic effect. They are generally well absorbed from the G.I and metabolized in the liver [58].

Sulfamethoxazole-Trimethoprime Combination (Co-Trimoxazole)

The Sulfamethoxazole trimethoprime combination (Figure 37) act synergistically in killing bacteria. This combination is available for oral and intravenous administration. They are both well absorbed from the G.I, trimethoprim is mainly excreted renally while sulfamethoxazole is primarily metabolized in the liver [59].



Sulfamethoxazole Trimethoprime

Figure 37. Chemical structures of sulfamethoxazole and trimethoprime.

Mechanism of Action

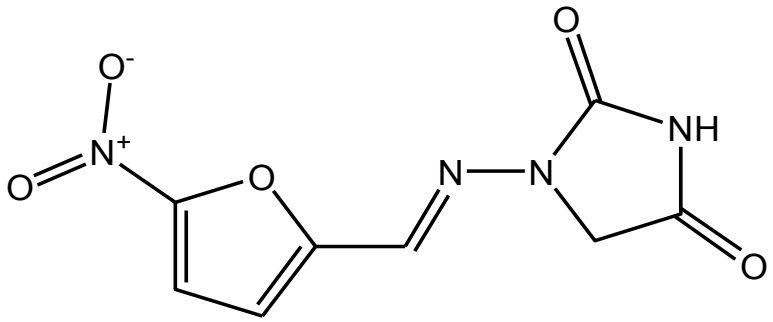
Sulfamethoxazole is a sulfonamide drug that is similar in structure to para-aminobenzoic acid. It inhibits dihydrobtroate synthetase enzyme and prevent the synthesis of dihydrofolic acid from its precursor. Trimethoprim inhibits dihydrofolate reductase enzyme and prevents the synthesis of the active tetrahydrofolic acid from dihydrofolic acid. Inhibition of these two steps blocks the synthesis of porins, thymidine and bacterial DNA [58, 59].

The most common use of sulfamethoxazole-trimethoprime combination is in urinary tract infections, it is also effective in lower and upper respiratory tract infections [58].

The most common side effects are gastrointestinal including nausea, vomiting and anorexia, and hypersensitivity skin reactions [58, 59].

Nitrofurantoin

This antimicrobial became available for clinical use in 1953. Nitrofurantoin (Figure 38) is effective in the treatment of lower UTI. It achieves therapeutically active concentrations only in the urinary tract, which makes it a target selective drug and does not change the normal flora growth. Nitrofurantoin does not reach effective concentration in the blood and its side effects are rare except for the pulmonary reaction that is rare [60].



Nitrofurantoin

Figure 38. Chemical structure of nitrofurantoin.

Summary and Conclusion

Antibiotics contributed over years in bacterial infections control. These drugs have an important role in the rise of life expectancy. Despite all the developments in antibiotic industry, infectious diseases remain the second cause of death worldwide; this is due to the development of antibiotics resistance organisms, which decreased current antibiotics effectiveness. The development of new antibiotics have slowed and since 1970 only three new classes of antibiotics have been marketed [61].

The majority of antibiotics is considered safe, but any antibiotic can cause side effects and in some cases life threatening side effects. β-lactams and sulfamethoxazole cause leukopnia, thrombocytopenia, anemia and skin rash. In addition, both antibacterial groups cause hypersensitivity reactions including drug fever. β-lactams are the most frequent antibiotic class associated with anaphylactic reaction. Photosensitivity reaction is a common side effect of tetracycline and sparfloxacin. Erythromycin and some quinolones cause prolongation of QT interval. Generally antimicrobials cause G.I side effects; macrolides are the least orally tolerated. Most antibiotic associated side effects are reversible [62].

Resistance to antibiotics is caused by many mechanisms including decrease in antibiotic diffusion through the glycocalyx diffusion layer, that acts like a bacterial barrier to the antimicrobial agents, enzymatic degradation of the antibiotic such as β-lactamases that hydrolyze the β-lactam ring of penicillins, cephalosporins and related drugs, the gram negative cell envelope that prevents the drug from reaching inside the cell, bacterial adaptation as a result of exposure to sub-inhibitory concentrations of antibiotics, such as the alteration in the penicillin binding proteins structure that decrease the affinity of penicillin to the target site and decrease in the antibiotic concentration that reaches the target site because of increase or decrease in certain outer membrane proteins and multidrug efflux pumps [63, 64].

New antibiotics are needed to treat infections caused by resistant pathogens. There are two strategies for the development of new antibiotics: (1) to modify the existing scaffolds by modifying chemical groups at the periphery of the core structure and (2) to develop a new

scaffold such as phytochemicals, that are derived from plants [65]. These scaffolds must be active against gram positive and negative bacteria, have no cross resistance with the existing antibiotics and be easily synthesized [30].

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Chapter 3

Pain Killers

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Abstract

Pain is an unpleasant feeling often caused by intense or damaging stimuli, such as stubbing a toe, burning a finger, putting alcohol on a cut, and bumping the funny bone. Pain motivates the individual to withdraw from damaging situations, to protect a damaged body part while it heals, and to avoid similar experiences in the future. Most pain resolves promptly once the painful stimulus is removed and the body has healed, but sometimes pain persists despite removal of the stimulus and apparent healing of the body.

In this chapter we discuss the current used medicines for the treatment of pain. The wide availability of generic and over-the-counter analgesics based on non-steroidal anti-inflammatories (NSAIDs), acetaminophen and opiates (and their combinations) provides many individuals with an accessible source of relief for mild to moderate pain. However, many patients with chronic conditions remain poorly treated as sometimes pain arises in the absence of any detectable stimulus, damage or disease such as congenital insensitivity to pain (CIP), also known as congenital analgesia, is one or more rare conditions where a person cannot feel (and has never felt) physical pain. By studying genotype of different diseases, the result was that this pain arises from gene SCN9A that encodes the Na^+ voltage gated channel ($NaV_{1.7}$). By mimicking phenotype of CIP for the treatment of painfully disease, Xenon pharmaceutical develop a novel analgesic XEN402 to treat pain by blocking voltage dependent Na^+ voltage gated channel ($NaV_{1.7}$).

Keywords: COX-1, COX-2, G.I., NSAID's, selective COX-2 inhibitors, genetics, opioid analgesics

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Abbreviations

GABA	Gamma amino butyric acid
CNS	Central nervous system
CIPA	Congenital insensitivity to pain with anhidrosis
NGF	Nerve growth factor
OA	Osteoarthritis
NSAID's	Non-steroidal anti-inflammatory drugs
COX	Cyclooxygenase
ASA	Acetyl salicylic acid
G.I.	Gastrointestinal
ACEI	Angiotensin-converting-enzyme inhibitor
FDA	Food and drug administration
IBP	Ibuprofen
TRPV1	Transient receptor potential vanilloid 1
DRG	Dorsal root ganglia
CRPS	Complex regional pain syndrome
PNS	Peripheral nerves system
CGRP	Calcitonin gene-related peptide
BH4	Tetrahydrobiopterin
Accn3	Amiloride-sensitive cation channel 3
TCAs	Tricyclic antidepressants
SNRIs	Serotonin norepinephrine re-uptake inhibitors
COMT	Catechol o- methyl transferase enzyme
MAO	Mono amino oxidase enzyme
GCH1	Guanosine- triphosphate cyclohydrolase1
UGT UDP	glucuronosyl transferase
REMS	Risk evaluation and mitigation strategies
DAWN	Drug abuse warning network
CR	Controlled release version
TrkA	Tyrosine kinase receptor A
FAAH	Fatty acid amide hydrolase
MAGL	Monoacylglycerol lipase
VGSCs	Voltage-gated sodium channels
IEM	Inherited erythromelalgia
PEPD	Paroxysmal extreme pain disorder
CIP	Congenital indifference to pain
LOF	Loss of function
GOF	Gain of function
h	Hour

Introduction

Pain is one of the most common reasons for patients to seek medical attention and one of the most prevalent medical complaints in the word. According to the 2011 Institute of Medicine Report-Relieving Pain, approximately 116 million Americans are burdened with chronic pain. Three in five of those 65 years or older said that they experienced pain that lasted a year or more; more than 60% of U.S. nursing home residents report pain, most commonly attributable to arthritis, and 17% have substantial daily pain [1]. More than one-quarter of adults said they had experienced low back pain, and 15% of adults experienced migraine or severe headache in the past three months. For the millions of Americans who experience persistent pain, the impact on function and quality of life can be profound [1].

Pain is associated with high utilization of health care and the societal costs related to treatment are compounded by the loss in productivity associated with persistent pain. Lost productivity from common pain conditions among workers costs $61.2 billion per year and most of this is related to reduce performance while at work. The annual economic cost associated with chronic pain most likely exceeds $560 billion [1].

Opioid medications are prescribed commonly for acute pain and pain associated with advanced illness, and although the use of these drugs to help manage chronic non-cancer pain continues to be limited, their use for the latter indication has increased substantially during the past two decades. In parallel with this increase in medical use has been a deeply concerning rise in prescription drug abuse and unintentional overdose. Drug overdose deaths in the United States exceed 36,000 annually with prescription drugs involved in more than 55% of such deaths. Prescription opioid drugs were involved in nearly 75% of the 20,000 plus prescription drug overdose deaths reported in 2008. Unintentional poisoning deaths from these medications now exceed those attributable to car accidents in some states and show no signs of abating. Consequently, federal actions such as FDA-mandated risk mitigation strategies for long-acting opioids, federal support for requiring mandatory education for DEA registration, and state-based initiatives designed to more tightly regulate opioid use have emerged. Physicians and other clinicians need current, state-of-the-art education to assist in developing the necessary skills to manage patients with persistent pain, including the skills needed to use opioid drugs safely and effectively. This CME program reviews assessment and management of persistent pain syndromes that are frequently seen in primary care [1].

Pain

History of Pain

The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [1].

This definition suggests that a pain experience has two essential components. The first, the perception of the actual, threatened or imagined tissue damage, requires the presence of an appropriate sensory mechanism. This sensory mechanism, in addition to detecting appropriate signals, must be able to code for these stimuli in terms of their intensity and location as well

as their physical and temporal properties. The second component of pain is that of aversion or unpleasantness. This requires the presence of a neural mechanism which, subsequent to such interpretation, will motivate appropriate physiological and psychological changes such as various somatic, autonomic or emotional responses [2].

Two types of nociceptive pain are usually distinguished: pain emanating from the skin and deeper tissues (e.g., joints and muscle) is referred to as somatic pain while pain emanating from the internal organs is referred to as visceral pain. Somatic pain is usually well localized whereas visceral pain is harder to pinpoint [3].

Nociceptive primary afferent neurons are varied. Most are "silent", active only when supra-threshold stimuli impinge. Some are specific to one type of stimulus, such as mechanical or thermal, but most are polymodal. The number and size of the receptive fields served by each fiber may be small or large, respectively. The meaning of this variability in terms of physiology or disease is not yet known, and research linking different types of nociceptors to disease states, or potential therapeutic targets, is still rudimentary [1].

Depolarization of the primary afferent involves a complex neurochemistry, in which substances produced by tissues, inflammatory cells and the neuron itself influence transduction. The role of prostaglandins, bradykinin, protons, nerve growth factor, and other compounds provide opportunities for the development of new analgesic drugs. Once depolarization occurs, transmission of information proceeds proximally along the axon to the spinal cord and then on to higher centers. Complex systems that modulate this input occur at all levels of the neuraxis and are best characterized in the spinal cord. The neuroanatomy, neurophysiology and neurochemistry of these processes are very complex [1].

Transmission across the first central synapse may be influenced by activity in the primary afferent itself and modulatory neural pathways that originate segmentally or at supraspinal levels; further modulation results from processes initiated by glial cells. The neurochemistry of these processes involves an extraordinary array of compounds, including endorphins, neurokinins, prostaglandins, biogenic amines, GABA, neurotensin, cannabinoids, purines, and many others [1].

The endorphinergic pain modulatory pathways are characterized by multiple endogenous ligands and different types of opioid receptors: mu, delta, and kappa. Endorphins and their receptors are present in various tissues (e.g., immune cells and the gastrointestinal tract), on nerve endings, and in multiple areas of the central nervous system (CNS). They are involved in many neuro-regulatory processes apart from pain control, including the stress response and motor control systems. Opioid drugs mimic the action of endogenous opioid ligands. Most of the drugs used for pain are full mu receptor agonists. Other pain modulating systems, such as those that use monoamines (serotonin, norepinephrine and dopamine), histamine, acetylcholine, cannabinoids, growth factors and other compounds, are targets for nontraditional analgesics, such as specific antidepressants and anticonvulsants. It is likely that entirely novel analgesic compounds will become commercially available in the future as drug development programs target these systems [1].

Pain can be divided into three classes: (i) Nociceptive, (ii) inflammatory and (iii) Neuropathic.

Nociceptive pain such as a stubbed toe results in a felt sensation (pain) matching the stimulus (noxious). This is a classic example of "normal" pain. Pain arising, for instance, from tissue injury or infections involves increased responsiveness because of the release of

inflammatory mediators in the injured tissue. Thus, the felt sensation (pain) may no longer match the stimulus (non-noxious).

In inflammatory pain, a reduction of the threshold of the nociceptors is observed. Both normal and inflammatory pains represent a key feature of the pain system – its operation as an alarm bell. The pain felt provides warning and protection.

Neuropathic pain reflects an abnormal functioning of the pain system. Pain no longer acts as an alarm factor; rather, it becomes a problem by producing a ”false alarm”. Pain initiated or caused by a primary lesion in the nervous system.

Due to their lack of nerve growth factor (NGF)-dependent neurons, patients with congenital insensitivity to pain with anhidrosis (CIPA) cannot detect various noxious stimuli nor trigger emotional responses to noxious stimuli in the same way as normal individuals. Accordingly, they may be impaired in their ability to modify their behaviors in order to protect their bodies and maintain homeostasis.

Recent studies indicate that NGF-dependent neurons play crucial roles in brain–immune–endocrine interactions in pain, itch and inflammation and suggest that the NGF-TrkA system is involved in various disease states. Targeting the molecular mechanisms of NGF-TrkA signal transduction is an active area of research that may help to develop novel analgesics, anti-pruritic and anti-inflammatory drugs.

Balance — Pain Management, Drug Safety, and the FDA

Food and Drug Administration (FDA) has been engaging physicians, pharmacy groups, patients, and other stakeholders in an ongoing effort to strike the right balance between two important goals: on one hand, providing access to pain medications for those who need them, and on the other hand, managing the variety of risks posed by analgesic drugs. Recent FDA advisory committee meetings and actions reflect this effort.

Acetaminophen is one of the most commonly used analgesics. In 2008, approximately 25 billion doses were sold in the United States. Acetaminophen is marketed as a single-ingredient drug but can also be found in a multitude of over-the-counter combination products, such as cough and cold medicines, as well as in prescription opioid–acetaminophen combination products (e.g., Vicodin, Abbott), Percocet (Endo Pharmaceuticals), and Darvocet (AAIPharma). Although acetaminophen, when used as labeled, is generally safe, the ubiquity of the drug and its relatively narrow therapeutic index create the potential for serious harm from both inadvertent and intentional overdoses. Approximately 30,000 hospitalizations are associated with acetaminophen overdose in the United States annually — approximately half of them resulting from unintentional overdose. Acetaminophen is also a leading cause of acute liver failure [4].

In June 2009, the FDA held a 2-day public advisory committee meeting to discuss acetaminophen toxicity. The FDA presented multiple options for improving the management of acetaminophen-related risk. The top three recommendations of the committee were to reduce the maximum single dose of over-the-counter acetaminophen from 1000 mg to 650 mg or switch the 1000-mg single dose to prescription status, to standardize the range of over-the-counter liquid concentrations (to reduce dosing confusion), and to eliminate prescription

acetaminophen combinations or require a boxed warning on the labels of these products. The first and third recommendations, in particular, could have a considerable effect on the use and availability of acetaminophen-containing products. The agency is currently considering its next steps [4].

Strong opioid analgesics (e.g., morphine) are the drugs of choice for the management of moderate-to severe pain following surgery or trauma. However, there is considerable inter-patient variability in opioid analgesic dosing requirements as well as opioid-related side-effects with genetic factors proposed as a possible explanation by the FDA. In February 2009, the agency announced that it was initiating a process under the FDA Amendments Act (FDAAA) that would require manufacturers of high-potency opioids to institute risk-evaluation and mitigation strategies (REMS) to address the risks of abuse, misuse, and the exposure of persons who are not opioid-tolerant. In one month in 2007, an estimated 5.2 million people 12 years of age or older used pain relievers non-medically. In 2006, there were approximately 57,000 emergency department visits for nonmedical use of hydrocodone or hydrocodone combinations, 65,000 for nonmedical use of oxycodone or oxycodone combinations, and 45,000 for nonmedical use of methadone. An analysis of poison-control data from 2003 through 2006 identified 9179 children who were inadvertently exposed to prescription opioids. The median age of the children was 2 years, and 92% of the poisonings occurred in the child's home. Such data highlights the need for additional measures to limit the abuse and misuse of prescription opioids and prevent the accidental exposure of children [4].

Although the risks of serious or fatal gastrointestinal bleeding from nonsteroidal Antiinflammatory drugs (NSAIDs) have long been recognized, additional safety concerns have also emerged about these agents. In April 2005, the FDA implemented the recommendation of an advisory committee to require a boxed warning on the labels of NSAIDs (except aspirin) about the risk of excess myocardial ischemia, particularly in patients with preexisting heart disease [4].

Despite increased awareness of the harm resulting from the use of NSAIDs, acetaminophen, opioids, and other drugs for pain, it is likely that extensive prescribing and use of these drugs will continue. Given this reality, there is a need for more vigorous risk-management efforts by the FDA and other stakeholders in the health care system. The FDA cannot address these risks on its own; prescribers and users of analgesics must also participate in this effort. Any risk-management option must be considered in the light of its potential effect on the use of other analgesics, given that most analgesic drugs have substantial liabilities.

The unintended consequences of shifting use from one drug class to another, for example, must be considered carefully [4]. Although management of the risks posed by the current armamentarium will be a predominant theme for the foreseeable future, the FDA is also exploring ways to improve analgesic-drug development, primarily through research into better designs for pain trials, in the hope that highly effective drugs with more easily managed risks may be developed [4].

NSAIDs

History of NSAIDs

The history of anti-inflammatory drugs begins with the early use of decoctions or preparations of plants containing salicylate. Salicylic acid and salicylates are constituents of several plants long used as medicaments. About 3500 years ago the Egyptian Ebers papyrus recommended the application of a decoction of the dried leaves of myrtle to the abdomen and back to expel rheumatic pains from the womb. A thousand years later Hippocrates recommended the juices of the poplar tree for treating eye diseases and those of willow bark to relieve the pain of childbirth and to reduce fever. All of these medicinal remedies contain salicylates. In AD 30, Celsus described the four classic signs of inflammation (redness, heat, pain and swelling) and used extracts of willow leaves to relieve them. Throughout the Roman times of Pliny the Elder, Dioscorides and Galen the use of salicylate-containing plants was further developed and willow bark was recommended for mild to moderate pain. In China and other parts of Asia, salicylate-containing plants were being applied therapeutically. The curative effects of Salix were also known to the early inhabitants of North America and South Africa. Through the Middle Ages further uses for salicylates were found, such as plasters to treat wounds and various other external and internal applications, including the treatment of menstrual pain and discomfort of dysentery. However, willows were needed for basket making so the women herbalists of those days turned to other related plants: they grew meadowsweet (Spir (£a ulmaria) in their herb gardens and made decoctions from the flowers [5].

The anti-inflammatory analgesic drugs have their origins in the use of extracts of salicylate-containing plants, especially the bark of the willow tree (Salix alba and other members of the Salix species), in the treatment of fever, pain and inflammatory conditions. These treatments date from early Chinese, Indian, African and American eras and were initially described in some detail by Roman and Greek medical authorities. During the 17th–19th centuries, the popularity of these plant extracts became evident following the publication by Reverend Edward Stone in the 17th century of probably what were the first clinical trials of willow bark extract for the treatment of agues or fever. Isolation of the principally active salicylate components was followed in the early 19th century and with advances in chemistry in Europe and developments in the German chemical industry in the mid-late 19th century. The synthesis or salicylic and acetylsalicylic acids, the latter being highly successfully commercialized by Bayer AG as Aspirin™ was accomplished 100 years ago [6].

During the period of the exploitation of the by-products of the coal tar industry in Germany in the 19th century antipyretic/analgesic agents such as antipyrine, aminopyrine, phenacetin were developed which was followed by the recognition of paracetamol (acetaminophen) as the active metabolite of phenacetin, this was eventually commercially developed for use as an analgesic/antipyretic agent in the 1950's [6].

Discovery of NSAIDs

The development of the first category of what is now known as the non-steroidal anti-inflammatory drugs (NSAIDs) class of which aspirin has now become recognized as the progenitor, was phenylbutazone in 1946 and later indomethacin in the 1960's. Phenylbutazone was initially employed as a combination with antipyrine in the belief that it would enhance the actions of the latter. However, it emerged to have greater anti-inflammatory/analgesic activity than antipyrine and was successfully used for 30 years in the treatment of arthritic and other painful inflammatory conditions until its popularity progressively declined after associations with life-threatening agranulocytosis and bone marrow suppression (still essentially not conclusively proven today), upper gastrointestinal ulcers and bleeding, and subsequent popularity of more advanced NSAIDs [6].

Ibuprofen was developed by Boots (UK) in the 1950–1960's and after establishing its favorable safety profile at dose ranges for analgesic and anti-pyretic efficacy (up to 1200mg daily) it was the first NSAID (other than aspirin) to be approved for non-prescription (over-the-counter) use in UK (in 1963), USA (in1964) and later in many other countries worldwide. Just after ibuprofen was developed, a large number of pharmaceutical companies undertook the discovery and development of NSAIDs with a range of chemical and biological properties [6].

Most of these drugs developed in the 1960's were discovered in the pre-prostaglandin era (i.e., before Vane and coworkers had discovered the inhibitory actions of aspirin and related drugs on the production of prostaglandins). Their anti-inflammatory, analgesic and antipyretic properties were discovered using animal models with some supportive properties being established in some biochemical systems which were known to be important in inflammation (e.g., mitochondrial oxidative, intermediary and connective tissue collagen and proteoglycan metabolism; stability of albumin; and later oxyradicals) [6].

Types of NSAIDs

By early 1900s, the main therapeutic actions of aspirin (and sodium salicylate itself) were recognized as antipyretic, anti-inflammatory and analgesic effects. With passing of time several other drugs were discovered which shared some or all of these actions. These drugs include antipyrine, phenacetin, acetaminophen (paracetamol), phenylbutazone and, more recently, the fenamates, indomethacin and naproxen. Because of the similarity of their therapeutic actions these drugs were regarded as a group and were generally known as the aspirin-like drugs. NSAIDs are relatively clinically equipotent; their subtle differences influence their selection in patient use. Many preparations of NSAIDs are available over-the-counter (OTC) and several have the convenience of once-daily dosing. While all NSAIDs can be taken orally, ketoprofen is available as a topical cream, and ketorolac can be given intramuscularly or intravenously. Studies have attempted to differentiate NSAIDs in-terms of potency, but one NSAID or class of NSAIDs has never been shown to be stronger than the others in terms of clinical efficacy. Patient response to NSAIDs varies, and if a patient does not respond to any NSAID drug, other NSAIDs can be tried. In most cases, the side-effect profile will determine NSAID selection rather than subtle differences in efficacy. Despite

their differences in chemical structures, NSAIDs share many common properties, especially in their use as analgesics. For example, all NSAIDs have a ceiling effect that limits their efficacy in severe, increasing pain. NSAIDs are advantageous because they lack addictive potential and do not result in sedation or respiratory depression. In addition, these drugs have analgesic properties at lower doses and anti-inflammatory effects at higher doses [7].

NSAIDs Mechanism of Action

Although the clinical efficacy of NSAIDs was well known in the 19th century, the mechanism of action eluded scientists until 1971. Sir John Vane demonstrated that the enzymatic production of prostaglandins could be attenuated by aspirin and indomethacin. It has been known that enzymes, including COX, and the 5-, 12-, and 15-lipoxygenases act on arachidonic acid and result in the production of inflammatory prostaglandins E, and I, and thromboxane. Vane further established that inhibition of COX by aspirin was the driving force for its effects, and he shared the 1982 Nobel Prize in medicine for this discovery [8].

Indications for Use of NSAIDs

NSAIDs have come a long way since their initial indication as an antipyretic. Osteoarthritis (OA) accounts for half of the prescriptions written for NSAIDs. It is estimated that 80% of the population will have radiographic evidence of OA by age 65 years, although typically only 60% of that group will be symptomatic. Problems with ambulation secondary to OA may account for 22.5% of visits to primary care physicians, so the burden to society is quite high. Although OA is typically described as a degenerative rather than an inflammatory condition, research has demonstrated that an inflammatory process is present. Whether inflammation is primary or secondary is debatable, but NSAIDs have proved helpful in this condition. It has been suggested that the primary benefit of NSAIDs on OA is analgesia. One study comparing acetaminophen to high (anti-inflammatory) and low (analgesic) doses of ibuprofen found similar efficacy in a 4-week trial of patients with OA. It seems reasonable to suggest that acetaminophen or low-dose NSAIDs are appropriate for short-term, symptomatic OA relief. If longer-term treatment is required, NSAIDs can be prescribed with careful monitoring and periodic reevaluation. It would be expected that inflammatory suppression is more effective with the long-acting NSAID preparations. Recent evidence suggests that physical therapy improves function in OA, and it may be that the short-term analgesic effects of NSAIDs allow for more effective physical therapy to be performed. However, continual use of NSAIDs should never be a substitute for physical therapy, activity, modification, or the education of patients with OA about NSAID use and effects. Another key indication for NSAID use is the efficacy of aspirin in treating inflammatory arthropathies, which has been demonstrated in countless studies. Other NSAIDs may offer an advantage over aspirin in that they are generally better tolerated and have dosing schedules that favor patient compliance. For example, it is generally acknowledged that indomethacin is superior for the treatment of ankylosing spondylitis. Among the COX-2 inhibitors, only celecoxib has been approved for the treatment of rheumatoid arthritis (RA). As the trend in the treatment of conditions such as

RA has been toward disease-modifying agents, NSAIDs are generally reserved as an adjunct to reducing inflammation or as a short-term analgesic associated with disease flares. The most common use of NSAIDs given by OTC is for the treatment of acute and chronic pain. Their efficacy no doubt reflects the role of prostaglandins in the pathophysiology of pain. Because of a more favorable adverse-effect profile, it seems reasonable to use acetaminophen initially and then move to an NSAID if pain relief is not achieved. With severe pain, the ceiling effect of NSAIDs limits their usefulness, and a codeine analog can be added if pain control is not achieved. Parenteral NSAIDs are indicated for acute pain and their rapid onset of action is advantageous. An interesting indication for the use of NSAIDs is the combination of pain and inflammation brought on by physical activity (e.g, sports injuries). NSAIDs are a mainstay of treatment in athletic injuries, although there is a paucity of well-done studies to support their use. In acute injuries such as ankle sprain, studies have not been able to demonstrate that NSAIDs reduce the inflammatory response. However, some studies have suggested that the acute inflammatory response to injury is beneficial. While NSAIDs do not seem to compromise healing, their greatest effect may be as an analgesic. Early mobilization of ligaments leads to healing, and it is possible that NSAID analgesia allows for increased range of motion and recovery. The use of topical NSAIDs may have great application in this area as pain is usually limited to a distinct region and only small amounts of topical NSAIDs are systemically absorbed. NSAIDs can be helpful in a variety of other conditions. The symptoms of dysmenorrhea have been well studied and seem to be mediated by prostaglandins. NSAIDs are the treatment of choice in this disorder and can be efficacious [8].

NSAIDs are heterogeneous compounds, often chemically unrelated (although most of them are organic carboxylic acids), but nevertheless share certain therapeutic actions and side effects. Aspirin is the prototype of this group; hence these compounds are often referred to as aspirin-like drugs. More frequently they are known as non-steroidal anti-inflammatory drugs (NSAIDs). There is no internationally agreed upon classification of analgesics/antipyretics. Most textbooks classify them depending on their efficacy, dividing them into two groups; Non-narcotic analgesics (for the mild to moderate pain, some of which may also have antipyretic actions), and narcotic/opioid analgesics (which are principally used in the relief of severe pain, and may produce dependence). Many analgesics also have marked anti-inflammatory actions and therefore are used for the treatment of arthritis and other inflammatory conditions. Most exhibit their effect, at least in part, by the inhibition of prostaglandin synthesis [8].

Analgesics are drugs used to relieve pain- "pain killers". Pain is one of the most common symptoms, and one of the most frequent reasons why people seek medical care [9].

Antipyretic activity results in lowering the temperature, and is considered to involve the hypothalamus. Normal body temperature varies according to the individual's age, sex, level of physical and emotional stress, the environmental temperature, time of the day, and the anatomical site at which the temperature is measured. Body temperature may be measured at rectal, axillary, oral, or tympanic (ear canal) sites. The method used to measure the temperature should be indicated in the reported patient's temperature. Paracetamol, aspirin, and ibuprofen have similar antipyretic activity. Product selection should be based primarily on patient acceptance, the side effects of each agent, concurrent diseases that may prohibit the use of each agent, convenience of administration, and cost of therapy [9].

Anti-inflammatory agents are drugs that alleviate symptoms of inflammation, but do not necessarily deal with the cause. NSAIDs have been shown to be as effective as aspirin (ASA), but not superior [9].

NSAID Drugs

Acetyl Salicylic Acid [9]

Acetylsalicylic Acid (ASA), Aspirin (Figure 1), is a salicylate that relieves headaches, muscular and joint pains, and reduces inflammation. ASA has been considered the drug of choice in the treatment of arthritis, but its anti-inflammatory action occurs only when given in large doses (3-4 g/day). At these large doses, ASA produces adverse effects that are the main disadvantage when used for arthritis conditions. NSAIDs tend to be more appropriate for arthritis conditions. The mechanism of action of ASA is that it inactivates cyclooxygenase irreversibly and inhibits prostaglandin synthesis and platelet aggregation [9].

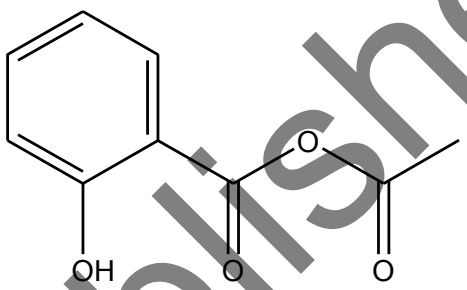


Figure 1. Chemical structure of acetyl salicylic acid (aspirin).

Indications

Used for pain, fever, inflammatory conditions such as rheumatic fever, rheumatoid arthritis, osteoarthritis, dysmenorrhea and symptomatic relief of the common cold pain and fever. It is used for reducing the risk of recurrent Transient Ischemic Attacks (TIA/stroke), or Myocardial Infarctions (MI/heart attack) at low doses.

Contraindications

In patients with history of hypersensitivity, asthma, peptic ulcer/dyspepsia, those with bleeding tendencies or disorders.

Dosage Forms

Tablets.

Recommended Dosage

Adult: 350 - 650 mg q. 4 h. for minor aches and pain.

500 - 1000 mg q. 4-6 h.; max. 4 g/24 h., for moderate to severe pain.

75 - 325 mg/day q.d. continued indefinitely for: Ischemic stroke & TIA, and the prevention of recurrent MI, unstable angina pectoris, chronic stable angina pectoris (FDA, 1998).

Child: Use not recommended, unless for certain conditions. (Refer to special cases).

Directions: Take with or after food to avoid GI disturbances (including ulcers).

*The drug is hydrolyzed in the stomach, and primarily absorbed in the stomach and upper small intestine. Peak level is within 15 minutes to 2 hours, so patient should expect the drug's effect to be noticed within 15 minutes from taking the medication.

*ASA should not be used for self-medication of pain for longer than 10 days in adults or 5 days in children, unless directed by a physician.

*ASA preparations should not be used if a strong vinegar-like odor is present.

Use in Special Cases

- *Pregnancy*- Contraindicated at analgesic doses. ASA crosses the placenta, and may harm the fetus (Category D). Paracetamol may be a better choice for analgesia. ASA may be used in low doses (100 mg) as anticoagulant and for prophylaxis of preeclampsia in high-risk pregnant women.
- *Lactation*- Salicylates are excreted in breast milk in low concentrations, but no adverse effects on infants have been reported. Use with caution.
- *Children*- Use is not recommended specially for undiagnosed fever when influenza is suspected, due to risk of Reye's syndrome (a rare disorder presented by symptoms of encephalitis combined with evidence of liver failure). This potentially fatal condition occurs following certain viral infections like chickenpox, or those with minor febrile illness. It is characterized by vomiting and lethargy that may progress to delirium and coma. Paracetamol should be used instead.
- *Renal Disease*- Caution in these patients, ASA may aggravate chronic kidney disease, fluid retention, and increased risk of GI bleeding. In severe cases avoid the use. In minor cases reduce the dose. (50% of the dose is eliminated in the urine.)
- *Liver Disease*- The drug is metabolized in the liver. Use caution in patients with impaired liver function, pre-existing hypoprothrombinemia and vitamin K deficiency may increase risk of bleeding.

Precautions and Warnings

- Not to be taken on an empty stomach.
- Avoid ASA for at least 1 week prior to surgery. Patients should inform the dentist or doctor of taking this medication before doing any lab or dental work.

– Avoid alcohol while taking this medication since it increases the risk of GI ulceration and bleeding.

Adverse Effects

Dizziness, cinchonism (ringing in the ear), skin eruptions, epigastric discomfort, peptic ulceration and bleeding, increase bleeding tendency, hypersensitivity reactions.

Interactions

Drug-Drug Interaction

Drug Interaction

– ACE inhibitors (ACEI)

Hypotensive and vasodilator effect of ACEI may be reduced .Monitor patients, and discontinue ASA if possible.

– Anticoagulants

Anticoagulant effect enhanced effect of ASA on gastric mucosa and platelet function may enhance the possibility of hemorrhage. Avoid concomitant use.

– β-blockers

Their antihypertensive effectiveness may be decreased. Use with caution.

– Corticosteroids

Corticosteroids reduce serum salicylate levels and decrease salicylate effectiveness.

Monitor plasma salicylate concentration when adding or withdrawing corticosteroids.

Pharmacological effects of certain NSAIDs may be decreased. Increased risk of GI disturbances if used concomitantly.

– Oral hypoglycemic

ASA increases hypoglycemia effect of sulfonylureas. Monitor the patient's blood glucose, if hypoglycemia occurs decrease sulfonylurea dose.

Overdose

Overdose can be fatal, particularly in children. Acute lethal dose is approximately 10-30 g for adults, and 4 g in children. It requires immediate referral to hospital. It presents with confusion, rapid deep breathing, sweating, tinnitus (noises in the ear), and deafness followed in severe cases by unconsciousness. Chronic Salicylate toxicity may occur when > 100 mg/kg/d is ingested for 2 or more days. It is more difficult to recognize and is associated with increased morbidity and mortality. Compared to acute poisoning, hyperventilation, dehydration, systemic acidosis and severe CNS manifestations occur more frequently. Treatment includes supportive measures.

Bioavailability: 80-90%.

Brands

Acetosal (Rekah), Aspirin (Bayer), Cartia (Smith Kline).

Paracetamol [9]

Paracetamol or acetaminophen (*N*-Acetyl-*p*-amino- phenol-APAP) (Figure 2) is a non-narcotic CNS agent. It is equivalent to aspirin in relieving pain and reducing fever, but it has little effect on platelet function, does not affect bleeding time and generally produces no gastric bleeding or ulcers. It has no anti-inflammatory action in usual doses. Paracetamol reduces fever by direct action on the hypothalamus heat-regulating center with consequent peripheral vasodilatation, sweating and dissipation of heat [9].

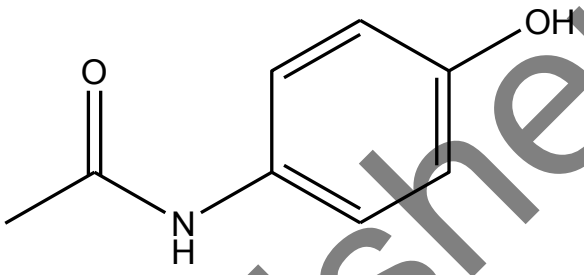


Figure 2. Chemical structure of paracetamol.

Indications

Used for pain and fever. Good substitute for ASA, when ASA is not tolerated or is contraindicated.

Contraindications

In patients with history of hypersensitivity. In patients with severe liver and kidney damage.

Dosage Forms

Tablets, capsules, suspension and suppositories.

Recommended Dosage

Adult: orally (per os): 325-650 mg q. 4-6 h. as needed; max. 4 g/24 hours.
Child: orally (per os): 10-15 mg/kg/dose.

Age Dose

0-3 months 10 mg/kg (5 mg/kg if jaundiced). 3 months-1 year 60-120 mg. 1-5 years 120-250 mg

6-12 years 250-500 mg.

*****The doses may be repeated every (q.) 4-6 h. not to exceed 4 doses in 24 hours.

Directions

- -Can be taken with fluids, but before meals or 2 hours after meal, 4 times daily for 2-3 days or as required.
- -The drug is completely absorbed from the GI tract; less complete absorption takes place from rectal suppository.
- -Peak effect occurs within 0.5-2 hours, and duration is 3-4 hours.
- -If fever does not subside within 3 days, patient has to contact the physician.

Use in Special Cases

- *Pregnancy*- Safe if used as directed (Category B). It is the drug of choice in pregnant women
- for aches and pains, or fever. It does cross the placenta, but no reports of harmful effects
- have been noted.
- *Lactation*- Paracetamol is excreted in low concentration in breast milk. No harm on infants has been noted. It is safe when used as recommended.
- *Children*- Can be used prophylactically (30 minutes before) in children receiving DPT vaccination to decrease incidence of fever and injection site pain. Use caution and do not exceed the recommended doses.
- *Renal Disease*- Kidney tubular necrosis may occur with chronic use of very high doses of the drug (> 4 g/d) [10].
- *Liver Disease*- The drug is exclusively metabolized in the liver. Hepatotoxicity and severe hepatic failure occurred in chronic alcoholics following therapeutic doses. Avoid large dose in liver cases (< 2 g/d is acceptable for these patients).

Precautions and Warnings

- Do not exceed recommended doses. Chronic excessive use (> 4 g/d) eventually may lead to transient hepatotoxicity.

Adverse Events

If used as directed it rarely causes any side effects. Heavy alcoholics and smokers are more susceptible to liver toxicity. Skin rashes and neutropenia are very rare.

Interactions

Drug Interaction

Alcohol, barbiturates, carbamazepine and rifampin.

The potential hepatotoxicity of paracetamol may be increased by large doses or long term use of the these agents due to hepatic microsomal enzyme induction.

Overdose

Symptoms: Acute poisoning symptoms include nausea, vomiting, drowsiness, confusion, liver tenderness, low blood pressure, cardiac arrhythmia, jaundice and acute hepatic and renal failure.

Brands

Dexamol (Dexxon), Acamol (Teva), Acamoli (Teva), Febramol (BPC), Panadol (smith Kline), Otamol (JePharm), Paracare (Pharmacare), Paramol (JCL). Paracetamol bioavailability is 63-89%.

Ibuprofen [9]

Ibuprofen (IBP) (Figure 3) is a propionic acid derivative. Comparable to aspirin (ASA) in its analgesic action, but higher doses are required for anti-inflammatory effect. It has been reported to have less GI symptoms than aspirin in equal-effective doses. Cross-sensitivity with ASA and other NSAIDs has been reported. IBP inhibits platelet aggregation and prolongs bleeding time, but does not affect prothrombin or whole blood clotting times [9].

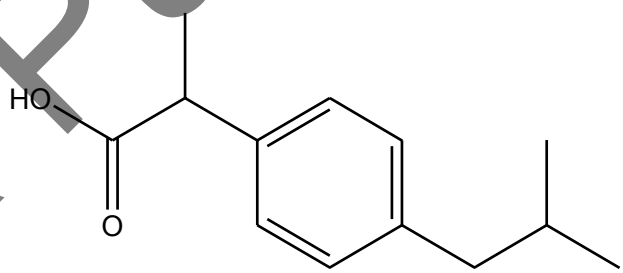


Figure 3. Chemical structure of ibuprofen.

Contraindications

In patients who are hypersensitive where urticaria, severe rhinitis, bronchospasm or angioedema are precipitated by ASA or other NSAIDs. Active peptic ulcer or bleeding abnormalities.

Dosage Forms

Tablets, suspension (100 mg/5ml), gel 5%.

Recommended Dosage

Adult**:** 200-400 mg PO q. 4-6 h., max. 1800 mg/24 hours for pain and fever. 400-800 mg t.i.d. or q.i.d.; max. 3200 mg/d for inflammation cases. Emulgel dose: A thin layer of the gel is applied to affected area as needed, up to three times daily.

Child**:** Use is not recommended for children under 6 months;

Doses of IBP in Children

1-12 years: 5-10 mg/kg q. 4-6 h. 6 - 11 months 25-50 mg. 6 - 8 y. 125-250 mg. 12 - 23 months 50-100 mg, 9 - 10 y. 150-300 mg. 2 - 3 years 75-150 mg. 11 - 12 y. 200-400 mg/ 4 - 5 years 100-200 mg (all given q . 4-6 h. prn). Maximum daily dose is 40 mg/kg/d.

Directions: IBP should be taken with food or milk if GI disturbances occur.

- -80% of the drug is absorbed from the GI tract. Peak effect is 1-2 h.
- -Onset for analgesia is 0.5 h, and for antirheumatic action is 7 days.
- -If patient misses a dose, take as soon as they remember unless it is too close to the
- following dose, so they need to skip the following dose and continue with the usual
- schedule. Dose should not be doubled.

Use in Special Cases

- *Pregnancy*- Better to avoid use (Category B).
  Paracetamol is a better choice for analgesia.
- *Lactation*- Safe. IBP has not been detected in breast milk in analgesic doses.
- *Children*- Safety and efficacy has not been established for children < 6 months old. Normally, not recommended for children < 1 year or less than 7 kg.
- *Renal Disease*- Use with caution. Reduce dose. NSAID metabolites are excreted by kidney into urine.
- *Liver Disease*- Use with caution, and decrease the dose. The drug is metabolized in the liver.

There is an increased risk of GI bleeding or fluid retention.

Precautions and Warnings

- Patients with history of cardiac decompensation should be observed closely for evidence of fluid retention and edema.

- Instruct patient to report immediately any passage of dark tarry stool, coffee-ground emesis, blood or protein in urine. This can be an indication for GI bleeding. Medication should be stopped and patient should be re-evaluated. Caution if skin rash, itching, visual disturbances or persistent headache should occur.
- *-Caution in hypertension, chronic renal failure and patients with Systemic lupus erythematous SLE. Advise patient not to drink alcohol, to avoid increased risk of GI ulceration and bleeding.*

Adverse Effects

GI disturbances are most common; i.e., heartburn, nausea and dyspepsia, abdominal distress, gastritis and ulceration. Also, dizziness, drowsiness, jaundice, and fatigue may occur. Side effects are dose related. Incidence or aggravation of epilepsy and Parkinsonism has been reported with use of NSAIDs.

Interactions

Oral anticoagulants and *heparin*
May prolong bleeding time. Avoid concomitant use.
Lithium, *digoxin* and *methotrexate*
Increased toxicity of these drugs with concomitant NSAIDs use. Monitor each drug serum levels and adjust dose as needed.

Overdose

Symptoms: may include drowsiness, dizziness, mental confusion, lethargy, vomiting, abdominal pain, tinnitus, convulsions, hypotension, tachycardia, and metabolic acidosis.

Brands:

Adex 200 (Dexxon), Advil (Whitehall), Artofen (Teva), Ibufen (Dexxon),
Isofen (BPC), Nurofen (reckitt benckiser), Trufen (JePharm).
Ibuprofen's bioavailability is 87-100% when given orally and 87% rectally.

Diclofenac [9]

Diclofenac sodium (Figure 4) is an acetic acid derivative. It has analgesic, antipyretic, and anti-inflammatory properties. At therapeutic doses it has little effect on platelet aggregation. Patients not responding to IBP can be given diclofenac instead. Do not co-administer with other NSAIDs or salicylates [9].

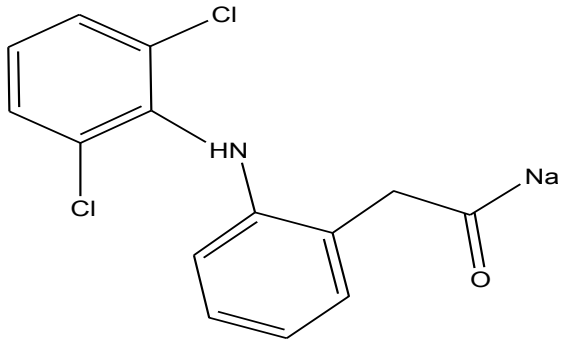


Figure 4. Chemical structure of diclofenac sodium.

Dosage Forms

Tablets, sustained release tablets, suppositories, emulgel and ampoules.

Recommended Dosage

Adult: 75-150 mg/24h given by mouth in divided doses. Total daily dose should not exceed 150 mg/daily, such doses have not been studied. Suppository form is given in a dose of 75- 100 mg each evening. The emulgel form (1%) should be applied to painful site, 2-4 gm, 3-4 times daily. Therapy should be reviewed after 14 days.

Child: Not recommended for children < 1 year. unless JRA.

Child > 1 year. for RA: 1-3 mg/kg in divided doses by mouth or rectum.

Directions: Diclofenac is readily absorbed from the GI tract, and 50-60% reaches the systemic circulation. Peak effect is within 2-3 h.

- Absorption is delayed by food; take with a full glass of water. For chronic use take after food to avoid GI problems.
- Sustained release forms are given once or twice daily.
- If simple GI disturbances occur, an antacid may be used, but not administered at the same time of the drug intake.
- If patient misses a dose, this dose should be taken as soon as remembered, unless it is too close to the following dose, so skip and maintain schedule. Do not double the dose.

Use in Special Cases

- *Pregnancy*- Should not be used unless there are compelling reasons for doing so, (Category B).
- *Lactation*- Do not use in nursing mothers because of possible effects on infant's cardiovascular system.

- *Children*- Use in child < 1 year is not recommended. Safety and efficacy in children have not been established.
- *Renal Disease*- NSAID metabolites are eliminated by the kidneys, 50-60% excreted in urine. Reduce dose to avoid accumulation.
- *Liver Disease*- Effects are not known. Metabolism of the drug occurs in liver. Use caution to avoid increased risk of GI bleed.
- *Drug Interaction* Lithium, digoxin and methotrexate Increased toxicity of these drugs with concomitant NSAIDs use. Monitor each drug serum levels and adjust dose as needed.
- *Diuretics* May decrease blood pressure lowering effects of diuretics. May lead to an increase in serum K^+, if using K^+ sparing diuretics.

Relatively long acting (6 to 8 hours) but it has a relatively very short half-life. This could partly be due to a particular high concentration achieved in synovial fluids. Diclofenac may also be a unique member of the NSAIDs. There is some evidence that diclofenac inhibits the lipoxygenase pathways, thus reducing formation of the leukotrienes (also pro-inflammatory autacoids). There is also speculation that diclofenac may inhibit phospholipase A2 as part of its mechanism of action. These additional actions may explain the high potency of diclofenac - it is the most potent NSAID on a broad basis. Arthrotec which contains both diclofenac and misoprostol is designed to relieve the symptoms of arthritis in people who are also prone to ulcers.

Brands

Abitren (Abic), Betaren/Betaren S.R (Dexxon), Diclofen (JePharm, Rufenal (BPC), Voltaren/ Voltaren S.R. (Novartis).

Indomethacin [9]

Indomethacin (Figure 5) is a very potent aryl acetic acid NSAID derivative. Because of its high potential to cause side effects when used in high doses, it should be carefully considered for active disease unresponsive to adequate trials with salicylates. It has equal or a little superior action than naproxen, but higher incidence of side effects. This medication will enable reduction of steroid doses in severe forms of Rheumatoid Arthritis. (In this case reduce steroid dose slowly!) [9].

Indication

It is used as IV for Patent Ductus Arteriosus in premature infants.

Contraindication

In patients with recent rectal bleeding or proctitis if using suppositories.

Dosage Forms

Capsules, suppositories and gel.

Recommended Dosage

Adult: Rheumatoid Arthritis

25-50 mg b.i.d. or t.i.d., or 75 mg sustained release 1-2 times a day; max. 200 mg/d.

Dysmenorrhea: up to 75 mg daily.

Acute Gout: 50 mg t.i.d. until pain is tolerable (usually within 2-3 days), then taper off to 25 mg t.i.d. until total resolution of attack.

(If administering both PO and rectal dosage forms combined, dose should not exceed 200 mg/d).

Child: Not recommended due to effect on liver function.

Directions: Administer immediately after meals, or with food, milk or antacid to minimize GI side effects. (Food or antacid may cause somewhat delayed and reduced absorption, but advantage of safety outweighs risk of impaired absorption.)

-If patient misses a dose, take as soon as remembered unless it is too close to the following dose, so skip and maintain schedule. Never double doses.

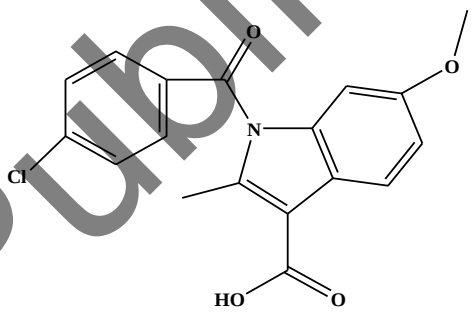


Figure 5. Chemical structure of indomethacin.

Use in Special Cases

- *Pregnancy*- Category B in the 1st and 2nd trimester, and D in 3rd trimester.
- *Lactation*- Use not recommended.
- *Children*- Contraindicated for children < 14 years. Hepatotoxicity including fatalities has occurred in children with juvenile rheumatoid arthritis when taking this medicine.
- *Renal Disease*- Use in caution.
- *Liver Disease*- Use in caution, better to use lower doses, high risk of GI bleeding.

Precaution and Warnings

Indomethacin has been reported to aggravate depression or other psychiatric disturbances, epilepsy and Parkinsonism. Extreme caution should be taken in susceptible patients. In case of hemorrhoids, caution use or avoid rectal administration.

Drug Interaction

Probenecid

Increases in plasma concentration of indomethacin; enhancing the pain relief effect, but increasing its adverse effects. Use in caution.

Sympathomimetic

Concomitant use may result in increased blood pressure. Monitor patient.

Brands

Indocaps (JCL), Indolin (BPC), Indopharm (JePharm), Indovis (CTI). Indomethacin's bioavailability is %100(oral) and 80-90% (rectal).

Enolic acids
Piroxicam [9]

Piroxicam (Figure 6) is an oxicam NSAID derivative. Is as effective as naproxen, and has a prolonged duration of action which permits once daily administration. Use is not recommended unless other NSAIDs have failed or patient compliance would be improved with once daily dose [9].

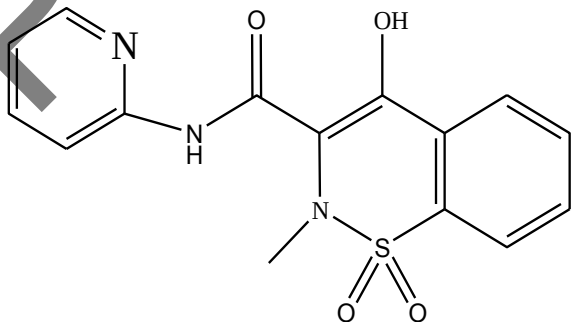


Figure 6. Chemical structure of piroxicam.

Dosage Forms

Capsules, suppositories and gel.

Recommended Dosage

Adults: 10-20 mg PO 1-2 times/day. For acute gout, 40 mg initially, then 40 mg daily in single or divided doses for 2 days, then 20 mg q. d. for 7-14 days.

Child: Not to be used.

Directions: Take with or after food. Peak effect is 3-5 hours. for analgesia, and 2-4 weeks for anti-rheumatic action. Onset is 1 hour. for analgesia, and 7 days for anti-rheumatic action. Duration is 48-72 hours.

-If patient misses dose, it should be taken as soon as remembered unless it is too close to the following dose, so skip and maintain schedule. Do not double dose.

Use in Special Cases

- *Pregnancy*- Category B in 1st and 2nd trimester, and Category D in 3rd trimester.
- *Lactation* + *Children*- Not established.
- *Renal Disease*- Use with caution to avoid risk of accumulation.
- *Liver Disease*- Use with caution to avoid risk of GI bleedings.

Brands

Feldene (Pfizer), Pirox (JePharm).

Meloxicam [9]

Meloxicam (Figure 7) has long half-life and roughly 10-fold COX-2 selectivity on average in ex vivo assays. There is significantly less gastric injury compared with piroxicam (20 mg/day) in subjects treated with 7.5 mg/day of meloxicam, but the advantage is lost with 15 mg/day. Meloxicam's bioavailability is 89% [9].

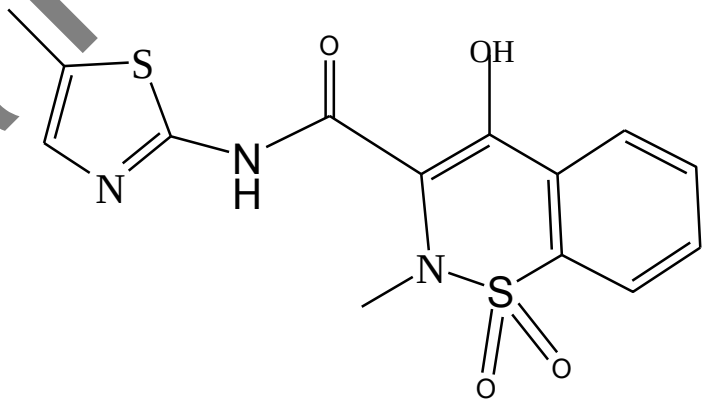


Figure 7. Chemical structure of meloxicam.

Sulindac [9]

Sulindac (Figure 8) is a prodrug that is converted to the active sulfide which has a long half-life (7 to 18 hours). 95% of this drug is bound to plasma proteins and thus drug interactions at this level may occur. This drug has a somewhat lower frequency of GI upset. Sulindac bioavailability is approximately 90% (oral) [9].

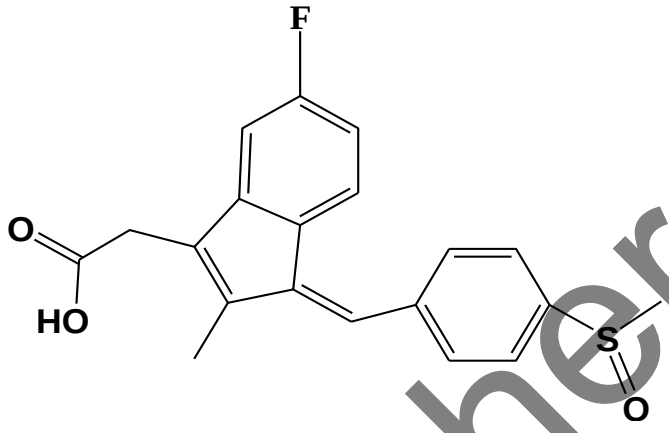


Figure 8. Chemical structure of sulindac.

Pyrrolacetic acids
Ketorolac [9]

Ketorolac (Figure 9) is a Pyrrolacetic acid, which is available in injection form. An initial dose of 30 mg followed by 10 to 15 mg intravenously (IV) every 6 hours is equianalgesic to 6 to 12 mg of IV morphine. Ketorolac may precipitate renal failure especially in elderly and hypovolemic patients. It is therefore recommended to limit the use of Ketorolac to 5 days only. Also, clinicians should try to use the lowest dose felt to be needed. This is the only NSAID available for IM administration. Ketorolac is used for moderate to severe pain (e.g postoperative pain) since it has an analgesic potency equal to a moderate dose of morphine. Its bioavailability is 100% in all routes.

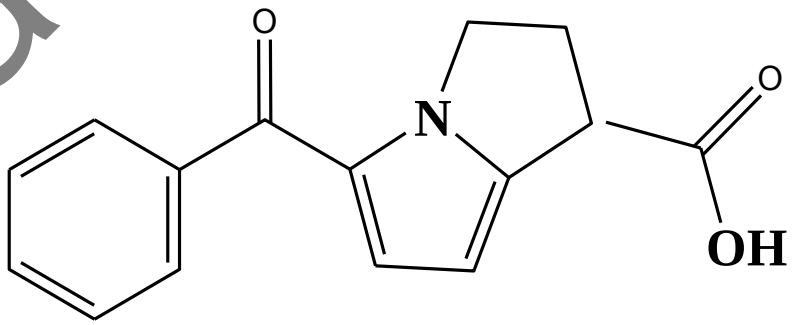


Figure 9. Chemical structure of ketorolac.

Naproxen [9]

Naproxen (Figure 10) is available both over the counter and by prescription. It is used for the treatment of mild to moderate pain, inflammation and fever. Perhaps naproxen has a lower risk of provoking heart attack or stroke at any commonly used doses. Its bioavailability is 95% (oral) [9].

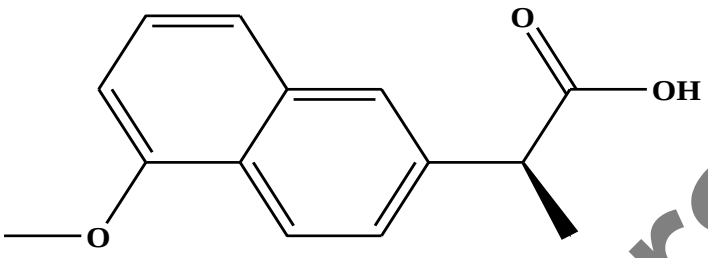


Figure 10. Chemical structure of naproxen.

Naphthylalkanone Nabumetone [9]

Nabumetone (Figure 11) is a prodrug; it is absorbed rapidly and is converted in the liver to one or more active metabolites, principally 6-methoxy-2-naphtylacetic acid, a potent nonselective inhibitor of COX. The incidence of gastrointestinal ulceration appears to be lower than with other NSAIDs (perhaps because of its being a prodrug or the fact that there is essentially no enterohepatic circulation) [9].

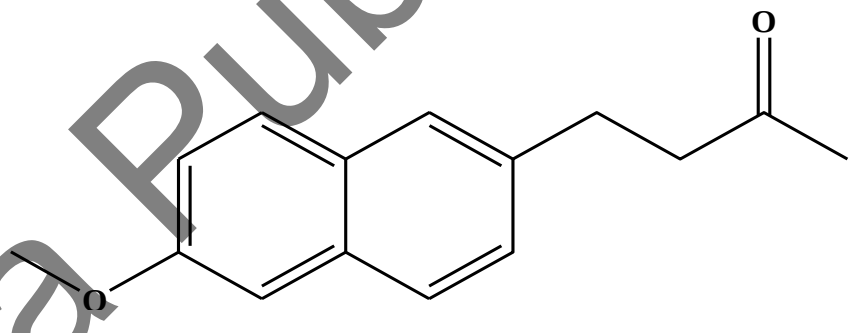


Figure 11. Chemical structure of nabumetone.

Selective COX II Inhibitors

At therapeutic doses these drugs selectively inhibit COX II with little or no inhibition of COX I. Current thinking is that these drugs should reduce inflammation and produce analgesia without causing GI damage [9].

Celecoxib (CELEBREX) is the ONLY COX II selective drug currently marketed in the US. Rofecoxib (VIOXX) and Valdecoxib (BEXTRA) have been withdrawn due to cardiac

side effects. Etoricoxib (Arcoxia) was approved for the use in Europe and other countries (63 in total), but permission for use in the US was denied [9].

Both rofecoxib and valdecoxib have now been withdrawn from the market in view of their adverse event profile. Valdecoxib has been associated with a three-fold increase in cardiovascular risk in two studies of patients undergoing cardiovascular bypass graft surgery. Based on interim analysis of data from the Adenomatous Polyp Prevention on Vioxx (APPROVe) study, which showed a significant (two-fold) increase in the incidence of serious thromboembolic events in subjects receiving 25 mg of rofecoxib relative to placebo, rofecoxib was withdrawn from the market worldwide. The FDA advisory panel agreed that rofecoxib increased the risk of myocardial infarction and stroke and that the evidence accumulated was more substantial than for valdecoxib and appeared more convincing than for celecoxib. Effects attributed to inhibition of prostaglandin production in the kidney (hypertension and edema) may occur with nonselective COX inhibitors and also with celecoxib. Studies in mice and some epidemiological evidence suggest that the likelihood of hypertension on NSAIDs reflects the degree of inhibition of COX-2 and the selectivity with which it is attained.

Thus, the risk of thrombosis, hypertension, and accelerated thermogenesis may be mechanistically integrated. The coxib drugs should be avoided in patients prone to cardiovascular or cerebrovascular disease. None of the coxib drugs has established clinical efficacy over NSAIDs. While selective COX-2 inhibitors do not interact to prevent the antiplatelet effect of aspirin, now it is thought that they may lose some of their gastrointestinal advantage over NSAIDs alone when used in conjunction with aspirin [9].

Black-box warning for all NSAIDs (including both nonselective COX and COX II inhibitors) issued by the FDA June 27, 2005. A black-box warning indicates a high level of concern on the part of the FDA.

Cardiovascular: NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk [10].

Gastrointestinal: NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events [11].

Nonsteroidal Anti-Inflammatory Drug-Associated Upper Gastrointestinal Damage [12]

The damage of gastric and duodenal mucosa caused by NSAIDs has been widely studied. These upper GI side effects include troublesome symptoms with or without mucosal injury, asymptomatic mucosal lesions, and serious complications, even death.

About 30 to 50% of NSAIDs users have endoscopic lesions (such as sub epithelial hemorrhages, erosions, and ulcerations), mainly located in gastric antrum, and often without clinical manifestations.

Generally, these lesions have no clinical significance and tend to reduce or even disappear with chronic use, probably because the mucosa is adapted to aggression. On the contrary, up 40% of NSAIDs users have upper GI symptoms, the most frequent being gastroesophageal reflux (regurgitation and/or heartburn) and dyspeptic symptoms (including belching, epigastric discomfort, bloating, early satiety and postprandial nausea). The onset of these symptoms seems to vary depending on the type of NSAID. The most important upper GI side effects are the occurrence of symptomatic and/or complicated peptic ulcer. NSAID-related upper GI complications include bleeding, perforation and obstruction. About 1 to 2% of NSAID users experienced a serious complication during treatment.

Risk Factors for Gastrointestinal Complications [12]

The main risk factors for NSAID-related GI complications are: older age (age ≥65 years, especially ≥70 years); prior uncomplicated or complicated ulcer; concomitant use of other drugs, including aspirin, other non-aspirin antiplatelet agents, anticoagulants, corticosteroids or selective serotonin reuptake inhibitors; severe illness; alcohol and tobacco use; and *Helicobacter pylori* infection. *H. pylori* infection and NSAID use have synergistic effects on risk.

Traditional or Nonselective NSAIDs [12]

Traditional or ns-NSAIDs, including high dose of ASA, are considered the most GI harmful kind of NSAID. GI damage is dose dependent and slow-release formulations and drugs with longer half-life also have greater toxicity.

Selective Cyclooxygenase-2 Inhibitors [12]

The identification of the gene for the COX-2 isoenzyme in 1991 opened the door to development of NSAIDs that selectively inhibit COX-2. This isoenzyme expression can be induced by inflammatory mediators in multiples tissues and can have an important role in the mediation of pain, inflammation and fever.

Selective COX-2 inhibitors inhibit this enzyme, but keep prostaglandin production via COX-1, which is involved in the maintenance of GI mucosal integrity. As a result, these drugs should in theory be safer than ns-NSAIDs for the development of upper GI complications, although COX-1 inhibition is not the only mechanism involved in GI toxicity.

The Major Adverse Reaction to All Nsaids (Especially Nonselective COX Inhibitors) Is GI Ulceration and Bleeding [11]

Methods to reduce the GI side effects of NSAIDs:

1-Use the lowest effective dose for the shortest duration.

2-Co-administer a proton pump inhibitor such as omeprazole (PRILOSEC)

3-Co-administer a prostaglandin receptor agonist such as Misoprostol (CYTOTEC). This prostaglandin analogue stimulates PG receptors to counteract the GI irritation of NSAIDs (cytoprotection). Note this drug has several disadvantages which limit its use; high cost, causes abortions and diarrhea.

Other health risks from the use of NSAIDs:

NSAIDs can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV (cardiovascular) events. Long-term administration of NSAID has resulted in renal papillary necrosis and other renal injury.

In February of 2007, the American Heart Association (AHA) released a scientific statement advising that, when possible, physicians should avoid using NSAIDs in patients at high risk for heart disease. When pain relief is necessary, the AHA advises that doctors should preferentially use acetaminophen or certain older, non-COX-2 selective NSAIDs [11].

How to Reduce G.I. Side Effects of NSAID's [13]

The cyclooxygenase active site is created by a long hydrophobic channel that is the site of non-steroidal anti-inflammatory drug binding. This active site extends from the membrane-binding domain (the lobby) to the core of the catalytic domain .The arachidonate-binding site is located in the upper half of the channel, from Arg-120 to near Tyr-385. Ser- 530, positioned in the middle of the channel, is the site of acetylation by aspirin. Three amino acid differences result in a larger (about 20%) and more accessible channel, in COX-2. The exchange of a valine at position of 523 in COX-2 for a relatively bulky isoleucine (Ile) residue in COX-1 at the same position of the active site of the enzyme causes a structural modification. This modification in the COX-2 enzyme allows the access to an additional side pocket, which is a pre-requisite for COX-2 drug selectivity. Access to this side pocket is restricted in the case of COX-1. In addition, the exchange of Ile-434 for a valine in COX-2 allows a neighboring residue phenylalanine-518 (Phe-518) to swing out of the way, increasing further access to the side cavity. There is another essential amino acid difference between the two isoforms, which does not alter the shape of the drug-binding site but rather changes its chemical environment. Within the side pocket of COX-2 is an arginine in place of histidine-513 (His-513) in COX-1, which can interact with polar moieties. These differences between the COX active sites have major implications for the selectivity profile of inhibitors.

COX-2 inhibitors: this class of enzyme inhibitors is lacking a carboxylic group, thus effecting COX-2 affinity by a different orientation within the enzyme without formation of a salt bridge in the hydrophobic channel of the enzyme.

Modified NSAIDs

Modifying well known NSAIDs into selective COX-2 inhibitors represents an interesting strategy. Indomethacin, diclofenac and many other NSAIDs have been successfully elaborated into the selective COX-2 inhibitors. Novartis group described conversion of diclofenac into lumiracoxib, which exhibits 500-fold selectivity for COX-2 over COX-1. Amongst the NSAIDs studied so far, the indomethacin template appears the most flexible in delivering COX-2-specific inhibitors following the functional group manipulations. However, the methodology utilized in NSAID modification does not follow a general scheme. Various attempts have been made to shift the enzyme selectivity of indomethacin from COX-1 to COX-2 while keeping the potency on the same level and reducing the unwanted side-effects at the same time. In principle, the strategy consisted of introducing larger substituents to fit into the active site volume of COX-2.

Conversion of non-selective NSAIDs to esters and amides is a facile strategy for generating COX-2 inhibitors from known drugs but it has the limitation that indomethacin esters have.

Opioid Analgesics [10]

Opioid analgesics are mainly centrally acting (brain and spinal cord) which are used for severe pain. Most clinically used opioid drugs are mu opioid receptor agonists. A few, however, are kappa agonists. Although administration of delta agonists results in nociception in animals, none are currently available for clinical use. There is growing evidence that opioids may have an analgesic action at the site of tissue damage.

Central Modulation of Pain:

1. Direct electrical stimulation of certain brain regions results in analgesia. Periaqueductal gray (third ventricle) areas of thalamus.
2. Administration of low dose of opiates directly into specific brain regions results in analgesia [10].

Effect On Central Nervous System:

ANALGESIA – Opiates are used to treat both chronic and acute pain. But mainly used to treat the neuropathic pain. Syndromes. For instance, they are used to treat phantom limb, differentiation pain and trigeminal neuralgia.

EUPHORIA – Opioids cause a powerful sense of contentment and well-being. It thus reduces the agitation and anxiety caused by painful illness and injury. Euphoria is mediated through μ receptor. Euphoria is more prominent in those previously addicted to opioids.

RESPIRATORY DEPRESSION – Respiratory depression, resulting in increased arterial Pco2, occurs with the normal dose of opioids. It occurs due to decrease in the sensitivity of the respiratory system to Pco2.

DEPRESSION OF COUGH REFLEX – Generally. Increasing substitution on the phenolic hydroxyl group of morphine increases antitussive relative to analgesic activity. For example, codeine suppresses cough in sub analgesic doses and is often used in cough medicine.

NAUSEA and VOMITING – It occur in nearly 40% of the patients. The site of action is the area postrema, a region of the medulla where chemical stimuli of much kind initiate vomiting.

PUPILLARY CONSTRICTION – It is caused by μ and k receptor, mediated stimulation of the oculomotor nucleus. Pinpoint pupil is an important diagnostic feature in opiate poisoning, because most other cases of coma and respiratory depression cause pupillary dilatation.

Effect On The Gastrointestinal Track: Opioids increases tone and reduces motility in many parts of the gastrointestinal system, resulting in the constipation, which may be severe. The resulting delay in gastric emptying can considerably retard the absorption of other drug. Pressure in the biliary track increases because of the contraction of the gallbladder and the constriction of the biliary sphincter.

Side Effects

Some people experience drowsiness, dizziness, lightheadedness, or a false sense of well-being after taking opioid analgesics. Anyone who takes these drugs should not drive, use machinery, or do anything else that might be dangerous until they know how the drug affects them. Nausea and vomiting are common side effects, especially when first beginning to take the medicine. If these symptoms do not go away after the first few doses, the person should check with the physician or dentist who prescribed the medicine. Dry mouth is another common side effect, which can be relieved by sucking on sugarless hard candy or ice chips or by chewing sugarless gum. Saliva substitutes, which come in liquid or tablet forms, may also help. Patients who must use opioid analgesics over long periods and who have dry mouth should see their dentists, as the problem can lead to tooth decay and other dental problems.

The following side effects are less common. They usually do not need medical attention and will go away after the first few doses. If they continue or interfere with normal activity, the patient should check with the physician who prescribed the medicine for:

- Headache
- Loss of appetite
- Restlessness or nervousness
- Nightmares, unusual dreams, or problems sleeping
- Weakness or tiredness
- Mental sluggishness
- Stomach pain or cramps
- Blurred or double vision or other vision problems
- Problems urinating such as pain, difficulty urinating, frequent urge to urinate, or decreased amount of urine
- Constipation

Other side effects may be more serious and may require quick medical attention. These symptoms could be signs of an overdose. The person should get emergency medical care immediately:

- Cold, clammy skin
- Bluish discoloration of the skin
- Extremely small pupils
- Serious difficulty breathing or extremely slow breathing
- Extreme sleepiness or unresponsiveness
- Severe weakness
- Confusion
- Severe dizziness
- Severe drowsiness
- Slow heartbeat
- Low blood pressure
- Severe nervousness or restlessness

Opioid Agonists Prototype [14]
Morphine

Morphine, IUPAC Name - (5α,6α)-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol (Figure 12) is an alkaloid used to relieve pain [14].

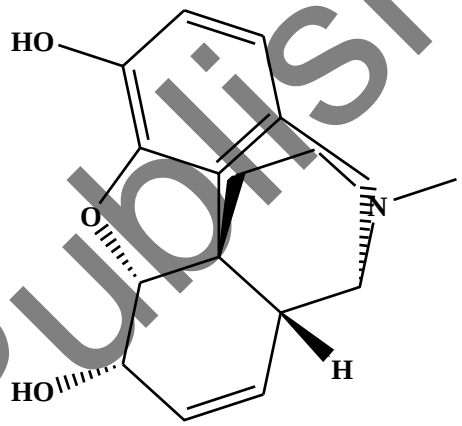


Figure 12. Chemical Structure of Morphine.

Mechanism of Action

Morphine relieves both the perception of pain and the emotional response to it, as a result of its action as a full agonist on opioid receptors (especially m, but also d and k) in the brain and spinal cord. Morphine causes pupillary constriction by stimulating m/d-receptors in the Edinger-Westphal nucleus in the mid-brain, Morphine also causes peripheral histamine release and thus vasodilation and, in some patients, bronchoconstriction. In some patients it may also cause bradycardia due to stimulation of the vagal center in the medulla.

Pharmacokinetics

Absorption - opioids are well absorbed. After intramuscular injection the peak therapeutic effect is achieved in about 1 hour and it lasts for 3-4 hours. Bioavailability is approximately 30%. Protein Binding is 30-40%

Metabolism - Morphine is metabolized largely by combination with glucuronic acid but also by N-dealkylation and oxidation. Metabolism occurs in the liver and gut wall. Primarily hepatic (90%), converted to dihydromorphinone and normorphine. Also converted to morphine-3-glucuronide (M3G) and morphine-6-glucuronide. Virtually all morphine is converted to glucuronide metabolites. Only a small fraction (less than 5%) of absorbed morphine is demethylated.

Excretion - About 10% being excreted in the urine as morphine and 60-70% as the glucuronide.

HALF LIFE - 2-4 hours

Dose

- For acute pain following injury an average adult requires 10 mg subcutaneously or intramuscularly repeated at 4-6 hour intervals.
- A large patient suffering severe pain may need 15-20 mg.
- The elderly or individuals with renal or hepatic insufficiency will require less than the usual dose (one-quarter to one-half).

Administration

Intravenous - Morphine may be given as an intravenous bolus if rapid relief is required (e.g., during myocardial infarction) and the usual dose is 5 mg.

Postoperatively - Morphine can be given continuously by an infusion pump, either intravenously or subcutaneously.

Orally – Morphine is given by mouth initially regularly 4 hourly as an elixir, Spinal (epidural or intrathecal) administration - Morphine is effective at much lower doses than when given by other routes and therefore causes fewer systemic side effects.

Side Effect

- Overdose leads to coma.
- Morphine depresses the sensitivity of the respiratory center to carbon dioxide, thus causing a progressively decreased respiratory rate.
- Morphine increases smooth muscle tone throughout the gastrointestinal tract, which is combined with decreased peristalsis, due to an action on receptors in the ganglion plexus in the gut wall.

Activates Mu opioid receptors at multiple points along the pain pathway (including brain and spinal cord) resulting in a reduction in pain perception.

Other effects of Morphine:

1. Central Nervous System euphoria
   sedation (drowsiness and mental clouding)
   respiratory depression
   nausea and vomiting (especially if ambulatory)
   cough suppression
   miosis (pin point pupils)
2. Biliary tract
   Morphine causes constriction of biliary smooth muscles resulting in biliary colic.
3. GI tract
   Morphine inhibits propulsion in the GI tract resulting in constipation.
4. Endocrine system

Morphine acts at the hypothalamus to reduce the release of GnRH (gonadotropin releasing hormone) and CRF (corticotropin releasing factor). Reduced GnRH results in reduced levels of LH and FSH whereas decreased CRF results in lower levels of ß-endorphin and ACTH (causing lower cortisol levels).

Opioid Poisoning Triad of symptoms; coma, pinpoint pupils and low respiratory rate. Other symptoms include decreased blood pressure, depressed urine formation and urinary retention. Treatment includes ventilation and the use of narcotic antagonists. Caution should be employed since the narcotic antagonist; naloxone has a short duration of action relative to morphine.

The repeated use of opioids results in tolerance and physical dependence and may result in addiction.

Addiction Liability Is Apparently Very Low in Chronic Pain Patients

Definitions of Tolerance, Physical Dependence and Addiction

Tolerance: Upon frequent, repeated drug administration, the dose required to obtain a given effect (e.g., level of pain relief) increases.

Physical Dependence: Cellular adaptation occurring in response to repeated drug administration such that discontinuance of the drug results in a characteristic withdrawal or abstinence syndrome. Abrupt stoppage of opioid administration results in symptoms that are, in general, the opposite of initial effects of the drug. These signs include sweating, nausea, diarrhea, insomnia and muscular aches and pains.

Addiction: The compulsive use of a substance resulting in physical, psychological or social harm to the user and continued use despite that harm. Another definition of addiction is

a pattern of compulsive drug use characterized by a continued craving for the drug and the need to use the drug for non-medical conditions.

Other Mu Opioid Agonists
Methadone [14]

Methadone, IUPAC Name - (*RS*)-6-(Dimethylamino)-4,4-diphenylheptan-3-one (Figure 13) is an analgesic.

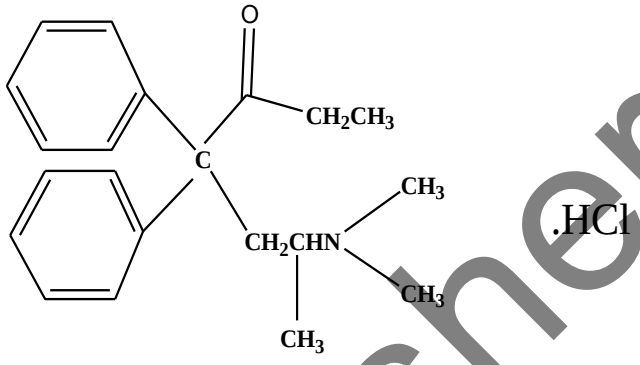


Figure 13. Chemical Structure of Methadone.

Methadone was introduced into the United States in 1947 by Eli Lilly and Company as an analgesic (They gave it the trade name Dolophine ®, which is now registered to Roxane Laboratories). Since then, it has been best known for its use in treating narcotic addiction, although such a use never became widespread and common until the early 1990's when public policy sought to find ways to reduce the spread of HIV and AIDS.

Methadone is an orally active long acting mu opioid receptor agonist. Methadone exhibits cross tolerance with morphine or heroin and therefore is useful as a treatment for heroin addicts [14].

Mechanism of Action

Methadone is a synthetic, long-acting opioid with pharmacologic actions qualitatively similar to morphine. It is primarily a μ-receptor agonist and may mimic endogenous opioids, enkephalins, and endorphins and affect the release of other neurotransmitters—acetylcholine, norepinephrine, substance P, and dopamine.

Pharmacokinetics

Methadone is readily absorbed orally, it is highly protein bound so remains in tissues for a prolonged period. It is transformed in the liver and excreted by the urine as mostly inactive metabolites.

Onset of action - Oral: Analgesic: 0.5-1 hour

Parenteral: 10-20 minutes

Peak effect - Parenteral: 1-2 hours

Oral: continuous dosing then 3-5 days

Duration of analgesia - Oral: 4-8 hours, increases to 22-48 hours with repeated doses

Protein binding - 85% to 90%

Metabolism - Hepatic, by N-demethylation and cyclization primarily via CYP3A4, CYP2B6, and CYP2C19 to inactive metabolites.

Bioavailability - Oral: 36% to 100%

Excretion - Urine (<10% as unchanged drug); increased with urine pH <6

HALF LIFE - 15 to 60 hours

Dose

Children:

Oral - 0.1-0.2 mg/kg 4-8 hours initially for 2-3 doses, then every 6-12 hours as needed.

Dosing interval may range from 4-12 hours during initial therapy, decrease in dose or frequency may be required (~days 2-5) due to accumulation with repeated doses (maximum dose: 5-10 mg)

I.V. - 0.1 mg/kg every 4-8 hours initially for 2-3 doses, then every 6-12 hours as needed.

Dosing interval may range from 4-12 hours during initial therapy, decrease in dose or frequency may be required (~days 2-5) due to accumulation with repeated doses (maximum dose: 5-8 mg)

Adults:

Oral - Opioid-naive: Initial: 2.5-10 mg every 8-12 hours; more frequent administration may be required during initiation to maintain adequate analgesia.

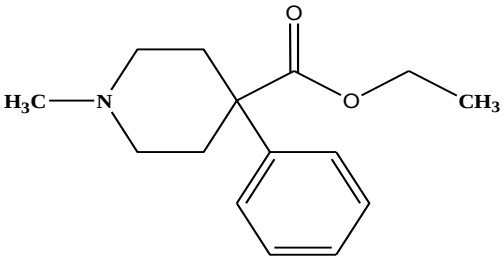
Dosage interval may range from 4-12 hours, since duration of analgesia is relatively short during the first days of therapy, but increases substantially with continued administration.

Adverse Effect

It causes miosis, respiratory depression, biliary spasm and constipation just like morphine.

Mepridine [14]

Meperidine, IUPAC NAME – Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate (Figure 14) is an opiate pain reliever.



. HCl

Figure 14. Chemical Structure of Meperidine.

Meperidine: is a weak mu opioid agonist that is widely used for analgesia during delivery. It does not delay the birth process and does not antagonize oxytocin.

CAUTION: use of meperidine with MAO inhibitors causes severe reactions (respiratory depression, excitation, delirium and convulsions) [14].

Mechanism of Action

Inhibiting adenylate cyclase. Subsequently, the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine and noradrenaline is inhibited. Opioids also inhibit the release of vasopressin, somatostatin, insulin and glucagon. Meperidine analgesic activity is, most likely, due to its conversion to morphine.

Pharmacokinetic

Absorption: Oral bioavailability is 50-60% in patients with normal hepatic function. It is well absorbed from GI track. I.M. - Erratic and highly variable.

Onset of action: Oral -10-15 minutes; I.V - minutes

Peak effect: SubQ. - 1 hour; Oral - 2 hours

Duration: Oral, SubQ. - 2-4 hours

Distribution: Crosses placenta; enters breast milk

Protein binding: 65% to 75%

Metabolism: Meperidine is metabolized in the liver by hydrolysis to meperidinic acid followed by partial conjugation with glucuronic acid. Meperidine also undergoes N-demethylation to normeperidine, which then undergoes hydrolysis and partial conjugation. Normeperidine is about half as potent as meperidine, but it has twice the CNS stimulation effects.

Bioavailability: 50% to 60%; increased with liver disease

Excretion: Urine (as metabolites)

HALF LIFE: 3-4 hr.

Dose

Children: Oral, I.M., I.V.: 1-1.5 mg/kg/dose every 3-4 hours as needed

1-2 mg/kg as a single dose preoperative medication may be used maximum 100 mg/dose

Adults: Oral: Initial 50 mg every 3-4 hours as needed

usual dosage range: 50-150 mg every 2-4 hours as needed (I.M., SubQ: Initial 50-75 mg every 3-4 hours as needed; patients with prior opiate exposure may require higher initial doses

Slow I.V.: Initial 5-10 mg every 5 minutes as needed

Elderly: Oral: 50 mg every 4 hours

I.M.: 25 mg every 4 hours

Dental Usual Dosing

Adults - Oral: Initial 50 mg every 3-4 hours as needed

usual dosage range: 50-150 mg every 2-4 hours as needed

Side Effects

- Agitation, disorientation, or hallucinations.
- Shakiness, seizures, muscle twitches, or other abnormal muscle movements.
- A slow heart rate (bradycardia) or fast heart rate (tachycardia).
- Low blood pressure (hypotension) or high blood pressure (hypertension).
- Fainting.

Codeine [15]

Codeine (Figure 15) is a weak mu opioid agonist used as an antitussive and as an analgesic in mild pain. Codeine is also combined with NSAIDs. Codeine is considered a prodrug, since it is metabolized *in vivo* to the primary active compounds morphine and codeine-6-glucuronide.

Oxycodone: is also a weak opioid agonist used in combination with NSAIDs for analgesia (oxycodone plus aspirin = PERCODAN; oxycodone plus acetaminophen = PERCOCET). Codeine's bioavailability is 90% (oral) [15].

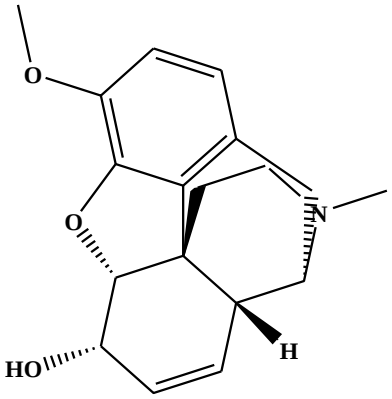


Figure 15. Chemical Structure of Codeine.

Fentanyl [14]

Fentanyl, IUPAC NAME - N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenyl-propanamide (Figure 16) is a powerful opioid analgesic with a potency approximately 81 times that of morphine. It is also available as a transdermal patch (DUROGESIC/ DURAGESIC) for continuous delivery [14].

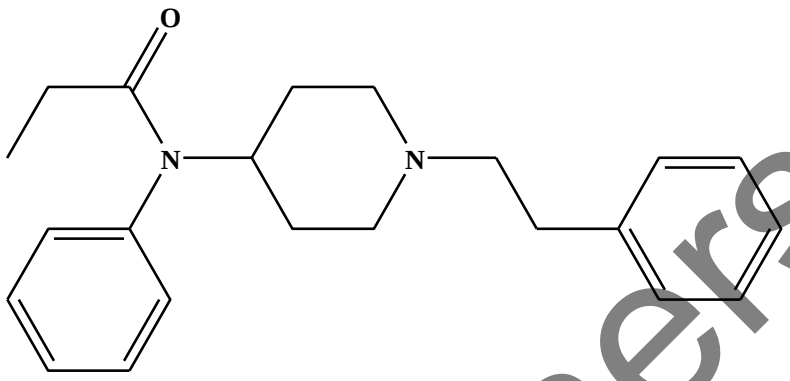


Figure 16. Chemical Structure of Fentanyl.

Mechanism of Action

Fentanyl is a powerful synthetic opiate with mechanism of action similar to morphine. It is considered both faster acting and of shorter duration than morphine. It interacts with opiate receptors decreasing pain impulse transmission at the spinal cord level and higher in the CNS.

Fentanyl is a potent μ-opiate receptor agonist. Since it decreases both preload and afterload it may decrease myocardial oxygen demand.

Pharmacokinetics

Fentanyl is metabolized to an inactive metabolite by the cytochrome p4503A4 system. Drug metabolites are eliminated through the urine

HALF-LIFE - 7 hours

Dose

Adults: IV/IM: 25-50 mcg slow IV push, 100 mcg for ACS/ischemic chest pain.
200 mcg for Pain Control/Sedation/Intubation.
Pediatrics (Greater than 2 years of age): IV, IO, IM: 2-3 mcg/kg to a max of 100 mcg.
For Intubation: 2-5 mcg/kg to a max of 100 mcg.
IN: 1-2 mcg/kg (rare).
Transdermal patch (Duragesic -- CII) in 25, 50, 75 and 100 ug/hour strengths.

Adverse Effect

A particular risk of the trans mucosal or transdermal routes is respiratory depression; these delivery routes create a reservoir of drug in the skin or mucosa.

Bupernorphine [14]

Bupernorphine, IUPAC NAME- (2S)-2-[(-)-(5R,6R,7R,14S)-9α-cyclopropylmethyl-4,5-epoxy-6,14-ethanomorphinan-7-yl]-3-hydroxy-6-methoxy-3,3-dimethylbutan-2-ol (Figure 17) is an analgesic drug.

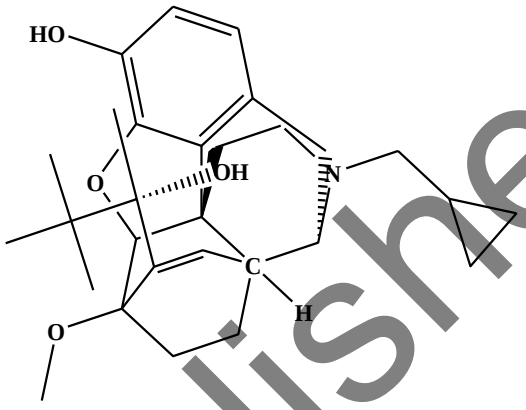


Figure 17. Chemical Structure of Bupernorphine.

Mechanism of Action

Buprenorphine is a thebaine derivative with powerful analgesia approximately 25 to 40 times as potent as morphine, and its analgesic effect is due to partial agonist activity at μ-opioid receptors, i.e., when the molecule binds to a receptor, it is only partially activated in contrast to a full agonist such as morphine. Buprenorphine also has very high binding affinity for the μ receptor such that opioid receptor antagonists (e.g., naloxone) only partially reverse its effects.

Intravenous bupernorphine is more effective and has fewer side effects than morphine in post-operative pain management. Buprenorphine is available in Europe as a transdermal formulation ("patch") for the treatment of chronic pain.

Pharmacokinetics

Metabolism - Buprenorphine is metabolized by the liver, via the CYP3A4 isozyme of the cytochrome P450 enzyme system, into norbuprenorphine (by N-dealkylation) and other metabolites. The metabolites are further conjugated with glucuronic acid.

Elimination - Eliminated mainly through excretion into the bile. The elimination half-life of buprenorphine is 20–73 hours (mean 37). Due to the mainly hepatic elimination there is no risk of accumulation in patients with renal impairment and in the elderly.

Buprenorphine's main active metabolite, norbuprenorphine, is a μ-opioid, δ-opioid, and receptor full agonist, as well as a κ-opioid receptor partial agonist.

Administration

Buprenorphine hydrochloride is administered by intramuscular injection, intravenous infusion, via transdermal patch, or as a sublingual tablet. It is not administered orally, due to very high first pass metabolism.

Dose

To treat opioid addiction in higher dosages (>2 mg).
To control moderate pain in non-opioid tolerant individuals in lower dosages (~200 μg).
Market preparations - Temgesic 0.2 mg sublingual tablets.
Buprenex 0.3 mg/ml injectable formulation.
HALF LIFE - 37 hours.

Mixed Agonists-Antagonists Analgesics

The analgesic effects of these opioids result from their kappa agonist activity. These drugs are mu receptor antagonist or weak partial agonists at the mu receptor. Thus, administration of these drugs to morphine tolerance patient or heroin addict may cause withdrawal.

The advantage of this class of drugs is that the extent of respiratory depression is limited. κ-agonism can cause dysphoria at therapeutic or super therapeutic doses, thus kappa opioid receptor agonists have a lower abuse potential relative to mu opioid receptor agonists.

Nalbuphine [13]

Nalbuphine (Figure 18) is a kappa opioid receptor agonist and a mu opioid receptor antagonist. Nalbuphine produces a lower incidence of post-operative nausea and vomiting compared to morphine and is used to supplement anesthesia during surgery. Nalbuphine is also indicated for use during labor.

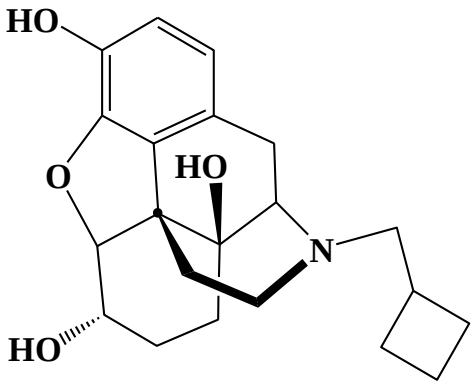
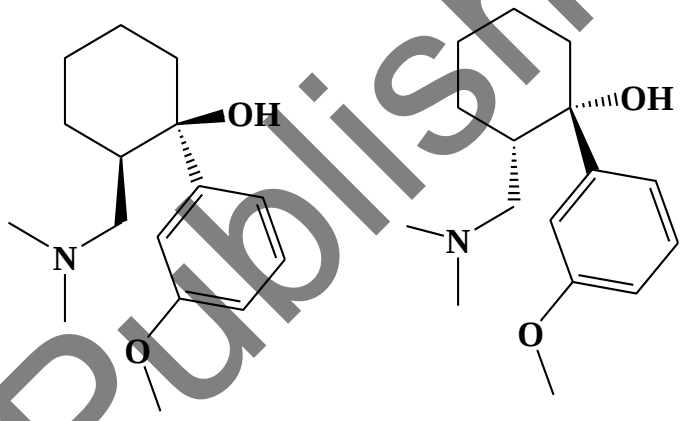


Figure 18. Chemical Structure of nalbuphine.

Tramadol

Tramadol (Figure 19) is an orally acting analgesic weakly binds to opioid receptors and inhibits the uptake of norepinephrine (NE) and serotonin.



(1S,2S)-tramadol (1R,2R)-tramadol

Figure 19. Chemical Structure of tramadol.

Opioid Antagonists [14]
Naloxone (Short Acting)

Naloxone, IUPAC NAME - (1*S*,5*R*,13*R*,17*S*)- 10,17-dihydroxy- 4-(prop-2-en-1-yl)- 12-oxa- 4-azapentacyclo octadeca- 7,8,10-trien- 14-one (Figure 20) is a drug used to counter the effects of opioid overdose, for example heroin or morphine overdose. Naloxone is specifically used to counteract life-threatening depression of the central nervous system and respiratory system. Naloxone is also experimentally used in the treatment for congenital insensitivity to pain with anhidrosis (CIPA).

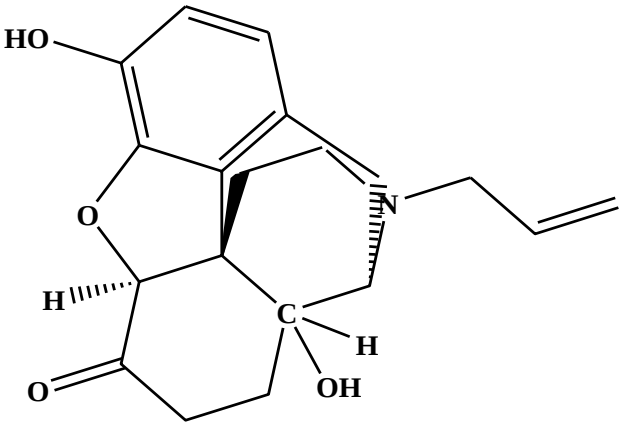


Figure 20. Chemical Strucutre of Naloxone.

Mechanism of Action

Naloxone has an extremely high affinity for μ-opioid receptors in the central nervous system. Naloxone is a μ-opioid receptor competitive antagonist, and its rapid blockade of those receptors often produces rapid onset of withdrawal symptoms. Naloxone also has an antagonist action, though with a lower affinity, at κ- and δ-opioid receptors .

Pharmacokinetics

1. Naloxone is administered parenterally. Although it is relatively well absorbed after oral administration, it undergoes extensive first-pass metabolism, making this route of delivery ineffective.
2. After intravenous (IV) administration, naloxone is rapidly distributed throughout the body.
3. It is highly lipophilic and readily crosses into the brain. Onset of action after IV dosing is within 2 minutes, and is only slightly longer with intramuscular (IM), subcutaneous, or endotracheal administration.
4. Duration of action is dependent on route and dose. IV dosing typically provides a duration of action of 20 to 60 minutes. IM use produces a longer effect than IV administration, but absorption from this route is erratic.
5. Metabolism - Naloxone is hepatically metabolized, primarily through conjugation to naloxone-3-glucuronide.
6. Elimination - The elimination half-life in adults is approximately 60 minutes.

Administration

Naloxone is most commonly injected intravenously for fastest action. The drug generally acts within a minute, and its effects may last up to 45 minutes. It can also be administered via

intramuscular or subcutaneous injection. Use of a wedge device (nasal atomizer) attached to a syringe to create a mist delivering the drug to the nasal mucosa may also be utilized, although this solution is more likely utilized outside of a clinical facility.

HALF LIFE - 30-81 minutes

Dose

Infants - 0.1 mg/kg ,children from birth to 5 years of age or 20 kg of body weight.
Children - 2.0 mg , 5 years of age or weighing more than 20 kg may be given.
Pediatric - ranging from 0.005 to 0.4 mg/kg have.

Side Effect

Possible side effects include - change in mood, increased sweating, nausea, nervousness, restlessness, trembling, vomiting, allergic reactions such as rash or swelling, dizziness, fainting, fast or irregular pulse, flushing, headache, heart rhythm changes, seizures, sudden chest pain.

Naltrexone (Longer Acting)

Naltrexone, IUPAC NAME - 17-(cyclopropylmethyl)-4,5α-epoxy- 3,14-dihydroxy-morphinan-6-one.

(Figure 21) is used in the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids.

Naloxone and naltrexone are pure opioid antagonists. They are most potent at the mu opioid receptor but they will antagonize the actions of delta and kappa agonists. Used to reverse the effects of opioid overdose (eg respiratory depression and coma).

CAUTION: these drugs will cause abrupt withdrawal syndrome in opioid treated patient or heroin addict.

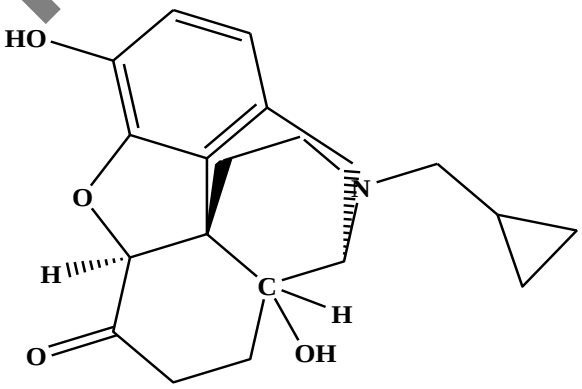


Figure 21. Chemical Structure of naltrexone.

Mechanism of Action

Naltrexone binds to the opioid mu receptor antagonistically, thereby preventing conventional opiate (heroin, morphine) drugs from binding and inducing opioid neural responses. The mechanism of action of naltrexone in alcoholism is not understood, however, involvement of the endogenous opioid system is suggested by preclinical data. Naltrexone competitively binds to such receptors and may block the effects of endogenous opioids.

Pharmacokinetic

Absorption - well absorbed orally, naltrexone is subject to significant first pass metabolism with oral bioavailability estimates ranging from 5 to 40%.

Protein Binding - 21% bound to plasma proteins over the therapeutic dose range.

Metabolism - Hepatic. Naltrexone is metabolized mainly to 6β-naltrexol by the liver enzyme dihydrodiol dehydrogenase. Other metabolites include 2-hydroxy-3-methoxy-6β-naltrexol and 2- hydroxy-3-methoxy-naltrexone. These are then further metabolized by conjugation with glucuronide.

HALF LIFE - 4 hours for naltrexone and 13 hours for the active metabolite 6 beta-naltrexol.

Dose

Oral - The initial dose of Nalorex should be 25 mg (half a tablet) followed by 50 mg (one tablet) daily.

A three-times-a-week dosing schedule may be considered if it is likely to result in better compliance e.g., 100 mg on Monday, 100 mg on Wednesday and 150 mg on Friday.

Side Effect

High doses of naltrexone (generally ≥1,000 mg/kg) produce salivation, depression/ reduced activity, tremors, and convulsions.

Pharmaceutical Companies Reformulate Pain Products [16]

Back in 1996, in a response to continued abuse of oxycodone, Purdue Pharma released Oxycontin CR, a controlled release version of traditional oxycodone. The premise for the CR version was that potential abusers would be deterred from abusing the drug because the CR version would prevent the "bolus effect," limiting the instant "high". The "bolus effect" is a sharp peak in blood levels of an active ingredient, like oxycodone, immediately post dose. The quick spike in blood levels gives the abuser the feeling of a heroin-like "high" or "fix."

the CR version of oxycodone was developed to control delivery and prevent that "fix." But abusers found ways to get a quick dose. By freezing, crushing and grinding Oxycontin CR, they could then inject or dissolve the pill in alcohol to give them a quick "fix." What was once thought to be an abuse deterrent, quickly became obsolete.

Clearly there is a large potential market for new formulations. Several drug manufacturers, biotechs, and pharmaceutical companies have worked diligently to introduce their respective formulations into this new market of tamper-proof medicine [16].

Oxycontin OP [16]

In August 2010, Purdue Pharma, released a new version of its wildly successful Oxycontin. The re-formulated tablet was designed to prevent abuse by giving it rubbery characteristics. The stamp on the front of the new formulation is labeled "OP" instead of "OC." While the colors and the overall appearance are almost identical, the abuse deterrent properties are quite different.

The new tamper-proof Oxycontin pill is still a controlled-release formulation but the newly designed polymer system makes it more difficult for opiate addicts to crush, melt, or inject the pill. When heated, the polymer pill becomes a viscous gel, but doesn't release the active ingredient, making it almost impossible to inject. The polymer still surrounds the active ingredient even when forcefully crushed [16].

In 2009, Oxycontin's annual sales were more than $3 billion worldwide. Purdue hopes that it can transition patients to the new version. But according to some news reports, some patients feel that the new formulation is not working as intended. Although Purdue's product was the first to market, the moot reception may present an opportunity for competitors [16].

Remoxy [16]

According to Durect's senior management, Oxycontin's pitfalls may lead to Remoxy's success. Remoxy, like the new Oxycontin formulation, is a tamper-proof version of oxycodone. The gummy texture of the capsule is difficult for abusers to convert into a form that can be injected or snorted. The capsule also resists dissolving in water or alcohol. Even after 2 hours in vodka, Remoxy is able to retain most of the active ingredient.

Embeda [16]

Embeda is an extended-release morphine pill that has a kernel of sequestered naltrexone in the center. Naltrexone is an opioid receptor antagonist that competes for and prevents the binding of morphine. When taken as directed, Embeda's long acting pellets release morphine, while the naltrexone core passes out of the body without effect. If Embeda is crushed, chewed or extracted, the naltrexone releases and mixes with morphine and neutralizes its effects. This prevents the sense of euphoria or "high" that abuser's seek. Embeda was approved by the FDA in August of 2009. Embeda's current annual run-rate is about $100 million. But King's

management previously expressed that peak sales are closer to $400 million annually, and if that's the case, Pfizer stands to gain.

Acurox [16]

Acurox is a short-acting oxycodone formulation that was developed by Acura Pharmaceuticals and partnered with King. Acurox is composed of gel forming agents which prevents IV drug abuse. Acurox also contains nasal tissue irritants that discourage snorting. A previous version of Acurox contained niacin, a vitamin that causes flushing if taken in excess. The premise was that if potential abusers sought to get a "high" from swallowing excessive tablets, the dose of niacin will cause flushing. But in early 2010, in response to a FDA panel-vote against the niacin-containing Acurox, King and Acura created a version of Acurox without niacin. In December 2010, King resubmitted an NDA for Acurox without niacin. The PDUFA goal date for Acurox has been set to June 17th, 2011. Acura stands to earn a royalty ranging from 5% to 25% on net sales.

The Discovery and Development of New Analgesics: New Mechanisms, New Modalities [17]

Current Strategies in Advancing Analgesics

The approaches taken to select and advance analgesics through development and onto the market may be described in five broad categories. First, there are approaches designed to enhance the utility or increase the safety of existing medicines through the design of novel formulations or dosing forms. Examples include novel extended-release or abuse-resistant formulations of existing medicines such as oxycodone, morphine, and tramadol; and alternative delivery methods, such as patches for local administration of agents such as fentanyl, diclofenac, and lidocaine, as well as the oral fentanyl lozenge. Second, researchers have developed compounds directed against known mechanisms, especially of opiates and NSAIDs. Third, combination products of existing compounds have been developed, designed to improve efficacy or reduce unwanted side effects. Examples include combination products of oxycodone with ibuprofen, and naproxen in combination with the proton pump inhibitor esomeprazole (Vimovo). Fourth, there are a number of examples where the analgesic utility of medicines originally developed for other therapeutic indications has been recognized and led to products specifically directed toward the treatment of pain or where novel analgesics have been designed from known mechanistic classes of compounds. Examples of these include celecoxib, rofecoxib, pregabalin, duloxetine, ropivacaine, and tapentadol. Last and largely in the minority are therapeutics derived from the identification of novel mechanisms. These include the N-type calcium channel blocker Prialt (ziconotide; Endo) and Sativex (GW Pharma), which has a cannabinoid-based mechanism. While recognizing the benefits of maximizing the utility of existing medicines, and based on the clear evidence that current medicines have failed to deliver significantly improved benefits, we conclude that more

analgesics based on novel molecular mechanisms are necessary to address the unmet needs of patients in pain. The discovery and development of such medicines rely on an increased understanding of the pathophysiological mechanisms that drive pain and significant investment in R&D to translate this knowledge into novel, safe, and efficacious analgesics. Here, we describe a number of examples of emerging approaches and their mechanistic context.

Nerve Growth Factor [17]

It is now known that nerve growth factor (NGF), originally identified for its role in embryonic development of the nervous system, has the capacity to alter the function of nociceptors in the adult long after it has ceased to be a requirement for neurotropic maintenance. Exogenous administration of NGF induces pain in animals and humans. NGF is released following tissue injury or inflammation from a range of cells including mast cells, macrophages, lymphocytes, fibroblasts, and keratinocytes and may become an important driver of pain symptoms in patients experiencing chronic pain, especially where inflammation is an important component. Pro inflammatory actions of NGF have been described, and following burn or trauma it can result in release of inflammatory mediators, which in turn drive peripheral sensitization and pain. However, NGF may also act via direct effects on the sensory nerve endings themselves. Thus, in a study in healthy volunteers, intradermal injections of NGF induced local hypersensitivity with no associated neurogenic flare or inflammation. In this regard, it is interesting to note that it has been suggested that NGF released from keratinocytes following tissue damage may result in sensory hyper excitability.

The directly affected population of nociceptors expresses the neurotrophin receptors tyrosine kinase receptor A (TrkA) and/or p75, which mediate the actions of NGF via both transcriptional and non-transcriptional mechanisms to increase excitability. Relatively rapid effects of high levels of NGF on nociceptors include the increased phosphorylation of key ion channels such as transient receptor potential vanilloid 1 (TRPV1), Nav1.7, or Nav1.8, thus increasing excitability and decreasing the threshold for firing. NGF bound to its receptor complex is internalized, and a proportion is transported retrogradely to the cell body of the sensory nerves within dorsal root ganglia, where, via regulators such as NF-κB or CREB, it up-regulates expression of ion channels such as Nav1.8 and TRPV1 and peptide transmitters. Up-regulation of brain-derived neuro-trophic factor (BDNF) might also occur in response to NGF, and it is interesting to speculate that this could contribute to central sensitization via actions on TrkB receptors on post-synaptic neurons in the dorsal horn of the spinal cord.

A number of clinical programs are being pursued with a view to bringing therapeutics to patients based on the sequestration of NGF or the inhibition of the activation mechanism via TrkA. The most advanced of these is a humanized monoclonal antibody, tanezumab (RN-624, PF-04383119), derived from the murine anti-NGF monoclonal antibody muMab-911. The humanized monoclonal antibody is being studied in a range of phase and phase III clinical trials to evaluate its efficacy, safety, and tolerability in patients with a number of painful syndromes. These include osteoarthritis of the knee or hip, chronic low back pain, interstitial cystitis/painful bladder syndrome, and cancer bone pain, endometriosis, chronic prostatitis, and neuropathic pain. Phase II data are yet to be published, and the antibody is being further

evaluated in phase III clinical studies of osteoarthritis patients as monotherapy in NSAID failures, in combination studies with NSAIDs, and studies to directly compare the therapeutic utility versus NSAIDs or opioids. Extensive evaluation is ongoing to determine the benefits and risks of this new therapeutic approach. The current thinking on the pivotal role played by elevated NGF in driving peripheral sensitization such as that occurring in chronic inflammatory conditions is reflected in investment by a number of pharmaceutical companies in the development of monoclonal antibody approaches against NGF.

The Johnson & Johnson corporation is exploring the efficacy, safety, and tolerability of the human anti-NGF antibody JNJ42160443 (formerly AMJ-403) in a number of phase II studies as adjunctive therapy in subjects with moderate to severe knee or hip pain from osteoarthritis, subjects with inadequately controlled moderate to severe chronic low back pain, and patients with chronic bladder pain from interstitial cystitis and/or painful bladder syndrome, painful diabetic neuropathy, cancer pain, and post herpetic or posttraumatic neuralgia.

Regeneron Pharmaceuticals, in collaboration with Sanofi Aventis, is conducting a phase I/II randomized, double blind, placebo-controlled, parallel-group, repeat-dose study of the safety and efficacy of REGN475 in patients with osteoarthritis of the knee. The antibody will be given in two intravenous doses. The company is also recruiting for a series of phase II studies to explore efficacy in patients with sciatica, moderate to severe abdominal pain due to chronic pancreatitis of at least 6 months duration, moderate to severe pain due to non-traumatic vertebral fracture, and pain due to thermal injury. Similarly, MedImmune has announced a study to assess the potential of MEDI-578 in patients with osteoarthritis of the knee. At the time of writing, Abbot Laboratories is recruiting into a phase I clinical trial to evaluate the safety and tolerability of a monoclonal antibody to NGF (PG110) in patients with osteoarthritis of the knee. The single-dose study will assess the pain score of subjects as part of the secondary assessments.

Targeting Ion Channels [17]
Sodium Channels

The pain-killing effects of extracts derived from the coca leaf have been recognized for millennia, and it has been known for decades that drugs refined from the active ingredient cocaine and developed as alternatives, such as procaine, lidocaine, and bupivacaine, can provide powerful analgesia and be used as local anesthetics. It is now known that these compounds act by blocking voltage-gated sodium channels, and the high efficacy is consistent with the critical role of these channels in the generation and propagation of action potentials. However, sodium channels sub serve this critical role in all excitable cells, including cardiac cells, and local anesthetics are nonselective in their actions. Thus, the use of systemic analgesics of this class is limited, and the developmental focus has been to maximize their therapeutic potential with topical approaches. The development of patch technologies has expanded the utility of local anesthetics, and they are used successfully in some neuropathic pain conditions such as post herpetic neuralgia and the control of postoperative pain, although not in HIV-associated pain.

Anticonvulsants such as lamotrigine, phenytoin, and carbamazepine, acting in the central nervous system, have been used in the treatment of chronic pain for a number of years. It is known that they all bind to sodium channels preferentially in conditions of high neuronal excitability. There has been considerable interest and investment in recent years in approaches based on the selective targeting of specific sodium channel subtypes. Some nine different subtypes have been identified (Nav1.1–1.9), differentiated on the basis of their α-subunits. A number of these channels have been shown to be present in human nociceptors, primarily Nav1.7, 1.8, and 1.9, and their expression is precisely regulated. The attention has thus far been on the search for subtype-specific sodium channel blockers of Nav1.8 and Nav1.7. The rationale is supported by an impressive and growing body of human genetic data, such as the linkage of Nav1.7 mutations to extreme positive and negative pain phenotypes, and extensive mouse knockout data that have emerged in recent years. However, this effort has yet to result in any compound emerging from human clinical trials. It has been suggested that one reason for the lack of progress has been that the discovery strategies have included primary screens that tend to select compounds that bind at, or very close to, he pore forming regions of the channel complex. This region is highly conserved between subtypes and constitutes the site at which local anesthetics bind. Emerging data from studies on the actions of a range of peptide toxins provide some encouragement that targeting non-pore regions may be possible, but it seems that it may be some time before a safe and truly selective subtype-specific sodium channel ligand emerges onto the market.

Calcium Channels [17]

Calcium channels are a key to neuronal function, particularly in regulating neurotransmitter release from nerve terminals, including those that transmit pain at the level of the spinal cord. Ziconotide is a synthetic peptide equivalent to the venom of the sea snail Conus magus. The compound, termed a conopeptide, blocks N-type voltage-gated calcium channels and is likely effective as an analgesic through an action that prevents transmission across the first synapse in the pain pathway. Consistent with the mechanism of action, the compound is effective in patients with intractable pain when delivered either alone or in combination with other analgesics and in whom intrathecal therapy is acceptable.

Maximal therapeutic benefit requires careful titration in order to minimize the range of CNS side effects associated with its use. These include dizziness, confusion, ataxia, memory deficits, and hallucinations. The compound must be administered using specified infusion protocols and patients kept under close supervision. Leconotide is an alternative conopeptide, and animal data have been described suggesting that it can be delivered systemically with fewer CNS side effects than ziconotide. Given the wide distribution and central role of voltage-gated calcium channels in neurotransmission, approaches based on channel blockade will likely continue to face significant challenges in terms of therapeutic index, but where this can be managed, they may provide an important option for the treatment of severe intractable pain.

Ziconotide blocks calcium entry through the channel by binding to a specific region of the pore-forming α-subunit. Pregabalin and its predecessor gabapentin, which are effective in the treatment of neuropathic pain, interact with voltage-gated calcium channels in a different

way than ziconotide. These compounds bind to the calcium channel accessory subunit α2δ, and it has been shown that binding to this subunit is a requirement for the analgesic efficacy of pregabalin. However, a greater understanding of the role of the subunit in neuronal function, its involvement in pain pathophysiology, and how the binding of pregabalin to this protein delivers efficacy in neuropathic pain conditions may lead to novel ways to modulate this mechanism and to new therapeutic approaches.

It has been shown that α2δ protein increases in both dorsal horn and dorsal root ganglia following peripheral nerve injury in animal models of neuropathic pain, suggesting that peripheral nerve injury may increase the number of calcium channels in the sensory presynaptic terminal. Indeed, evidence has been presented that the α2δ protein may be involved in the trafficking of calcium channel complexes into the membrane and that pregabalin or gabapentin may act by blocking this increase. This raises the interesting possibility that future therapeutic approaches based on targeting the mechanisms regulating trafficking of ion channels could be developed.

More recently it has been suggested that increased synaptogenesis occurring in the spinal cord following peripheral nerve injury may involve the binding of thrombospondin to α2δ-1 and that gabapentin and pregabalin may reduce central hypersensitivity by blocking this interaction. However, it is not clear whether active synaptogenesis or increased synaptic turnover is occurring in pain pathways in patients with stable neuropathic pain at presentation, and in whom pregabalin is therapeutically effective. Further work is therefore necessary to fully explore the significance of the thrombospondin pathway in driving pain conditions and its potential as a novel therapeutic approach for chronic pain. A recent study involving biochemical and immunocytochemical approaches suggests that the α2δ subunit may be anchored on the outside of the plasma membrane. This provides both a challenge and an opportunity to further explore the potential interactions of the α2δ subunit with the pore-forming complex of calcium channels and the consequences of pregabalin binding and may lead to the design of improved pain therapeutics acting through this mechanism.

KCNS1 (Kv9.1 Potassium Channel) [17]

Kv channels are tetramers of α- and β-subunits. In rats with peripheral nerve injury-induced neuropathic pain, KCNS1, the gene encoding the Kv9.1 α-subunit was identified by gene expression profiling as a putative pain gene. This is of interest as Kv9.1 is constitutively expressed in sensory neurons and it suppresses currents mediated by the Kv2 and Kv3 α-subunit families despite it not forming functional homomeric channels itself. The validity of KCNS1 as a 'pain gene' in humans was assessed by a genetic association study in five independent cohorts of patients with a range of clinical pain conditions as well as a group of healthy subjects administered standardized acute noxious nociceptive stimuli in a laboratory setting. In five of the six cohorts, the 'valine risk allele' of the non-synonymous SNP, rs734784 (I489V) in KCNS1 was associated with higher pain severity ratings; two copies of this allele conferred the highest risk, one copy an intermediate risk and none the least risk.

Ionotropic ATP-Gated Receptors [17]
P2RX7 (P2X Purinoceptor 7)

The P2X7 receptor is a member of the ionotropic ATP-gated receptor family. It is implicated in the etiology of chronic pain as its genetic deletion in mice reduces pain sensitivity and P2X7 receptor antagonists produce pain relief in rodent models of chronic inflammatory and neuropathic pain. P2X7 receptor function is transduced via its cation channel or by formation of non-selective pores that allow passage of molecules up to 900 Da in mass. The highly polymorphic P2RX7 gene (12q24.31 chromosomal region) spans 53 kb and has 13 exons and SNPs in this gene appear to affect chronic pain sensitivity. Genome-wide linkage analyses in multiple strains of mice with peripheral nerve injury-induced neuropathic pain showed that strains expressing the non-synonymous P451L SNP (rs48804829) in P2rx7 had impaired P2X7 receptor pore formation and reduced pain behavior compared with strains carrying the pore-forming Pro451 P2rx7 allele. In cohorts of patients with post-mastectomy or osteoarthritis pain, individuals with the hypo functional His270 (rs7958311) allele of P2RX7 had significantly lower pain intensity scores.

Transient Receptor Potential Channels [16]

There has been significant scientific interest and industry investment in recent years to under-stand the function of the broad family of nonspecific cation TRPV channels in transduction and transmission mechanisms. The first to be described was TRPV1, and the belief that it acts as an integrator of a variety of sensitization processes in the periphery has driven significant focus in attempts to identify molecules that inactivate the channel.

It is now some years since the emergence of capsazepine as the first TRPV1 antagonist, but despite significant investment, there are no definitive clinical studies demonstrating the effectiveness and safety of compounds that block or inactivate this channel. It is clear that one major stumbling block has been the effects of TRPV1 blockers on core body temperature. Thus, in one study, the Amgen compound AMG 517 administered following third molar extractions resulted in significant hyperthermia, with maximal body temperature exceeding 40°C. Much remains to be understood about the role of the channel in this physiological phenomenon, but preclinical data suggest that therapeutic strategies based on exclusion of compounds from the CNS may not be sufficient, since some of the actions on thermo-regulation reside in the periphery, and it is likely that some of the analgesic effects may be mediated by actions at spinal nociceptive synapses. The identification of compounds that pharmacologically distinguish between the analgesic and hyperthermic effects of TRPV1 antagonism will be required to explore fully the therapeutic potential of this channel for the treatment of pain. Indeed, TRPV1 antagonists (e.g., AMG8562) have recently been identified that are reported to have no effect on body temperature.

An alternative approach to exploit the mechanism and avoid side effects associated with systemic exposure has been to develop topical preparations. In order to avoid the acute irritation, capsaicin (8%) is administered following application of topical lidocaine and is reported to be well tolerated following repeated administration. It is interesting to note that the mechanism of action may involve both the desensitization of the peripheral nociceptor

endings and a decrease in epidermal fiber density. Other TRP channels, especially the non-desensitizing TRPV3, have received interest for their therapeutic potential, and Glenmark's TRPV3 agonist GRC 15300 is the first molecule to enter clinical trials. Earlier preclinical interest in TRPA1 was driven by studies in mutant mice suggesting a role for the channel in mechano-transduction and potentially noxious cold or cold allodynia, and it seems that some of these actions may be mediated via central mechanisms. It has been suggested that this channel may be a key mediator in specific inflammatory pathways such as those involving phospholipase C. More recently, a rare human gain-of-function mutation has been identified that results in an increase in channel function at nor-mal membrane potential and is associated with an episodic pain syndrome characterized by exaggerated hypersensitivity.

Mechanisms Based on Activated Microglia [17]

In recent years, there has been much interest in the potential role of non-neuronal cells in the pathophysiology of chronic pain. These include microglia, astrocytes, and oligodendrocytes, and consider-able efforts have been made to understand the molecular basis of their interaction with neuronal pain processing, especially at the level of the spinal cord. A number of excellent reviews of the experimental evidence gathered from animal models of chronic pain, especially those involving nerve damage, have been published. The studies recognize that the pathophysiology of neuropathic pain includes not only increased and chronic neurotransmitter activation of the neuronal pain pathway, but also activation of glial cells, altering their status in such a way that leads to the release of chemokines, cytokines, protease enzymes, and trophic factors, which in turn alter the excitability of the neuronal elements in the pathway. Intriguingly, evidence has been published indicating that opiates may also activate these non-neuronal elements and that this may reduce their therapeutic benefit via mediation of tolerance and respiratory depression [17].

It has been suggested that one of the consequences of glial activation is the down-regulation of the K^+Cl^- transporter KCC2 mediated by the release of BDNF, which results in the erosion of the chloride gradient across membranes of postsynaptic cells. Thus, inhibitory mechanisms that rely on the opening of chloride channels would be reversed or more likely reduced by glial activation. If this phenomenon occurs in patients, it would provide a rationale for a therapeutic approach based on restoration of KCC2 function, a fascinating if challenging endeavor.

Despite considerable research into the role of activated glia in the development of hypersensitive states in animal models, there remains little known of the temporal, anatomical, cytological, and pathophysiological role of these phenomena and their relation to the development and progression of pain symptoms in patients. Some insight may be gained by the application of imaging techniques such as the use of PET ligands at the peripheral benzodiazepine receptor to studies of the temporal pattern of "activation" in patients, but the true therapeutic opportunities offered by this phenomenon can only be realized by well-designed clinical trials coupled to validated biomarkers in patients. Two such examples of pioneering studies in this area involve the compounds ibudilast and propentofylline. Propentofylline attenuates pain behaviors in rodent models of neuropathic pain and has been

shown to modulate inhibitory tone following spinal injury by reducing glial activation via alterations in glutamate promoter activation.

Ibudilast reduces the release of pro inflammatory factors such as cytokines from activated microglia in culture and reduces pain responses in experimental animals. Both ibudilast and propentofylline have been entered into clinical trials to evaluate their therapeutic potential.

p38 MAP kinase is thought to be a key mediator of glial activation. In neuropathic conditions, fractalkine, released from neurons, activates the receptor CX3CR1 on microglia, and these results in phosphorylation of p38 and microglial activation. At the time of writing, participants are being recruited for a phase II study to evaluate a p38 inhibitor in patients experiencing neuropathic pain following nerve trauma.

Cannabinoids [17]

Cannabis has long been thought to bring benefit to patients experiencing chronic pain, but a recent review of randomized controlled trials concluded that the evidence indicated that the efficacy and tolerability of cannabinoids remained questionable and that they should be used as adjunctive agents where appropriate.

Sativex is a cannabinoid approved in Canada as an adjunctive analgesic treatment in patients with opiate-resistant cancer pain and for the relief of neuropathic pain in multiple sclerosis and is reported to provide statistically significant pain relief and improved sleep when given in addition to existing medication to patients with neuropathic pain or rheumatoid arthritis. Its use in pain management has been reviewed recently. The objective in maximizing the medicinal value of cannabinoids for pain has been to optimize the analgesic benefits while minimizing the unwanted central side effects. Two cannabinoid receptors have been cloned (CB1 and CB2) and a number of proposed endo-cannabinoid ligands identified. These include anandamide (AEA) and 2-arachidonylglycerol (2-AG). The enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) are the primary catabolic enzymes of AEA and 2-AG, respectively, and are considered as key in the regulation of the functional availability of these endogenous ligands. One therapeutic rationale is based on the possibility that endocannabinoids may provide an important component of the endogenous control of pain transmission and eventually perception, and that increasing their availability by specifically blocking the catabolizing enzymes may result in analgesia with minimal CNS side effects.

Indeed, it has been shown in experimental animals that blockade of FAAH reduces pain responses without substantially affecting motility or cognition. Recently, an FAAH inhibitor with high selectivity that covalently inactivates the enzyme by carbamylation of the serine nucleophile has been identified.

The compound completely inhibits FAAH activity and results in significantly elevated brain AEA levels. An FAAH inhibitor is currently in phase II development for osteoarthritis and will also be evaluated in other conditions where cannabinoids have been shown to bring some pain relief.

Summary and Conclusion

Aristotle called pain the "passion of the soul." While our notions of pain may not be quite as romantic as Aristotle's, it is important for us to recognize the constructive functions of pain. Pain is the body's mechanism of self-preservation. It tells you when your finger is touching a hot pan or when a fall has resulted in an injury that requires your attention. In this way, pain acts as a warning sign to alert you when damage to your body is occurring or may occur. In fact, the inability to experience pain is a dangerous condition because injury can occur and go unnoticed. For example, one common complication of diabetes is the loss of sensation in the feet. Because of this, people living with diabetes are cautioned to check their feet daily so that injuries are not missed. Because they lack a pain sensation, diabetic might miss being alerted to an injury.

It has been agreed generally by pain experts, that pain is subjective and individual. As Atkinsanya (1985) states; "Pain is a totally subjective experience." Merskey (1979) echoes this by saying that pain is always subjective. Steinbach (1968) believes that pain is a personal, private sensation of hurt.

According to Champagne and Weisse (1994), pain is now recognized as a complex experience with at least four main components. These are nociception, sensation, suffering or distress and behavior.

NSAIDs have a useful role in pain management. In patients for whom they provide sufficient analgesia, NSAIDs possess several advantages, including widespread availability, ease of administration through oral formulation, acceptance by patients and families, and low relative cost. However, potentially serious adverse effects of NSAIDs require that they be not be administered to patients at high risk for their various toxicities and that patients be closely monitored for the possible emergence of adverse reactions.

In the 19th century, Physician-scientists discovered that opium, morphine, codeine, and cocaine could be used to treat pain. These drugs led to the development of aspirin and NSAID's, to this day, the most commonly used pain relievers. Before long, anesthesia both general and regional was refined and applied during surgery.

All these drugs have side effects and opioids can cause addiction and many other problems like polymorphism in enzymes metabolizing these drugs, from here there is a need for a solution.

There are two suggested solutions:

1. Reformulation of opioids to reduce abuse and misuse of opioids.
2. a new novel analgesics, the purpose from these new drugs is to treat pain without serious side effects.

Now there is a better understanding of genetic risk factors for chronic pain. Channelopathies have provided a novel model for understanding pain pathophysiology; patients with excessive gene expression have exaggerated pain, and those with a deficit of the gene have congenital insensitivity to pain. New treatments have been designed around these discoveries.

From here came the idea of new novel analgesics like Na^+ channel blockers to treat IEM and other types of neuropathic pain, these drugs have low side effects compared to other analgesics.

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Chapter 4

Lipid Lowering Medications – Uses, Side Effects, Pharmacokinetic Properties and Approaches to Improve Bioavailability

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Abstract

Cardiovascular diseases (CVD) are common and very well-known diseases that affect a large number of people. One of the common leading causes of CVD is a high level of lipids which eventually leads to atherosclerosis and CVD. Various types of medications having different mechanisms of action were introduced to control CVD. Among the frequently used drugs is statins. Statins have a very intense effect on lowering lipids, yet they are associated with a variety of side effects. Moreover, statins have low bioavailability, similarly to other lipid lowering medications. Therefore, several attempts were made to enhance their bioavailability. This chapter discusses a number of drugs used to lower lipid levels in the blood, their adverse effects and methods to improve their bioavailability.

Keywords: Lipid lowering medications, statins, bioavailability, fenofibrate, solid dispersion, solubility enhancement

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Abbreviations

CVD	Cardiovascular disease
CHD	Coronary heart disease
AMI	Acute myocardial infarction
GIT	Gastrointestinal tract
LDL	Low density lipoprotein
HDL	High density lipoprotein
VLDL	Very low density lipoprotein
IDL	Intermediate density lipoprotein
TG	Triglycerides
NCEP	National Cholesterol Education Panel's
ATP III	Adult Treatment Program-3
HMG- COA	3-hydroxy-3-methyl-glutaryl-CoA
SREBP	Sterol regulatory element binding protein
CYP450	Cytochrome 450
OATP	Organic anion-transporting polypeptide
ABCA7	ATP-binding cassette transporter A7
PK	Pharmacokinetic
FPP	Farnesylpyrophosphate
GGPP	Geranyl-geranylpyrophosphate
CK	Creatine kinase
SNP	Single nucleotide polymorphism
AEs	Adverse effects
EFSA	European Food Safety Authority
ACC	American College of Cardiology
AHA	American Heart Association
NHLBI	National Heart, Lung, and Blood Institute;
ULN	Upper limit of normal
RCT	Randomized clinical trial
CoQ2	Coenzyme Q10
NA	Nicotinic acid
NM	Nicotinamide
IHN	Inositol hexanicotinate
SIM	Simvastatin
SIMA	Simvastatin β-hydroxy acid
ATO	Atorvastatin
BAR	Bile acid resins
IR	Immediate-release
SR	Sustained-release
PUD	Peptic ulcer disease
PPAR-α	Peroxisome proliferator-activated receptor-alpha
LPL	Lipoprotein lipase
SLNs	Solid lipid nanoparticles
SD	Solid Dispersions

HPMC	Hydroxypropyl methylcellulose
CD	Cyclodextrin
PEG	Polyethylene glycol
SAS	Supercritical anti-solvent
PVP	Polyvinylpyrrolidone
MCF	Mesocellular foam
Tgs	Glass transition temperatures
PVP	Polyvinylpyrrolidone
SMEDDS	Self-microemulsifying drug delivery system
GMO	Glyceryl monooleate
NLC	Nanostructured lipid carrier
LS	Liquisolid system
BCS	Biopharmaceutics Classification System
DSS	Dioctyl sodium sulphosuccinate
LBG	Locust bean gum
ODT	Oral disintegration tablet
ASD	Amorphous solid dispersion
DSC	Differential scanning calorimetry
SPC	Soybean phosphotidylcholine
SDC	Sodium deoxycholate
EE	Entrapment efficacy
FT-IR	Fourier transforms infrared spectroscopy

Introduction

Elevated levels of blood lipids are well documented as risk factors for cardiovascular disease (CVD), and it is one of the main causes of death worldwide. The incidence of CVD is correlated with elevated levels of blood lipids low-density lipoprotein (LDL) cholesterol, triglycerides (TG) and with low level of high-density lipoprotein (HDL) cholesterol. This disturbance in lipoprotein levels is the most firmly established and best understood risk factor for atherosclerosis.

Hyperlipidemia is defined as a heterogeneous group of disorders whose characteristic expression is elevated fasting total cholesterol and TG or both. Each variety of familial hyperlipidemia can be due to the action of a single gene (monogenic inheritance) or can reflect the interaction of several genes at many different loci (polygenic inheritance). It can be due merely to hereditary factors, but acquired condition is the most common. However, in some situations where neither hereditary nor environmental factors can be implicated, the condition is called sporadic hyperlipidemia [1, 2].

According to data from surveys, hyperlipidemia ranked the second place out of 10 as one of the most common chronic diseases. Therefore, physicians must be able to discriminate between different categories of dyslipidemia and be able to prescribe the best drug to treat each category efficiently. The currently used classification system and treatment plans for hyperlipidemia are based on the National Cholesterol Education Panel's (NCEP) Adult Treatment Program-3 (ATP-III) guidelines (Table 1) [1]. Because lipids are transported in

lipoprotein particles due to their insolubility in plasma, the classifications of hyperlipidemia are also based on abnormalities of lipoproteins (Table 2) [1].

Table 1. Classification of hyperlipidemias as defined by the NCEP ATP 3. All concentrations are expressed as mg/dL

LDL Cholesterol	**Description**
<100	Optimal
100- 129	Near or above optimal
130- 159	Borderline high
160- 189	High
≥190	Very high
Total Cholesterol	Description
<200	Desirable
200- 239	Borderline high
≤ 240	High
HDL Cholesterol	Description
<40	Low
≥ 60	High
Triglycerides	Description
<150	Normal
150- 199	Borderline high
200- 499	High
≥500	Very high

Table 2. Classes of Apo lipoproteins

Lipoprotein class	**Definition**
Chylomicrons	TG rich carrier of dietary fats
VLDL	TG rich carrier of hepatic synthesized TG
IDL & LDL	Cholesterol rich remnant particles derived from lipolysis of TG in VLDL
HDL	Cholesterol rich particles that transport cholesterol to liver for disposal or recycling

Goals of Treatment

Lowering low density lipoprotein (LDL) or cholesterol levels reduces rates of coronary heart disease (CHD) and ischemic stroke, which is considered as the main goal to be achieved. Generally, the first step in reducing cholesterol levels is life style modification, changing diet, weight reduction and increased exercise which are known to be effective. However, results of several studies conducted on patients who followed life style modifications, showed that it will be wiser to achieve lipid lowering goals by initiating medications sooner rather than later and once the goals are achieved, the need for medication can be reevaluated [1, 3].

Medications of Hyperlipidemia

After trying dietary and lifestyle modification, statins are first-line medications for lipid-lowering. They can be used alone or in combination with different types of lipid-lowering medications such as ezetimibe, niacin, bile acid sequestrates fibrates and omega-3 fatty acids. According to numerous studies, it was established that for most patients, statins are the drug of choice especially for lowering LDL. On the other hand, other classes of medications can be used, such as ezetimibe, fibrates, niacin and bile acid sequestrates [1, 3].

Statins

Statins are selective, competitive and potent inhibitors of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3- methylglutaryl coenzyme A to mevalonate, a precursor of de novo cholesterol. Lovastatin was the first statin agent which was approved in 1987. Since 1987, statins are heavily prescribed for cholesterol lowering in the primary and secondary prevention of cardiovascular disease. Statins were initially identified as secondary metabolites of fungi, ML-236B, which was isolated as a metabolite from Penicillium citrinum, and was the first natural inhibitors of HMG-CoA reductase [4-7]. Statin's pharmacological action is based on decreasing the level of cholesterol synthesis. In addition, they up regulate the LDL-C-receptor gene through the sterol regulatory element binding protein (SREBP) system that senses cellular cholesterol levels, causing a marked LDL-C reduction (20%–55%), moderate reduction of triglycerides (8%–30%) and producing minor increases in HDL-C (2%–10%) [7-13]. Statins also reduce levels of atherogenic lipoproteins by inhibiting hepatic synthesis of Apo lipoprotein B100 and reducing the synthesis and secretion of triglyceride-rich lipoproteins [14, 15]. Among the statins currently available are rosuvastatin which is ranked the most effective agent at lowering LDL-C, (63% with a daily dose of 40 mg), followed by atorvastatin, simvastatin and pravastatin [11,16, 17].

Pharmacokinetic and Pharmacodynamic Properties

Despite sharing the same mechanism of action, statins differ from each other in their chemical structures, pharmacokinetic profiles and lipid-modifying efficacy. Statins water solubility is governed by their chemical structures, which in turn impacts their absorption, distribution, metabolism and excretion. Lovastatin, pravastatin and simvastatin are fungal metabolites derivatives, and have elimination half-lives of 1–3 hours. Atorvastatin, fluvastatin and rosuvastatin are fully synthetic compounds, with elimination half-lives ranging from 1-19 hours. Atorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin are relatively lipophilic compounds, and are more vulnerable to metabolism by the CP450 system, whereas pravastatin and rosuvastatin are relatively hydrophilic and not significantly metabolized by CP450 enzymes [14].

Statins are hepatoselective, and hydrophobic statins pass by passive diffusion through hepatocellular and non-hepatocellular membranes, whereas hydrophilic statins are passed by extensive carrier-mediated uptake.

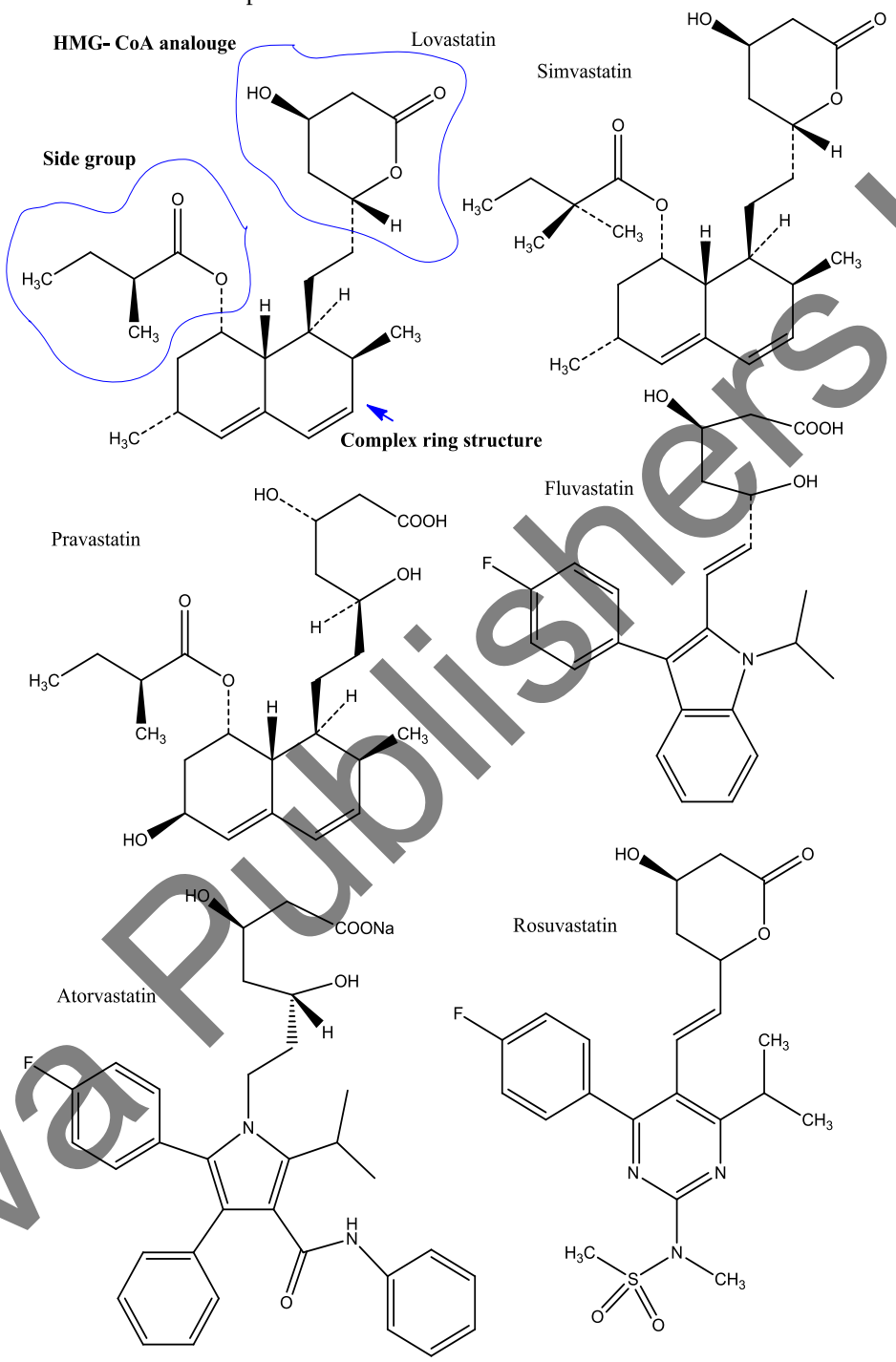


Figure 1. Chemical structures of Lovastatin, Simvastatin, Pravastatin, Fluvastatin, Atorvastatin and Rosuvastatin.

This indicates that hydrophilic statins are more hepatoselective, with reduced potential for uptake by peripheral cells. Statins are absorbed rapidly after an administration, reaching peak plasma concentration within 4 hours, and have the liver as their target organ. Unfortunately, they have low bioavailability mainly due to the extensive first pass effect and/or poor solubility, ranging from 5% for lovastatin to 60% for simvastatin [4, 14, 18, 19].

The chemical structures of the different statins are shown in Figure 1. In general, statins share a common chemical structure that can be divided into three parts: HMG-CoA substrate analogue, a complex hydrophobic ring structure that is covalently linked to the substrate analogue and is involved in binding of the statin to the reductase enzyme and functional groups on the rings that determine the solubility properties of the drug and hence its pharmacokinetic properties [4, 14, 18].

Statins bind to the active site of the reductase enzyme, thus sterically thwarting the natural substrate from binding. Moreover, the substrate-binding pocket of the enzyme undergoes a rearrangement, permitting the accommodation of the rigid, hydrophobic ring structures of the statins. Statins also exhibit subtle differences in their modes of binding as was revealed by comparing the six statin–enzyme complexes. For instance, atorvastatin and rosuvastatin enzyme complexes demonstrated an additional hydrogen bond along with a polar interaction unique to rosuvastatin, signifying that among all statins rosuvastatin has the most binding interactions with HMG-CoA reductase. The full significance of these differences is yet to be clarified [14].

PK Properties

Lovastatin and simvastatin are lactone prodrugs, and are enzymatically in vivo hydrolyzed to their active hydroxy acid form [14, 20]. The other statins are hydroxy acids and are active in this form [14,21, 22]. Some fundamental pharmacokinetic properties of the distinct statins are summarized in Table 3.

All statins are rapidly absorbed after administration, reaching peak plasma concentration (T_{max}) within 4 hours. The rate and extent of absorption of atorvastatin is affected by time-of-day administration, whereas for rosuvastatin, is unaffected; still, the lipid lowering effects for both agents are similar whether administered in the morning or evening [23-25]. This is consistent with their long half-lives in comparison with the other statins (half-lives of 3 hours or less), which are best to be administered in the evening, when the rate of endogenous cholesterol synthesis is the highest [14, 24]. The presently available statins possess a low systemic bioavailability due to extensive first-pass extraction [24, 26, 27].

Food consumption has a variable effect on statin absorption. For example, absorption of lovastatin is highly enhanced if taken with food, while the bioavailability of atorvastatin, fluvastatin and pravastatin is decreased. Simvastatin and rosuvastatin are not affected by food [14, 28-30].

Statins are predominantly metabolized by the CYP450 enzymes. The CYP3A4 isoenzyme metabolizes the greatest number of statins including lovastatin, simvastatin and atorvastatin, and fraction of their activity is linked to their active metabolites 2-hydroxy- and 4-hydroxy- atorvastatin acid for atorvastatin, and β-hydroxy acid and its 6-hydroxy, 6-hydroxymethyl and 6-exomethylene derivatives for simvastatin.

Table 3. Pharmacokinetic properties of statins

	Atorvas-tatin	**Cerivastatin**	**Fluvastatin**	**Lovastatin**	**Pravastatin**	**Simvastatin**	**Rosuvastatin**
Optimal time of dosing	Anytime of the day	Evening	Bedtime	With meal morning & evening	Bedtime	Evening	Anytime of the day
Bioavailability (%)	12	60	24	5	18	5	20
Solubility	lipophilic	lipophilic	lipophilic	lipophilic	hydrophilic	lipophilic	hydrophilic
Food effect on bioavailability	decreased	No effect	Decreased	increased	Decreased	No effect	No effect
Protein binding (%)	98	>99	>98	>95	≈50	95- 98	90
Active metabolites	✓	✓	×	✓	×	✓	minor
Elimination t 0.5 (h)	14	2.5	1.2	3	1.8	2	19
CYP450 metabolism & isoenzyme	3A4	3A4, 2C9	2C9	3A4	×	3A4	limited
Renal excretion	<5	30	6	10	20	13	10

On the other hand, fluvastatin is mainly metabolized by the CYP2C9 isoenzyme. Rosuvastatin undergoes only minimal metabolism in vivo by CYP2C9 and to a lesser extent by CYP2C19 [31-36]. In other words, lipophilic statins are more prone to oxidative metabolism by the CYP450 and as a result, these lipophilic statins carry a greater risk for muscle toxicity due to the risk of drug interaction with drugs that have the potential to inhibit the CYP450. [14, 37].

Statins are eliminated via the bile after metabolism by the liver, therefore, caution is recommended when treating patient with hepatic insufficiency. Pravastatin is eliminated by both the kidney and liver, mostly unchanged, and it's PK properties is altered in patients with hepatic dysfunction, whereas for rosuvastatin, the PK properties are not altered in patients with mild to moderate hepatic injury [28, 38, 39]. Rosuvastatin is eliminated mainly by a transporter-mediated excretion mechanism in the liver. It has a high affinity for the organic anion transporter protein 1B1 (OATP1B1, also known as OATP-C/OATP2, SLC01B1, SLC21A6), which is mostly expressed by hepatocytes [35, 40].

Recently, it was shown that statins exert extra-hepatic effects mediated by their ability to inhibit the synthesis of other important isoprenoid intermediates of the cholesterol biosynthetic pathway, such as Farnesylpyrophosphate (FPP) and Geranyl-geranylpyrophosphate (GGPP), found downstream from L-mevalonic acid. These intermediates were found to serve as vital lipid attachments for the post-translational modification of proteins, including nuclear lamins, Ras, Rho, Rac and Rap. This is referred to as the pleiotropic effects of statins, which include improving the endothelial function, augmenting the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response (Figure 2). In particular, inhibition of Rho and its downstream target, Rho-associated coiled-coil containing protein kinase (ROCK), has arisen as the standard mechanisms underlying the pleiotropic effects of statins [4, 41].

Interestingly, statins have also been shown to be able to interact with the leukocyte function-associated antigen-1 (LFA-1), which is independent of mevalonate synthesis. LFA – 1 belongs to the integrin family and exhibits an important role in leukocyte trafficking and T-cell activation. Lovastatin binds to an allosteric site within the beta2-integrin LFA-1 and inhibits the LFA-1 intercellular adhesion molecule-1 interaction [4, 42].

Furthermore, one study demonstrates that pravastatin, rosuvastatin and simvastatin enhance the phagocytic reaction, in vitro and in vivo, through the sterol regulatory element binding protein 2, ATP-binding cassette transporter A7 (SREBP-ABCA7) pathway, as cellular cholesterol was reduced and expressions of the cholesterol-related genes were modulated. ABCA7 is a key protein for HDL biogenesis and a major regulator for phagocytosis. The gene expression of the ABCA7 is regulated by cellular sterol via the SREBP system and is stabilized by helical apo lipoproteins, resulting in an increase of phagocytosis. These findings provide a molecular basis for host-defense system boosting by statins, indicating that one of their pleiotropic effects is achieved through their reaction with a primary target [12, 43, 44].

Despite the wide use of statins, they have side effects. Cholesterol itself is not the only final product of the pathway of the enzyme HMG-CoA reductase, but it is also an intermediate to additional products such as sex steroids, corticosteroids, bile acids and vitamin D; several of which have been shown to be affected by statin administration [45]. Adverse events (AEs) are dose dependent, and risk might increase by drugs that increase statin potency, mainly by inhibition of the CP3A4 system. An array of additional risk factors for statin AEs are those that amplify mitochondrial or metabolic vulnerability, such as metabolic syndrome factors, thyroid disease, and genetic mutations linked to mitochondrial dysfunction. Converging evidence supports a mitochondrial foundation for muscle AEs associated with statins, and suggests that mitochondrial dysfunction may also be the underlying cause of non-muscle statin AEs. Moreover, different studies and random clinical trials (RCTs) conducted on statins and patients receiving statins revealed that statins are linked to other different AEs such as cognitive loss, neuropathy, pancreatic, hepatic and sexual dysfunction. [45].

Muscle Related Adverse Effects

Most risk factors associated with statins can be viewed as sharing one or both of these two primary mediating pathways: increased statin exposure or mitochondrial derangement or vulnerability [45].

The most highlighted side effects of statins are known to be muscle AEs, referred to as drug- induced or toxic myopathy. This drug-induced or toxic myopathy stands for the acute or sub acute expression of myopathy symptoms as muscle weakness, myalgia, and elevation in creatine kinase (CK), or myoglobinuria, symptoms that are seen in patients with no history of muscle disease but exposed to certain drugs. The best documented and most commonly reported muscle AEs of statins are muscle pain, fatigue and weakness as well as rhabdomyolysis (Table 4). Interestingly, a potential for opposing effects in muscle and in other organs can be identified.

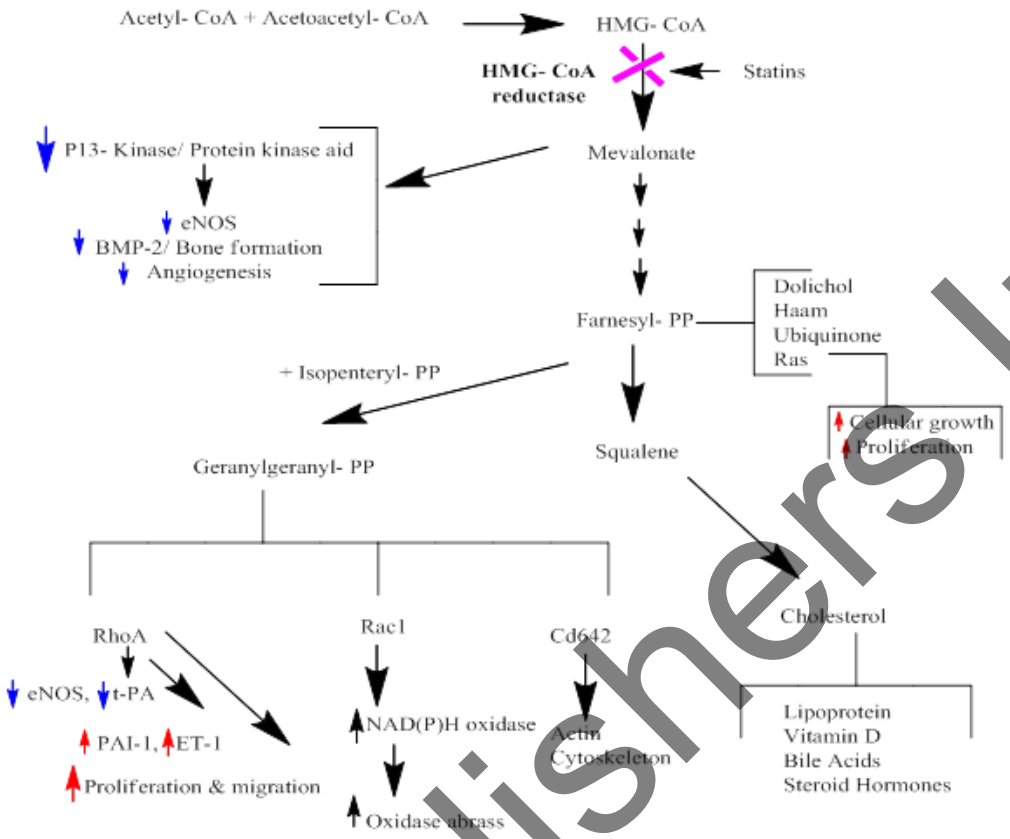


Figure 2. Biologic actions of isoprenoids.

BMP-2 is bone morphogenetic protein–2, CoA is coenzyme A, eNOS is endothelial nitric oxide synthase, ET-1 is endothelin-1, HMG-CoA is 3-hydroxy-3- methylglutaryl–CoA reductase inhibitor, PAI-1is plasminogen activator inhibitor–1, PP is pyrophosphate, t-PA is tissue-type plasminogen activator.

This is suggested by evidence supporting the assumption that antioxidant effects of statins inspire many essential statin benefits such as benefits to flow, oxygen delivery and inflammation, which may contribute to improvement in walking distance in patients received statins [45, 46]. Muscle effects arising from administration of statins do not uniformly resolve fully with statin discontinuation.

Table 4. Various definitions for statin related muscle disease

Clinical term	ACC/ AHA/ NLHBI	FDA
Myopathy	Any disease of the muscle	creatine kinase ≥ 10 times upper limit of normal
Myalgia	Muscle ache/ weakness in absence of creatine kinase increase	Not defined
Myositis	Muscle symptoms with elevated creatine kinase	Not defined
Rhabdomyolysis	Muscle symptoms with significant creatine kinase elevation (usually> 10 times upper limit of normal) and creatinine elevation (with brown urine)	creatine kinase > 50 times upper limit of normal and evidence of organ damage (e.g., renal failure)

Statins also lead to dose-dependent reductions in coenzyme Q10, a key mitochondrial antioxidant and electron transport carrier that helps bypass existing mitochondrial respiratory chain defects, and this is associated with reduction in cell energy, encouragement of oxidation, apoptosis and unmask silent mitochondrial defects [45, 47-49]. Additionally, the mevalonate pathway inhibited by statins is responsible for producing heme-A, which has its own central involvement in mitochondrial electron transport [45, 50]. Studies, in patients with recurrent muscle pain, showed a partially reversible mitochondrial myopathy. Statins elevate the respiratory exchange ratio even in asymptomatic patients, while patients who have been symptomatic with statins showed an elevated off-statin respiratory exchange ratio. This alteration of cell respiratory function may represent a cause and/or a consequence of statins [45, 51].

Rhabdomyolysis is a fulminant and acute necrotizing myopathy that can cause severe pain, muscle swelling and weakness, and elevated serum CK as high as 2000 times the upper limit of normal, and often accompanied with myoglobinuria which can cause acute renal failure and death. It is among the best documented and feared complications of statins.

One of the best known example is cerivastatin which was withdrawn from the US market in August 2001, only 3 years after its approval, due to high reported incidence of rhabdomyolysis in comparison to other statins in market [45, 52].

Several studies support a dose relation for statin AEs despite the existence of dose independent AEs. However, the FDA has stated that all statins should be prescribed at the lowest possible dose that achieves the goals of therapy [45, 53].

Interestingly, drug induced myopathy can be distinguished from other types of myopathies. Toxic myopathies can occur due to various reasons, mechanisms and types of muscle injury and they are typically categorized according to the types of injury to the muscle fiber or muscle organelle (Table 5).

Table 5. Types of drugs- induced myopathies

Type of myopathy	**Histologic findings**	**Drugs involved**
Necrotizing myopathy	Scattered necrotic fibers invaded by macrophages; absence of widespread MHC-1 up regulation	HMG-CoA reductase inhibitors (statins), fibrates, alcohol
Inflammatory myopathy	Non-necrotic muscle cells surrounded and invaded by T lymphocytes and macrophages; MHC-1–expressing fibers	Statins, D-penicillamine, interferon-α, procainamide
Mitochondrial myopathy	"Ragged red" or "ragged blue" fibers, COX-negative fibers, increased lipid accumulation	Zidovudine, germanium
Antimicrotubular myopathy	Lysosome accumulation, autophagic vacuoles	Colchicine, vincristine
Lysosomal storage myopathy	Storage of myeloid structures within lysosomes in the form of autophagic vacuoles	Chloroquine, hydroxy chloroquine, quinacrine, perhexiline, amiodarone
Myofibrillar myopathy	Disruption of Z discs, breakdown of myofilaments, accumulation of myofibrillar proteins	Emetine, ipecac
Type II muscle fiber atrophy	Atrophy of type II fibers	Corticosteroids

Drug induced myopathies are most commonly result in necrosis, vacuolar changes, or mitochondrial dysfunction. Necrotizing myopathies as those induced by statins lead to necrosis of muscle fibers and secondarily involve inflammatory cells such as macrophages. Nevertheless, they do not demonstrate widespread MHC-1 expression or the primary inflammation by aggressive T lymphocytes [46, 53, 54].

Genetics Association

Several studies hypothesized that a strong associations exist between the myopathy accompanying high-dose statin regimens and genetic variants, especially those affecting blood statin levels. Reduced-function single nucleotide polymorphisms (SNPs) with intron 11 of the SLCO1B1 gene on chromosome 12 were shown to be linked to statin myopathy. In the liver, statins enter hepatocytes via organic anion transport polypeptide (OATP) 1B1, that is coded by the SLCO1B1 gene. This SNP may illuminate up to 60% of cases of simvastatin associated myopathy. This polymorph is biologically creditable since SLCO1B1 encodes the enzyme AOTB1B1 that is responsible for liver transportation of statins [53]. Extension study demonstrated that in addition to the association of reduced allele function for this gene and CK elevation, there was also an association between the SLCO1B1*5 allele and myalgia without CK elevation [53, 55-57]. This SNP wasn't able to explain statin myopathy associated with the all statin drugs. For instance, the frequency of myalgia in patients taking atorvastatin and carrying this SNP was high and yet it didn't reach a statistical significance. Additionally, pravastatin metabolites didn't reach a significant high level in patients with homozygous SLCO1B1 genotype. It is most likely now to look for other candidate gene SNPs that may have a contribution to genetic predisposition to statin myopathy [53, 58].

Another multisite study recognized three genes as markers for myalgia in patients with statin-associated myalgia. They are CoQ2 that is responsible for pathways related to CoQ10 biosynthesis, ATP2B1, responsible for calcium regulation in the body and DMPK, responsible for muscular dystonia [55, 59]. On the other hand, homozygosis in a genetic variant of the CYP3A enzyme, CYP3A5*3, would also lead to a greater degree of muscle damage [55, 60].

Non- Muscle Statin Adverse Effects

Some studies documented that other organs such as brain, liver, heart and kidney are vulnerable to mitochondrial pathology, which may be involved in a range of non-muscle statin AEs [45, 61]. Cognitive problems are ranked secondary to muscle problems as AEs among patient on statin. Brain and muscle tissue share a high mitochondrial vulnerability as both are postmitotic tissues with high metabolic demand. These organs are the most likely to be affected in mitochondrial disease. Gastrointestinal and neurological symptoms, psychiatric symptoms, sleep problems, glucose elevations and a range of other symptoms reported on statins also arise in mitochondrial dysfunction [45, 62-72]. Also asymptomatic elevation of hepatic transaminases and extremely rare cases of hepatitis were also seen [52].

Drugs Interaction

Alteration of pharmacokinetic properties whether at the level of drug absorption, distribution, metabolism, or excretion is a major concern with statin-related drug–drug interactions. Factors that are related to drug interaction and enhance statins bioavailability include: increase the gut uptake or absorption of statins, decreased hepatic blood flow limiting the amount of statin that is carried to the liver for first-pass metabolism, inhibition of renal excretion due to renal insufficiency or reduced renal blood flow, and interruption in statin metabolism [55, 73].

Several drugs have the potential to interact with the CYP3A4 system, and they tend to compete with primarily lipophilic statins, such as simvastatin and atorvastatin, on the CYP3A4's active site. Table 6 lists some of the agents that have been identified to influence statin bioavailability. Gemfibrozil is a competitive inhibitor of certain CP450 isoenzymes and uridine diphosphate glucuronyltransferase, which are both required for hepatic metabolism of certain statins. Inhibition of the oxidation and glucoronidation processes causes a reduction in statin clearance. This increases the risk of rhabdomyolysis. Likewise, drugs that inhibit OATP1B1 increase plasma statin concentrations by reducing their hepatic uptake [55, 74, 75]. Other agents that are classified as weak CYP3A4 inhibitors such as calcium channel blockers also have the potential to increase the risk of rhabdomyolysis but to a lower degree as compared with strong CYP3A4 inhibitors. In general, this interaction effect depends mainly on the specific type of statin drug and on the patient physiological status. [45].

Table 6. Agents implicated in increasing statin bioavailability and their associated mechanism of action

Agent	Mechanism of action
Azole antifungals Clarithromycin/ erythromycin Diltiazem Verapamil Antiretroviral protease inhibitors Fibric acid derivatives Amiodarone Gemfibrozil Grapefruit juice	Inhibits CYP450 3A4
Red yeast rice	Competitively inhibits HMG-COA
Cyclosporine	Inhibits organic anion- transporting polypeptide 1B1 transporter
Phenytoin Clopidogrel Sulphonamide	Interferes with CYP29 metabolism

Other important inhibitors of CYP3A are fruit juices, and among the well-known is grapefruit and perhaps pomegranate juices, and they are associated with increased risk of rhabdomyolysis [45, 76, 77]. It is well known that CYP3A pathway plays a major role in the metabolism of a large number of drugs both in the liver and intestine. Therefore,

polypharmacy may lead to competition for a common metabolic pathway, which may increase statin concentrations and its dose-related AEs [45, 78].

Due to pharmacogenomics differences such as those that affect statin hepatic uptake, clearance, and CYP pathways between individuals, the response to individual statins in terms of efficacy and tolerability may differ among patients [45, 79-81].

Statins and Elderly

Drug toxicity of statins is of special concern in people over 80 years old., The majority of whom are women, have multiple comorbid conditions, reduced renal and hepatic function, and are taking many medications. Furthermore, dehydration is one of the major risk factors for lower drug tolerance in the elderly. It can interfere with normal drug clearance via reducing the ability of the body to eliminate drugs efficiently, therefore leading to higher drug levels [55, 82].

Due to the potential adverse effects of therapy, decisions concerning treating elderly should be individualized. One study has shown that satin therapy is associated with reduction of mortality in older patients with AMI younger than 80 years old but not in those aged 80 and older [55, 83].

While men weigh more than women in general, drug doses are rarely titrated according to weight in elderly. In certain situations, this may expose weak elderly women to higher dose than their bodies can tolerate to metabolize and eliminate efficiently. On the other hand, females tend to have a higher body fat percentage, which affects volume of distribution of some drugs and can considerably increase the half-life of a variety of medications, including the more lipophilic statins [55, 84, 85].

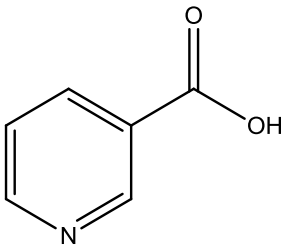
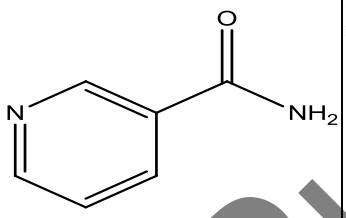
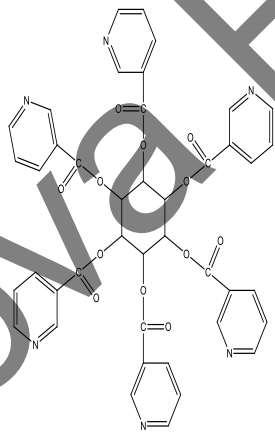
Several studies were conducted to compare the efficacy and benefits of using combination therapy vs. high-dose statin monotherapy in terms of mortality, MI, stroke, and revascularization procedures in patients requiring intensive lipid-lowering therapy. There was no benefit of combination therapy over high-dose statin monotherapy. Nevertheless, most of these studies were short and focused on surrogate markers, which limited their ability to perceive potential differences in important clinical outcomes. More intensive statin therapy is associated with a better reduction in LDL cholesterol levels and vascular events. Therefore, the appropriate comparator for combination therapies may be high-dose statin therapy [3].

Niacin (Nicotinic Acid)

Niacin, vitamin B3, nicotinic acid (NA) or nicotinamide (nicotinic acid amide), has been used as a lipid-modifying agent in high doses for 50 years. It modifies all major lipoproteins; HDL-C, LDL-C, and TGs and is one of the only cholesterol-lowering drugs to significantly reduce lipoprotein- A (LP-A). It is the most effective agent at raising HDL-C level. It is known that the risk of CHD is reduced by 2%- 3% for every 1mg/dL increase in HDL-C [86]. Niacin is available as unbound niacin, or free nicotinic acid (NA), a crystalline immediate-release (IR), sustained-release (SR), prescription as ER (Niaspan®), inositol hexanicotinate, six molecules of NA covalently bonded to one molecule of inositol; and nicotinamide, or

niacinamide, the amide form of NA, which is readily bioavailable (Table 7) [7, 87, 88]. The IR formulation is generally more effective at raising HDL-C and reducing triglycerides in comparison to the SR formulation [89]. For other compounds that are converted to NA or contain NA, NM or their releasable moieties to be referred as niacin, they have to meet certain criteria. This include the biological effects of the compound, rate of uptake and metabolism evidence interpretation, and/or the release of the chemical (apparent bioavailability) that produce similar effect to the primary forms of niacin [88].

Table 7. Different forms of supplemental niacin

Form of niacin	Biological effects	Indications/ effectiveness	Flushing effect
Nicotinic acid 	At physiological amounts, the effects of nicotinic acid and nicotinamide are Indistinguishable. Supraphysiological doses of nicotinic acid decrease total cholesterol, LDL cholesterol, and TG and increase HDL cholesterol.	Physiological amounts prevent vitamin B3 deficiency. Supraphysiological doses of nicotinic acid are indicated for dyslipidemia, atherosclerosis, and CVD	Yes. PGD2-mediated vasodilatation of small cutaneous blood vessels that result in cutaneous flush
Nicotinamide 	Precursor to nicotinamide adenine dinucleotide phosphate (NADP), which is required for ATP synthesis, oxidation-reduction reactions and ADP-ribose transfer reactions	Prevents vitamin B3 deficiency. No effect on lipid levels in individuals with dyslipidemia	None
Inositol hexanicotinate 	Research suggests inositol hexanicotinate metabolism does not result in peak free nicotinic acid levels high enough for a clinical effect on dyslipidemia. Other biological effects include reduced fibrinogen levels, vasodilation improved blood viscosity, and oxygen transport	Minimal to no effect on lipid levels in individuals with dyslipidemia. Indicated for peripheral vascular insufficiency and symptomatic relief of intermittent claudication and Raynaud's Phenomenon	None

Niacin's primary effect is achieved by the inhibition of hepatic VLDL-C synthesis and secretion which in turn reduces triglycerides (20%–50%) and LDL-C (5%–25%).

Furthermore, it is the best known agent to raise HDL-C (15%–35%), which is accomplished via slowing the catabolism of the predominant HDL-C Apo lipoprotein (Apo protein A-1) and decreasing triglycerides. On the other hand, niacin has proven to be able to transform the more atherogenic small-dense LDL-C particles into a larger, more floating LDL-C, thus, triggering a shift in the size of LDL-C [90-94].

Adverse Effects

Niacin is accompanied with a variety of AEs that are considered a major limitation for its use. Prostaglandin-mediated cutaneous flushing, the principal AE that results in discontinuation rates of 5%–50% depending on the dose and formulation, can be managed by using aspirin (325 mg) 30 minutes prior to the niacin dose or by using SR or ER formulations. Despite having less flushing, SR products are associated with hepatotoxicity, especially with doses greater than 2000 mg per day. Niacin has also been connected to metabolic effects that include slight elevation in blood glucose level. It is also competes with uric acid for renal elimination causing a mild elevation in uric acid levels. Therefore, it should be used with caution in patients susceptible to gout. Additionally, it can cause GI AEs such as nausea, abdominal pain that are more common with the SR formulation, but can be minimized with concomitant consumption of food. Yet, it is contraindicated with active peptic ulcer disease (PUD) [95, 96].

Clinical Use, Adverse Effects and Bioavailability Nicotinic Acid (NA)

NA at high intakes and ER- NA are effective antihyperlipidemic agents. They lower LDL-C (10–25%), VLDL-C and TGs (20–50%), and they also raise HDL-C (10–30%). Moreover, they have been shown to reduce mortality due to heart attacks. They also reduce lipoprotein levels by 10–30%, leading to reduction of the more atherogenic, small, dense LDL-C [96-99].

Intestinal uptakes of NA are rapid and nearly stoichiometric, and 15–30% of the plasma NA is bound to protein. Lower levels of intake (15–18 mg/day) are associated with the desired nutritional, functions related to NM-containing coenzymes, whereas the undesirable flushing effect due to vasodilation may occur when intakes exceed 50 mg/day. Importantly, the beneficial effects on serum lipid profiles occur at much higher levels of intake (500–3,000 mg/day) [88, 100].

Depending on the intake, this form of niacin has the potential to produce several different adverse effects. “Niacin flush” is an annoying effect that is a consequence of high NA intake. It leads to vasodilation, which in turn causes intensive warmth and a strong itching or burning sensation of the skin, commonly starts in the face and neck and can proceed down through the body. Some patients may also experience a rash, hypotension, and dizziness. Prostaglandin D2-mediated vasodilatation of small subcutaneous blood vessels is the triggering factor [88, 101]. Flushing occurs about 30 minutes after intake of NA, and 2–4 hours after intake of ER-NA, and it persists over only a few doses until the body develops a natural tolerance. The

daily dose is generally administered as a low dose divided in three parts which is then gradually titrated until the desired dose is reached. Flushing effect can occur at intakes as low as 50 mg/day and may occur infrequently at intakes as low as 30 mg/day, depending on the circumstances of the intake. Moreover, it is of importance to conduct tests for the liver function, uric acid, blood glucose and lipid levels as the dose is administered, and if any adverse effect occurs, the dose should be reduced [88].

Hepatotoxicity is detected most often when serum levels of certain liver enzymes are increased. Nonetheless, the severity of hepatotoxicity can range from elevated liver enzymes to acute liver failure. Despite that, intakes of up to 2–4 g/day may be used safely and effectively as an antihyperlipidemic drug under medical supervision [88, 102].

Different strategies or trails could be used to modify the flushing risk. This includes taking the medication on full stomach; dividing the dose over several hours, taking aspirin prior to NA or using ER-NA instead of NA. However, ER-NA preparations carry a greater risk of liver toxicity; the risk is twice as high with the ER-NA forms compared with the crystalline NA form [88].

Extended Release -Nicotinic Acid (ER-NA)

ER-NA and various formulations of IHN have shown to reduce or avoid the undesirable flushing effect of NA. Releasing NA from the matrix is directly related to its potential impacts on serum lipid concentrations. NA uptake from ER-NA formulations is reliant on the specific delivery matrix and is significantly slower than that of NA, yet, rapid enough to achieve effective plasma NA concentrations [88, 103]. Generally, the ER-NA forms yield lower peak serum concentrations, but these are sustained for longer periods. This form seems to carry risk of hepatotoxicity twice as the free form of NA. Accordingly, 250 mg/day has been recommended as the safe upper limit for supplemental ER-NA [88].

Inositol Hexanicotinate (IHN)

Nicotinate from IHN was concluded as a bioavailable source of niacin by the European Food Safety Authority (EFSA) Scientific Panel on Food Additives and Nutrient Sources Added to Food in 2009. Intestinal absorption of IHN varies widely, and 70% on average is absorbed into the blood stream.

Metabolism of IHN to release NA is attributed to the physiological actions of NA, depending on the rate and amount of release. The beneficial lipid-lowering effects of IHN are dependent on the uptake of IHN and the substantial succeeding release of the NA moiety from the IHN molecule {88]. Peak plasma levels of NA obtained from humans given oral doses of IHN is reached at 6–12 h, whereas after oral doses of NA the peak is achieved at 0.5–1 h. Additionally, the peak plasma levels of NA after oral doses of IHN are dramatically lower when compared with those obtained after oral doses of NA. Generally, evidence specifies that IHN produces only a slight increase in plasma NA and these changes are not sufficient to significantly alter plasma lipid profiles [104, 105].

IHN is marketed as "no-flush niacin." This is consistent with the modest NA plasma response following IHN intake. IHN has been discussed as a better tolerated and safer alternative to NA and ER-NA. However, limited evidence supports the ability of IHN to lower serum lipids and it is questionable if it could be an effective lipid control agent. One IHN clinical study involved 41 hyperlipidemic patients showed a mean reduction in total cholesterol of 8.2%. On the other hand, a published case report discusses a treatment failure using IHN titrated up to 2,000 mg/day for 6 months in a 49-year-old male with heart disease, where there was no beneficial or adverse effects after 6 months of treatment. In addition, and based on another conducted study, it was concluded that IHN preparations are not an effective treatment for dyslipidemia. Despite this, there were reports suggesting that IHN may have a beneficial effect on endothelium-dependent vasodilatation [103, 106-108].

Nicotinamide (NM)

NM is readily bioavailable. It is not adequately converted to NA to produce either the beneficial changes in plasma lipids or the undesirable flushing effect. NM is not generally documented as an effective treatment for high plasma triglyceride and cholesterol levels [88].

Bile Acid Resins (BAR)

BAR are currently used as adjunctive therapy with newer agents for additional LDL-C reduction. BAR include cholestyramine, colestipol and they both were approved in the 1970s, and colesevelam, which is available since 2000. They are non-absorbable resins with favorable safety profile [109].

BAR bind to bile acids in the intestine, interfere with enterohepatic recirculation and lead to increase fecal bile acid excretion. This in turn enhances LDL-C receptor activity leading to an increase in uptake of LDL-C from the systemic circulation, thus, reducing LDL-C levels. As a result, the liver increases its secretion of VLDL-C with a consequential increase in triglycerides and a limited effect on LDL-C levels, thus, the primary use for BAR is to lower LDL-C levels (15%–30%) [7, 110]. BAR are associated with minimal increases in HDL-C and potential increases in triglycerides among those with borderline or elevated levels. Hence, caution is to be exercised for patients with hypertriglyceridemia. Common side effects include bloating, constipation, flatulence, epigastric fullness, and nausea [111]. They also bind to many medications such as diuretics, digoxin, acetaminophen, warfarin, thus, they should be taken 1 hour before or 4 hours after colestipol or cholestyramine. Colesevelam on contrary has an advantage of being more specific for bile acids and possess less drug interaction [111, 112].

Fibrates

Fibrates include Bezafibrate, Ciprofibrate, Clofibrate, Gemfibrozil and Fenofibrate. These agents primarily affect peroxisome proliferator-activated receptor-alpha (PPAR-α) and

lipoprotein lipase (LPL). By stimulating LPL, lipolysis increases, resulting in a clearance of triglyceride-rich lipoproteins. This reduction in TG-rich lipoproteins is the primary cause of HDL-C elevation that is seen upon using fibrates. Moreover, stimulation of PPAR-α, which in turn increases the synthesis of Apo lipoprotein A, is a secondary cause. Overall, fibrates are able to reduce triglyceride up to 50% and HDL-C to10%–20%. They have a varying effect on LDL-C levels depending on the type of dyslipidemia. They are also able to improve LDL-C particle size [113, 114].

Fibrates are generally well tolerated. Adverse effects include GI complaints (nausea, abdominal pain), myalgia, increases in serum creatine levels (fenofibrate), cholelithiasis, and elevated transaminase levels [115].

Cholesterol Absorption Inhibitor (Ezetimibe)

Ezetimibe works by inhibiting the intestinal cholesterol absorption from dietary and biliary sources by approximately 50%, without affecting fat-soluble vitamins, bile acids, or triglycerides absorption. This results in approximately 20% reduction in LDL-C with minimal changes in HDL-C or triglycerides. It is usually given in combination with statin, and the overall result is an additional 12%–25% reduction in LDL-C. On the other hand, an additional potential benefit of ezetimibe is its ability to lower intestinal uptake of plant sterols; that is a possible contributor to atherosclerotic plaque. It has an excellent safety profile, low incidence of adverse effects and drug interactions [7, 116].

Ezetimibe is rapidly absorbed, extensively conjugated to its pharmacologically active glucuronide conjugate, and is eliminated slowly with evidence of significant enterohepatic recycling.

Table 8 below summarizes the drugs used, their effects and adverse effects.

Table 8. Statin alternatives

Drug	Effects	AEs
BAR Cholestyramine (4-16 g) Colestipol (5-20 g) Colesevelam (2.6-3.8 g)	LDL −15–30% HDL +3–5% TG, no change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs
Nicotinic acid Immediate release (crystalline) nicotinic acid (1.5–3 gm), extended release nicotinic acid (Niaspan®) (1–2 g), sustained release nicotinic acid (1–2 g)	LDL −5–25% HDL +15–35% TG −20–50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity
Fibric acids Gemfibrozil (600 mg BID) Fenofibrate (200 mg) Clofibrate(1000 mg BID)	LDL −5–20% (may be increased in patients with high TG) HDL +10–20% TG −20–50%	Dyspepsia Gallstones Myopathy

Table 8. (Continued)

Drug	Effects	AEs
Ezetimibe Zetia (10 mg daily) As monotherapy, often combined with a statin	LDL-C −18% HDL-C +3% TG −8%	Diarrhea Arthralgia Nasopharyngitis or Sinusitis Controversial regarding reduction of CVD events
Fatty acids Lovaza Fish Oil Plant sources	Prescription fatty acid ester indicated only for treatment of TG > 500 mg/dl to prevent pancreatitis. Plant sources of omega-3 FA have been subjected to few clinical trials with CVD endpoints	

Approaches to Improve Bioavailability of Lipid Lowering Medications

Simvastatin

Simvastatin is a potent lipid lowering agent; however, it is associated with a low oral bioavailability (5%) due to extensive hepatic first-pass metabolism by CYP3A4 and vulnerability to hydrolytic degradation in the GI tract, as acidic/alkaline condition of GI tract hydrolyzes lactone form of simvastatin to its hydroxyl acid derivative. To overcome hepatic first-pass metabolism and enhance bioavailability, drug's intestinal lymphatic transport can be exploited using lipids as drug carrier, which can enhance lymph formation and lymph flow rate. By using intestinal lymphatics to transport drugs, presystemic hepatic metabolism can be avoided, which in turn enhances bioavailability. This is achieved by using the thoracic lymph duct to transport the drug to the systemic circulation at the junction of the jugular and left subclavian vein [117, 118].

One of the lipid based drug delivery system is solid lipid nanoparticles (SLNs), which were introduced in 1991 as an alternative carrier system to old-fashioned colloidal carriers as emulsions, liposomes, polymeric micro- and nanoparticles. They combine the advantages of both colloidal lipid emulsions and particles with a solid matrix. They also offer good tolerability, lower cytotoxicity, and higher bioavailability, an increase in the drug stability and cost effectiveness. They are suitable for the incorporation of lipophilic, hydrophilic, and poorly water-soluble drugs within the lipid matrix in considerable amounts [117, 119-120].

In a study conducted by Shah et al., compritol 888 ATO was selected as a lipid carrier due to its favorable attributes of its non-polarity and low cytotoxicity, high drug entrapment efficiency (EE) due to high content of mono-, di-, and triglycerides that help in solubilizing the drug in the lipid fraction. In addition, the less-defined mixture of acylglycerol provides additional space for drug molecules to get entrapped [117].

Pharmacokinetic parameters analysis revealed that the elimination half-life of simvastatin from SLNs was 3.13 times higher than that from a suspension due to a sustained release of the drug from lipid nanoparticles that also resulted in reduced rate of absorption [117]. The AUC showed an increase in the bioavailability of simvastatin from SLNs. Furthermore, the relative

bioavailability of simvastatin SLNs was found to be 220 % (relative bioavailability = (AUC SLN / AUC suspension) × 100).

It was detected that simvastatin from SLNs was poorly accumulated in the liver in comparison with simvastatin from suspension within 2 hours of administration. This was attributed to the lymphatic uptake of SLNs. It was shown that even after 2 to 4 hours of administration, simvastatin from SLNs continuously entered into the liver [117].

Several different methods to improve solubility and dissolution were reported including micronization, complexation, solid dispersion, etc.; yet, each method has its limitations.

Table 9 shows a number of applied techniques that can enhance solubility without changing the chemical structure of the compound. On the other hand, solid dispersions (SD) can be produced by several other methods, as described in Table 10 [121].

The concept of solid dispersions was presented by Sekiguchi and Obi in the1960s as the dispersion of one or more active ingredients in an inert carrier matrix at solid state. Drug particles in SD don't necessarily have to exist in the micronized state; a fraction of the drug might molecularly disperse in the matrix, thus forming a solid dispersion. After SD exposure to aqueous media, the carrier dissolves and the drug is released as fine colloidal particles [122, 123].

Table 9. Methods used to improve the aqueous solubility of drugs

Method	Description
Micronization	Reduction of drug particle size to below 10 μm.
First generation SD	Formation of eutectic mixtures between drugs & water soluble carriers as urea & mannitol
Second generation SD	Decrease in the drug's crystalline form by mixing with amorphous polymers as peg, pvp and cellulose derivatives. This technique allows the formation of solid solutions, solid suspensions or a simple physical mixture of drug & polymer
Third generation SD	Mixture with surfactants (gelucire 44/14, polysorbates, etc.) this can increase the drug's solubility by decreasing its interfacial tension

Table 10. Methods used to obtain solid dispersions (SD)

Fusion	The drug is melted inside the carrier and the system is cooled down and then micronized. The melting process has the purpose of dissolving or dispersing the drug into the carrier, and the cooling process is responsible for the solidification of the mixture, which facilitate the micronization. However, this technique is not suitable for thermo-labile drugs
Solvent evaporation	The drug is dissolved in a suitable solvent and dispersed in the carrier, where it is evaporated within a rotary evaporator, dried in an oven or spray- dried

In solvent evaporation method, both the drug and carrier are first dissolved in a common solvent, and then the solvent is evaporated under vacuum to provide a solid solution. This method offers benefits such as prevention of thermal decomposition of drugs or carriers due to the low temperature needed for the evaporation of organic solvents. Yet, it has

disadvantages like a higher expenditure of formulation development, complexity in the entire removal of the liquid solvent, possible unfavorable consequence of the added solvent on the chemical stability of the drug, variety of a common volatile solvent and obscurity of reproducing crystal forms [124].

A study conducted by Pandya et al., in which a low viscosity grade hydroxypropylmethylcellulose (HPMC K3LV) with surfactant having good wetting properties was used. The formulation has led to drug solubility and dissolution enhancement and consequently to an efficient bioavailability. On the other hand, the co-solvent evaporation method offers advantage to use a lipophilic drug as simvastatin with hydrophilic polymer (HPMC K3LV). It was carried out by using spray drying and evaporation method. Solubility data established an increased solubility, dissolution rate and hence bioavailability of SIM with HPMC K3LV. In addition, solubility of SIM was higher in spray-dried product in comparison to the evaporated product [125] .

The co-solvent evaporation methods with HPMC K3LV enhances the solubility of SIM by transforming it into amorphous form via reducing the particle size and increasing wettability. Low molecular weight and low viscosity grade hydrophilic HPMC produces better wetting to drug particles, and spray-drying method gives efficient encapsulation of hydrophobic drug in polymer micelles of HPMC and boosts both, the solubility and dissolution of SIM effectively [125].

Inclusion complex formation procedure, on the other hand, is one of the most precisely employed techniques for the enhancement of solubility, dissolution rate, and subsequently bioavailability for drugs with poor water solubility. Inclusion complexes are prepared by addition of non-polar molecule(s) (guest substance) into other molecule(s) (host). Cyclodextrins (CDs) are frequently employed as host molecules [124]. CDs are soluble compounds with hydrophobic cavity in which lipophilic drugs are incorporated. It can be made by the degradation of starch, with 6, 7 or 8 glucose units, which are called α. ß and γ cyclodextrins, respectively. There are a number of means of producing CD inclusion complexes (Table 11) [121].

Table 11. Methods for preparing CD inclusion complexes

Kending	Drug & CD are mixed with a small amount of water or hyroalcoholic mixture & the resulting material is dried in air or oven
Coevaporation	The drug is dissolved in an appropriate solvent and an aqueous solution of CD is added. The mixture is stirred and dried under vacuum in a rotary evaporator
Lypholization	A drug- CD aqueous solution is prepared and then lyophilized, giving the resultant complex an amorphous character
Spray drying	The drug is first dissolved in ethanol and the CD in water and the two solutions are then mixed and subjected to spray- drying
Extraction in supercritical fluid	After water is added to a mixture of drug and CD, the complex is transferred to a pressure chamber, where supercritical CO_2 extracts the water, which is eliminated after depressurization

The use of hydroxypropylmethylcellulose (HPMC) to increase the solubility of drugs was proposed by Mourão et al., who proposed the usage of the polymer together with ß-CD (at room temperature), as HPMC has limited aqueous solubility [121].

On the other hand, Shiralashetti et al. had executed a study with the purpose of observing the influence of preparation techniques on the solubility and dissolution of SIM β-CD and hydroxypropyl β-cyclodextrin (HPβ-CD) inclusion complexes. Simple physical mixing, kneading and spray drying techniques were employed to construct the complexes. Then, the inclusion complexes were evaluated for phase solubility and in vitro release behavior. The physicochemical analysis results showed the conversion of SIM from a crystalline to an amorphous form. There was a noticeable increase in the aqueous solubility and dissolution rates of the drug in inclusion complexes compared to the drug alone. Further, spray dried complexes showed better performance in all evaluated factors as compared to the complexes made-up by other approaches [124].

Mandal et al. studied the impact of preparation techniques on the solubility and dissolution of simvastatin-PEG 4000, PEG 6000 or HPβ-CD inclusion complexes. Simple physical mixing, kneading and fusion techniques were employed to assemble the complexes. Phase solubility studies revealed that the highest dissolution rate and wettability of SIM was attained from the inclusion complex prepared with HPβ-CD by kneading method [124].

In another study, Jun et al. used supercritical anti-solvent (SAS) to prepare simvastatin-inclusion complex with HPβ-CD. FT-IR study revealed the presence of intermolecular hydrogen bonds between SIM and HPβ-CD in inclusion complex, showing the development of amorphous form. Solubility and dissolution test results demonstrated an outstanding increase in the dissolution rates of inclusion complex [124, 126].

Solid dispersion on the other hand, is an assembly of solid products consisting of no less than two unlike constituents, normally a hydrophilic medium and a hydrophobic drug. Polyvinylpyrrolidone (PVP), polyethylene glycols (PEG), Plasdone-S630 (PS630) and surfactants such as tween-80, docusate sodium, myrj-52, pluronic-F68 and SLS are the most commonly used hydrophilic carriers. To formulate the solid dispersion, various techniques are applicable such as hot melt (fusion), solvent evaporation and hot melt extrusion methods [124].

For example, Zhang et al. developed spherical mesocellular foam (MCF) loaded with SIM via a procedure involving a combination of adsorption equilibrium and solvent evaporation, for oral administration with the ability to enhance dissolution rate and improve drug loading capacity. Spherical MCF with an incessant 3-D pore system was developed using a surfactant (Pluronic 123 triblock polymer) and a co-surfactant (cetyltrimethyl-ammonium bromide). The physicochemical assessment revealed a successful amalgamation of SV into the MCF host. The results signified a high drug loading efficiency up to 37.5% using spherical MCF [124, 127].

Silva et al. prepared solid dispersions of SIM with polyethylene glycol (PEG 4000) using different drug: carrier ratios by the melting method. SIM solid dispersions with PEG 4000 in all percentages showed a great effect on both the solubility and rate of release. SIM and PEG solid dispersions caused a substantial boost in drug solubility with almost 100% increase at 1:5 drug: polymer ratio. It was concluded that the reduction in the crystalline size, as well as, the surface tension were the contributing factors for enhancing the wettability and dispensability, and hence the drug release [124, 128].

Zhang et al. used ball milling method to examine the development of kinetics of a solid dispersion of SIM with an amorphous copolymer by ball milled the physical mixtures of quench-cooled amorphous SIM and polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA64) in ratios of 1:1 and 1:4 for 3-40 minutes. As the milling time increased, the Tgs

(glass transition temperatures) (29.5 ˚C for the drug and 108.5 ˚C for the polymer) mainly present in the 1:4 samples gradually shifted closer to each other and eventually outlined a single Tg at 91 ˚C after 30 min, which validates the development of one phase solid dispersion. Alternatively, samples at the 1:1 ratio still demonstrated two Tgs (at 74.4 ˚C and 101.5 ˚C) after 30 min milling, revealing a two phase system with fractional miscibility. Moreover, amorphous SIM with PVP/VA64 in physical mixtures without milling have a tendency to transfer back to the crystalline form during storage at 45 ˚C [124, 127].

Ambike et al. used spray drying method to gain free flowing, stable, amorphous solid dispersions of SIM, with relatively lower Tg. In this study, SIM was suspended in dichloromethane either alone or in combination with PVP (1:1 or 1:2, w/w ratio between drug and PVP), which then spray dried with anticipated amount of Aerosil 200 (1:1, 1:1:1, 1:2:2 parts by weight of SIM, Aerosil 200 and PVP, respectively). In order to overcome the limitations associated with spray drying method for amorphization of low Tg drugs, combination of solid dispersions and surface adsorption techniques has been attempted. Solid dispersions of 1:2:2 was chosen as the optimized product based on powder features, drug content, saturation solubility and practicability of processing into tablets. After evaluation, the presence of amorphous form in solid dispersions of 1:2:2 was confirmed. In addition, there was a dramatic increase in the rate and extent of in vitro drug release of solid dispersions 1:2:2. Accordingly, this study proved that spray drying method has a promising ability for finding stable amorphous solid dispersions for drugs with low Tg [124].

On the other hand, surfactants are compounds known to decrease surface tension and increase solubility of drugs within an organic solvent; therefore they were used for the improvement of SIM solubility and dissolution.

Margulis-Goshen and Magdassi investigated a method for a preparation of SIM nanoparticles by solvent evaporation from spontaneously formed oil-in-water micro-emulsions. In this study, freeze-drying method was applied to convert microemulsions containing a volatile solvent as an oil phase into nanoparticles in the form of dry non-oily flakes. The flakes were dispersed in water and then filtered through a 0.1 μm pore size filter in order to evaluate the loading efficiency of SIM in nanoparticles and to assess the SIM concentration. The results showed that more than 95% of the drug was present in amorphous particles (size < 100 nm) after freeze-drying. Furthermore, dissolution studies showed a significant increase in the dissolution rate from the tablets with the flakes of SIM nanoparticles in contrast to conventional tablets. Test showed that SIM nanoparticulate flakes were originally amorphous, yet, a slow crystallization process occurred upon storage at room temperature [124, 129].

Likewise, it was documented by Meng and Zheng that self-microemulsifying drug delivery system is an excellent method to obtain better bioavailability of simvastatin via improving its apparent solubility. An empirical experimental model was used to mimic the effect of the mixture compositions on the apparent quantitative solubility of SIM. The reduced cubic polynomial equation efficaciously modeled the development of SIM apparent solubility. Response surface diagram showed a scale of possible SIM apparent solubility in a range of 0.0024 ~ 29.0 mg/mL. Furthermore, it was demonstrated by this technique that the apparent solubility of SIM was mainly affected by microemulsion quantity and suggested that the drug precipitation would occur in GIT due to dilution by GI fluids. Microemulsion based formulation of SIM was prepared to augment its solubility and dissolution. The self-microemulsifying drug delivery system (SMEDDS) was formulated by heating at 40 ˚C until

a clear solution was formed. The SMEDDS involved the drug, oil, surfactant and co-surfactant. The recorded solubility of SIM was over 130 mg/mL in light fatty alcohol and carbonates oils. The particles size of microemulsion was just about 90-300 nm and the dissolution rate of the SMEDDS formulations was much higher and faster than the marketed formulation (Zoco®), approaching 40-50% in simulated gastric media and 90-100% in simulated intestinal media. Overall, the SMEDDS was very fruitful in boosting the solubility and dissolution of SIM via preparing stable isotropic and transparent microemulsion with nano-sized particles [124, 130].

Other approaches utilizing particle size reduction include techniques involving an increase in the surface area of particles in addition to a decrease in particle size, which end up with an increase in drug solubility. Different methods can be used to reduce the size of the particles such as milling procedures, which can be accomplished by micronization, nanosuspensions and sometimes sonocrystallization. Production of nanosuspensions can be achieved using precipitation method. In this technique, the drug is dissolved in a solvent, which is then added to anti-solvent that causes precipitation of the fine drug particles. The nanoparticles show a larger surface-to-volume ratio than the bulk material allowing for lower dose and frequency of administration. Patil et al. prepared SIM nanoparticles using nano-precipitation technique in which a partially water-soluble solvents and a mutual saturation of the aqueous and organic phases were used earlier to form a nano-suspension with the purpose of lowering the initial thermodynamic instability of the nanoparticles. SIM and eudragit L100 were dissolved in methanol at definite concentration and then filtered through 0.45 μm pore size membrane to remove any contaminations. The nano-precipitation technique was employed in order to provide the desired SIM nanoparticles which were afforded by the addition of 5 mL of SIM solution into the formerly prepared mixture with continuous mechanical stirring followed by an immediate precipitation. The resulted nanoparticles were then filtered and dried [124].

On the other hand, Jie Lai et al. investigated glyceryl monooleate (GMO)/poloxamer 407 cubic nanoparticles as potential oral drug delivery systems to enhance SIM bioavailability. Fragmentation of GMO/poloxamer 407 bulk cubic-phase gel using high-pressure homogenization was applied to prepare simvastatin-loaded cubic nanoparticles. The mean diameter of the cubic nanoparticles was within the range of 100–150 nm. Because of SIM's high affinity to the hydrophobic regions of the cubic phase, almost complete entrapment with efficiency over 98% was accomplished. Pharmacokinetic profiles showed sustained plasma levels over 12 hours, and the relative oral bioavailability was 241%. The enhanced bioavailability of SIM was attributed to facilitated absorption by lipids in the formulation instead of release improvement [131].

Furthermore, Premchandani et al. conducted a study that involves preparation and characterization of floating microcapsules with simvastatin as model drug to prolong gastric residence time. Microcapsules contained a drug complex with a surrounding coat consisting of alginate and a floating polymer carbopol 941 which were prepared by an ionic gelation method. The goal was to enhance simvastatin β-CD complex (1:2) solubility by co-precipitation method and then to deliver it in sustained release microcapsules dosage form. The release profile and dissolution kinetic showed that the release of the drug from the microcapsules was slow and extended over long periods of time depending on the composition of the coat and followed zero order kinetics. Moreover, it was established that high concentration of sodium alginate obstructs both drug encapsulation efficiency and the

release percentage, while intermediate concentration showed improvement in the drug release percentage. In contrast, high concentration of carbopol and drug complex offers good encapsulation efficiency and a high release. It was concluded that porous carbopol 941 microcapsules are promising sustained release system as well as stomach specific carriers for delivery of simvastatin [132].

Furthermore, Tiwari et al. investigated the nanostructured lipid carrier (NLC) system of simvastatin in an attempt to improve its release, pharmacokinetics and biodistribution. The NLC formulations were prepared by solvent injection technique. The optimized NLC was a suspension of nano-sized homogeneous particles with significantly higher entrapment efficiency (>90%) and lower recrystallization properties ($p < 0.01$) than SLNs. The PK parameters of Tc99 labeled optimized NLC in mice exposed 4.8 fold increase in bioavailability in contrast to simvastatin suspension and 2.29 fold in contrast to SLNs that was directly a function of the presence of oily lipid in the NLC. Additionally, bio distribution study showed a good NLC accumulation in the liver; the target organ for simvastatin. The NLCs can also improve the gastrointestinal absorption of SIM, and level A correlation could be established between in vitro dissolution and in vivo absorption [133].

Recently, Luo et al. developed stable pellets-layered simvastatin nanosuspensions to enhance simvastatin dissolution and bioavailability. The nanosuspensions were prepared with 7% HPMC, antioxidant (0.03% butylated hydroxyanisole) and 0.2% citric acid by low temperature grinding. SDS with SIM 1:5 m/m) were uniformly dispersed in the nanosuspensions and layered on the surface of sugar pellets. The mean particle size of the SIM nanosuspensions was 0.74 μm. About 100% of the drug dissolved from the pellets within 5 minutes under sink conditions. The relative bioavailability of SIM and simvastatin β-hydroxy acid (SIMA) (Figure 3) for nanosuspensions layered pellets in comparison to the commercial tablets was 117% and 173%, respectively. Consequently, pellet-layered SIM nanosuspensions were shown to improve both the dissolution and bioavailability of SIM [134].

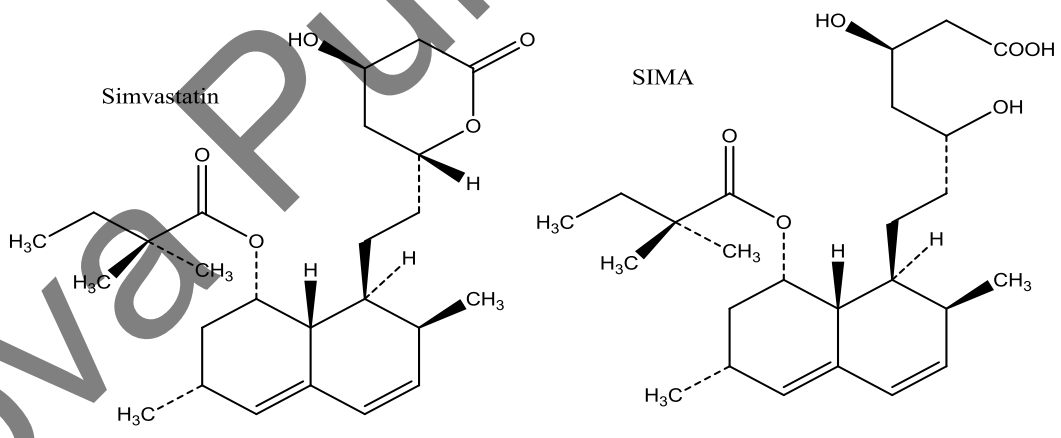


Figure 3. Chemical structures of SIM and SIMA.

Karaman and coworkers have used a novel approach by which computational methods and correlation between calculated and experimental values were utilized to design three simvastatin prodrugs with efficient bioavailability. For example, based on the calculated log

EM (effective molarity) for the three proposed prodrugs, the interconversion of simvastatin prodrug *ProD 3* to simvastatin is predicted to be about 10 times faster than that of either simvastatin prodrug *ProD 1* or simvastatin *ProD 2*. Hence, the rate by which the prodrug releases the statin drug can be determined according to the structural features of the promoiety (Kirby's enzyme model) (Figure 4) [18].

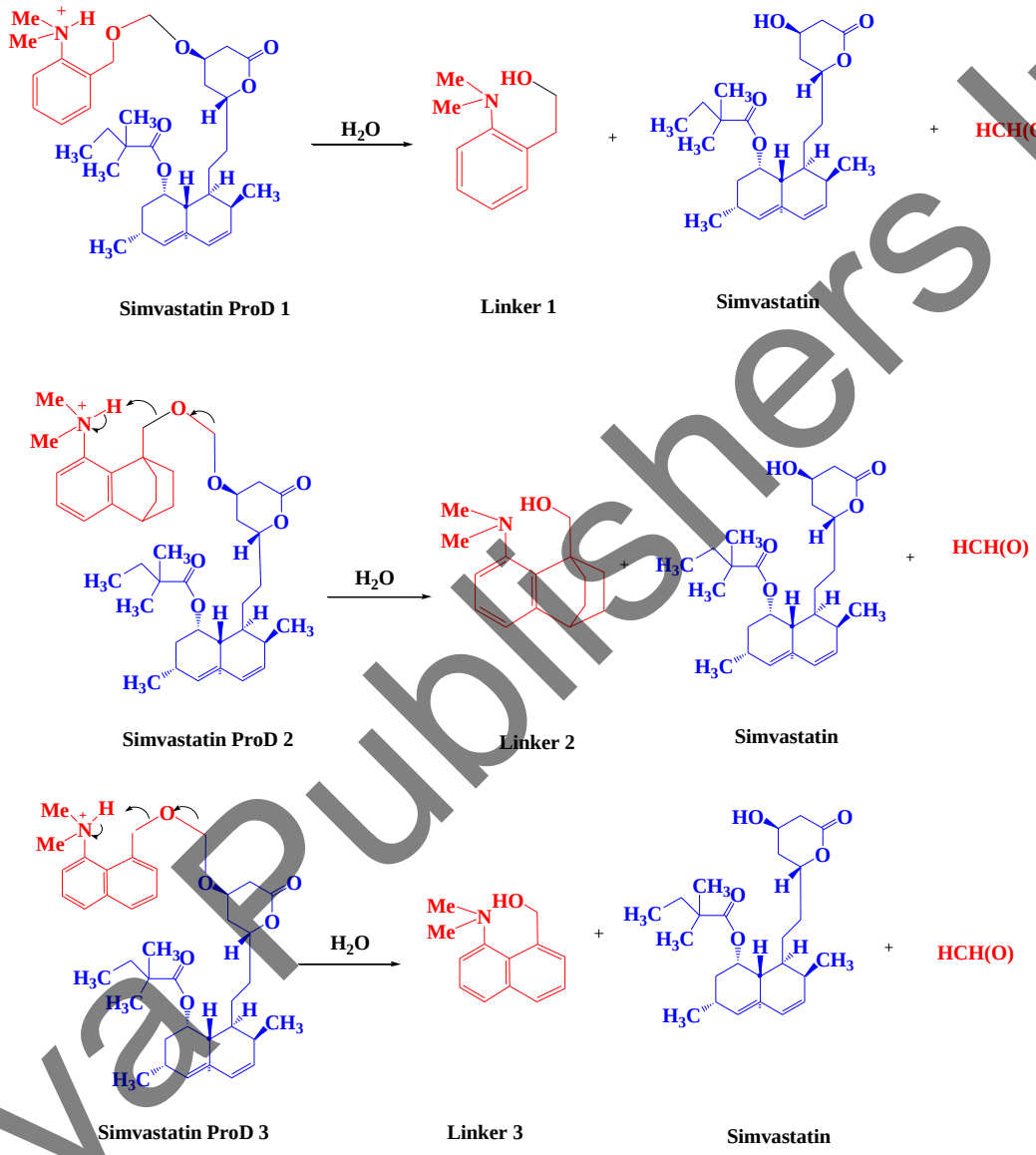


Figure 4. Interconversion of simvastatin ProD 1- ProD 3 via proton transfer reactions.

Atorvastatin (ATO)

Atorvastatin (ATO) is insoluble in aqueous solutions at pH equal or less than 4 and marginally soluble in water and phosphate buffer (pH 7.4) with very low bioavailability (≈14%) due to its low aqueous solubility (0.1 mg/mL), and hepatic first-pass metabolism. ATO is a BCS class II with high permeability and low solubility. Due to this fact, solubility enhancement of ATO is crucial for improving its absorption window. Further, ATO is unstable and when packed in the form of tablets, powders, granules, or within capsules is at risk upon exposure to heat, light, and moisture; as a consequence, the hydroxy acid form (HF) is converted to lactone form (LF). As the HF of ATO occurs as free acid form, it is about 15 times more soluble than the LF due to the ability of the carboxyl group to be ionized (Figure 5). Therefore, exploring different approaches to overcome the problems of poor solubility and bioavailability of ATO is crucial [135, 136].

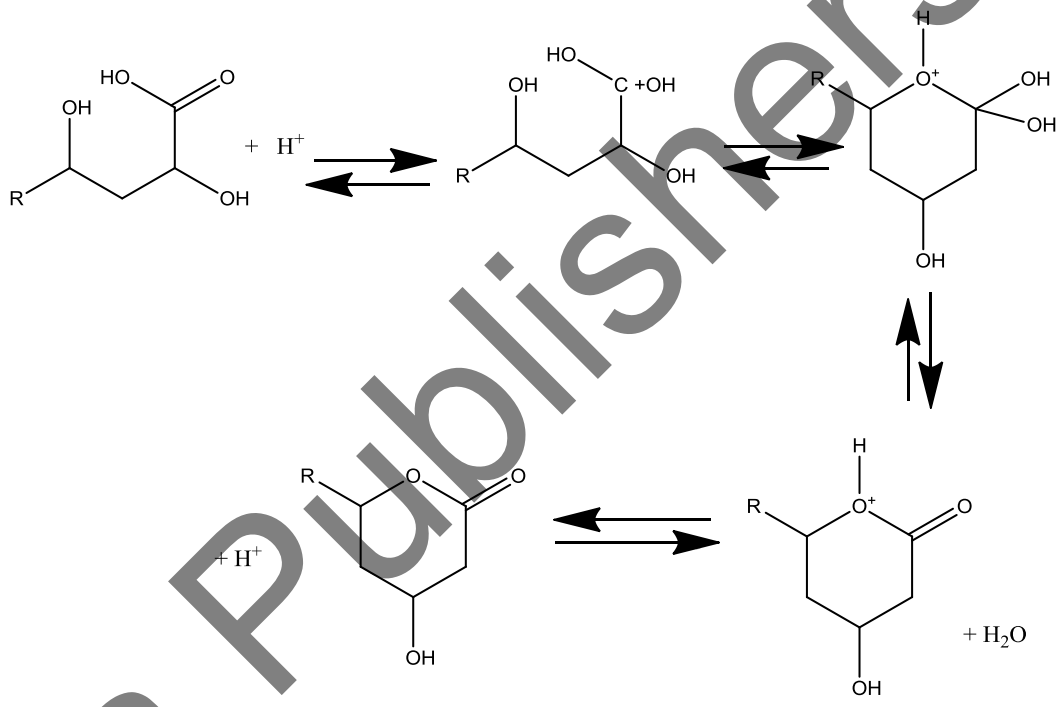


Figure 5. The mechanism for the specific acid catalyzed lactonization of the hydroxy acid form of ATO (forward direction) and the specific acid catalyzed hydrolysis of the lactone of ATO (reverse direction). R: reminder of the molecule.

For instance, Khan et al. prepared stabilized gastro-retentive floating tablets of ATO. The selected excipient used was docusate sodium that boosted the stability and solubility of ATO in gastric media and tablet dosage form. The best formulation was consisting of hypromellose, sodium bicarbonate, polyethylene oxide, docusate sodium, mannitol, crosscarmellose sodium and magnesium stearates, which gave a floating lag time of 56±4.16 seconds and good matrix integrity with in vitro dissolution of 98.2% in 12 hours. In vivo PK study in rabbits showed an enhancement in the bioavailability of this floating tablets, about 1.6 times compared with that of the conventional tablet (Storvas® 80 mg tablet) [136].

Moreover, in 2012, another study was conducted by Khan et al. in which they developed a multiple-unit floating microcapsules of atorvastatin calcium (ATC) to expand the gastric residence time of ATC that has a maximum rate of absorption in the upper GIT. The floating microcapsules were prepared by emulsion-solvent evaporation technique through integration of dioctyl sodium sulphosuccinate (DSS) as a dissolution enhancer. The ATC-loaded floating microcapsules were spherical with a particle size of about 28.10 μm and drug-loading efficiency of about 96.55 %. The floating microspheres containing DSS had significantly higher drug dissolution rates compared to those without DSS. The study revealed, the best formulation was consisting of ethyl cellulose, DSS and Poly Ox®, with a maximum drug dissolution rate of 97.86 %, as compared to Storvas 80 mg; the reference which had a rate of only 54% during a period of 12 hours in acidic media. PK study on rabbits demonstrated an increase in the bioavailability by nearly 1.7 times that that of Storvas 80 mg [137].

Panghal et al. conducted a study in which a solid dispersion technique using modified locust bean gum was utilized. Modified forms of the natural polymers such as locust bean gum (LBG), guar gum, and gum karaya have been used for preparing solid dispersions of hydrophobic drugs due to the drawbacks associated with the natural polymers as high viscosity and pulverization. Solid dispersions (SD) using modified locust bean gum were prepared by the modified solvent evaporation method. Physical mixing, co-grinding, and the kneading method were also used to prepare other mixtures.

The maximum rate (in the first 15 minutes) and extent of dissolution at the end of 2 hours (50% and 80%, respectively) was observed in the solid dispersion that consisted of 100 mg drug & 600 mg MLBG polymer (SD3). The co-grinding mixture exhibited a significant enhancement in the dissolution rate among the other mixtures. In vivo pharmacodynamic studies showed enhancement in efficacy of the optimized batch SD3 as compared to the pure drug. Equilibrium solubility improvement of the drug in SD led to improvement in dissolution. The overall enhancement of solubility was due to the wettability of MLBG, decreased particle size of the drug during formulation, and decreased crystallinity of the drug [138].

Recently, Salmani et al. studied the possibility to improve ATO bioavailability via increasing its gastric solubility in a stable oral disintegration tablet (ODT) formulation. Amorphous solid dispersion (ASD) of ATO with Eudragit® EPO was used as the active ingredient. In ASD, a uniform distribution of drug in the polymer was achieved with retention of the amorphous nature without any chemical interactions except for the possibility of hydrogen bond formation, with higher gastric solubility. Results showed that the dissolution profile of the ODT containing ASD was considerably improved above 90% within 15 minutes compared with 25% of the ordinary ATO formulation. An overall enhancement in the apparent bioavailability (83%) was achieved [135].

Rosuvastatin

Rosuvastatin calcium is a BCS class II drug. It has low water solubility and inefficient bioavailability. Therefore, different methods were employed to enhance its dissolution characteristics. One of the most promising methods is the use of liquisolid system (LS), a flowing and compressible powdered form of liquid medications [139].

Liquid medication is a term that involves the use of oily liquid drugs and solutions or suspensions of solid drugs that are water insoluble carried in appropriate nonvolatile solvent systems, named liquid vehicles. Employing this technique allows for a liquid medication to be converted into a dry-looking, non-adherent, free flowing and readily compressible powder by simple blending with selected carrier and coating materials such as Avicel PH 102 and Aerosil 200 [139].

In the experiment conducted by Kamble et al., several liquisolid tablets formulations with different concentrations of rosuvastatin in liquid medication (ranging from 15% to 25% w/w) were prepared. The ratio of Avicel PH 102 (carrier) to Aerosil 200 (coating powder material) was kept 10, 20, and 30. Results showed that the LS displayed acceptable flow properties, and revealed significantly higher drug release rates compared with conventional tablet due to increasing wetting properties and surface area of the drug. Additionally, the differential scanning calorimetry (DSC) study confirmed the absence of any interaction between the drug and excipients used in the preparation of this liquisolid compacts [139].

Fibrates

Fenofibrate is the isopropyl ester of 2-(4-[4-chloro-benzoyl] phenoxy)-2-methylpropanoic acid. It is water insoluble with high lipophilicity (log P = 5.24). Fenofibrate is a class II drug with low solubility and high permeability, indicating that the dissolution rate of fenofibrate may control its absorption in the GIT. It is a prodrug that is converted rapidly after oral administration through hydrolysis of the ester bond to fenofibric acid, the active form and major metabolite of fenofibrate (Figure 6). Therefore, several studies were performed in order to improve the bioavailability of the drug [140].

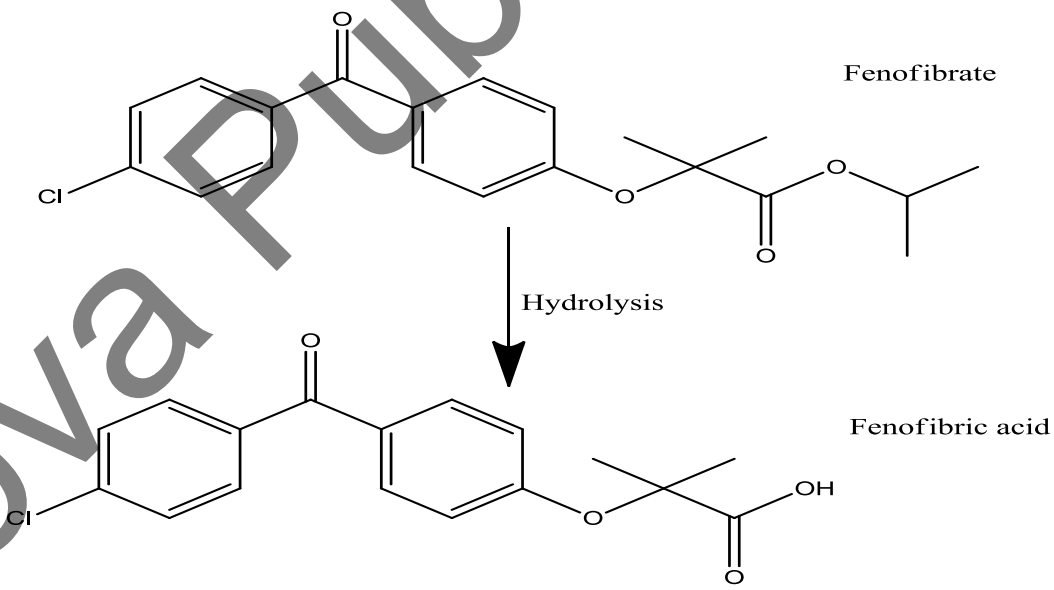


Figure 6. Chemical structures of fenofibrate and its active metabolite, fenofibric acid.

In a study conducted by Srinarong et al., it was shown that superdisintegrants incorporation in SD tablets with a high load of drug can significantly enhance the dissolution rate of the highly lipophilic drug fenofibrate. Yet, the proper way of incorporation of the superdisintegrants in the tablets and the proper choice of the type of superdisintegrants and carriers are crucial factors in determining and achieving an improved dissolution behavior of the drug. Enhancement in dissolution rate was in the order Polyplasdone® XL-10 < Polyplasdone ®XL << Ac-Di-Sol® ≈ Primojel®. In addition, the dissolution behavior was much faster in SD tablets based on inulin 4 kDa, polyethylene glycol 20K and polyvinylpyrrolidone K30 than those based on mannitol and hydroxypropyl-β-cyclodextrin [141]. Homogeneous distribution of Primojel® over the tablet prepared from the inulin 4 kDa-based solid dispersion is the reason for the enhanced dissolution rate. Apparently, a rapid disintegration time of tablets based on inulin 4 kDa resulted in an increase of the dissolving surface area of the drug and thus an increase in its dissolution rate. Swelling pressure and hydration capacity of the superdisintegrants are the most important factors affecting the disintegration time [141].

A study conducted by Chena et al. to estimate the oral bioavailability of fenofibrate where liposomes containing a bile salt were used as oral drug delivery systems. Liposomes composed of soybean phosphotidylcholine (SPC) and sodium deoxycholate (SDC) were prepared by a dry film dispersing method combined with sonication and homogenization. In vivo measurements of the pharmacokinetics and bioavailability of the preparation revealed higher absorption rates of fenofibrate from both SPC/SDC and SPC/CL liposomes than micronized fenofibrate. In addition, the bioavailability of SPC/SDC and SPC/CL liposomes were 5.13 and 3.28-fold higher than that of the micronized fenofibrate. Moreover, SPC/SDC liposomes showed a 1.57-fold increase in bioavailability compared to SPC/CL liposomes [142].

In 2010, Zhang et al. investigated the dissolution and oral bioavailability of immediate release tablets involving wet grinding of fenofibrate. The milled suspension was prepared using a Basket Dispersing Mill in the presence of a hydrophilic polymer solution which was granulated with common excipients and compressed into an immediate-release tablet with blank microcrystalline cellulose granules. The dissolution of wet-milled tablets was significantly enhanced (about 98% in 30 minutes) in comparison with un-milled tablets (56% within 30 minutes). In addition, the bioavailability study which was performed on dogs showed promising results with the wet-milled tablets (test) compared to Lipanthyl® supra-bioavailability tablets (reference). Further, the T_{max} of wet milled tablets was 2.63 hours compared with 3.75 hours of Lipanthyl®, indicating a faster rate of absorption of fenofibrate from the wet milled tablet [143].

Furthermore, formulation of a microemulsion system for oral administration was explored by Hu et al. in an attempt to improve the solubility and bioavailability of fenofibrate. In this experiment, different formulations were prepared using different ratios of oils, surfactants and co-surfactants (S & CoS). The ideal formulation consists of 25%, 27.75%, 9.25% and 38% of Capryol 90, Cremophore EL, Transcutol P and water (w/w) respectively, with a maximum solubility of fenofibrate up to ~40.96 mg/mL. The microemulsion was physicochemical stable with mean droplet size of about 32.5–41.7 nm. The PK study showed a significant increase in C_{max} and AUC (1.63 and 1.30-fold) with microemulsion compared to that of Lipanthy® capsule [140].

An experiment performed by Wang et al. by which they used wet-milled-drug layering process which has the potential to significantly improve the dissolution rate and oral bioavailability of fenofibrate pellets. In this experiment, fenofibrate was milled with HPMC-E5 for creating a uniform suspension in the micrometer and nanometer range (F1, F2 respectively), which then were layered on to sugar spheres to form the pellets. The results showed a significant reduction in the particle size (from 1000 μm to 1–10 μm and 400 nm). The dissolution rate of F1-F2 and Antara® capsules was 55.47 %, 61.27 % and 58.43 %, respectively. Further. The results proved the ability of drug layering method for a direct contact between drug particles and the intestinal juices which in turn decreased the time required for fenofibrate dispersion and improved the dissolution rate [144, 145].

Summary and Conclusion

Elevated level of lipids is a leading cause of atherosclerosis and CVD. Therefore, various types of medications with different mechanisms of action are currently available. Medications include statins, fibrates, bile acid resins, niacin and ezetimibe. Among these, statins are the most commonly prescribed. Despite their effectiveness, they have some side effects and low bioavailability like other lipid lowering medications. Therefore, approaches to improve their bioavailability have emerged. Different methods were used and showed promising results in enhancing solubility and solving problems linked to low bioavailability.

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Chapter 5

Antihyperglycemic Drugs

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Abstract

Diabetes mellitus is a group of metabolic diseases characterized by elevated blood glucose levels (hyperglycemia) resulting from defects in insulin secretion, insulin action or both. There are three main types of diabetes: type 1, type 2 and gestational.

Insulin administration is the fundamental treatment of type 1 diabetes mellitus. Insulin is a hormone manufactured by the beta cells of the pancreas, which is required to utilize glucose from digested food as an energy source. Orally administered ant hyperglycemic agents (OHAs) can be used either alone or in combination with other OHAs or insulin to treat type 2 diabetes mellitus. The number of these drugs has increased significantly in the last decade.

In this chapter, we describe the pathogenesis and types of diabetes and the current used drugs to treat this disease. In addition, a detailed description of the pharmacokinetic properties, mechanism of action, side effects of known ant hyperglycemic agents is presented.

Keywords: Diabetes mellitus, Type 1 diabetes mellitus, Type 2 diabetes mellitus, anti-hyperglycemic agents, insulin

Abbreviations

DM	Diabetes mellitus
T1DM	Type 1 diabetes mellitus

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T2DM	Type 2 diabetes mellitus
HbA1c	Glycosylated hemoglobin
OHAs	Orally administered ant hyperglycemic agents
SUs	Sulphonylureas
ATP	Adenosine triphosphate
NIDDM	Non-insulin- dependent diabetes mellitus
PCOS	Polycystic ovarian syndrome
TZDs	Thiazolidinediones
AGIs	α-glucosidase inhibitors
DPP-4	Dipeptidyl peptidase-4 enzyme
GIP 1	Glucagon like peptide 1
IV	Intravenous
IM	Intramuscular
SC	Subcutaneous

Introduction

Diabetes mellitus (DM) is probably one of the oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago. Diabetes mellitus is a chronic disease with one of the highest social and healthcare costs. It is associated with an increment in cardiovascular morbidity and mortality and is considered as the fourth or fifth leading cause of death in most high-income countries and there is a substantial evidence that it is epidemic in many economically developing and newly industrialized countries. Undoubtedly, it is one of the most challenging health problems of the 21st century [1-3].

Epidemiology of Diabetes

It is estimated that 382 million people had DM in 2013 and by 2035 it is predicted that the number will rise to 592 million. The number of people with type 2 DM is increasing in every country with 80% of them living in low- and middle-income countries. DM caused 4.6 million deaths in 2011. The incidence of type 2 DM varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors [4]. The majority of people with diabetes are aged between 40 and 59, and 80% of them live in low- and middle-income countries.

All types of diabetes are on the increase. The number of people with diabetes will increase by 55% by 2035. Type 2 diabetes accounts for 85% to 95% of all diabetes in high-income countries and may account for an even higher percentage in low- and middle income countries [5].

Type 1 diabetes, although less common than type 2 diabetes, is increasing each year in both rich and poor countries. In most high-income countries, the majority of diabetes in children and adolescents is type 1 diabetes.

Gestational diabetes is common and like obesity and type 2 diabetes is increasing throughout the world. The risk of developing type 2 diabetes is high in women who have had gestational diabetes [6].

Pathogensis of Diabetes

It is important to have a basic understanding of the pathogenesis of diabetes in order to better understand the role of each drug class in the treatment of diabetes. Elevations in serum glucose levels after meals stimulate insulin synthesis and its release from pancreatic β-cells. The secreted insulin present in the systemic circulation binds to receptors in target organs such as skeletal muscle, adipose tissue and liver. Insulin binding initiates a cascade of intracellular signal transduction pathways that inhibits glucose production in the liver, suppresses lipolysis in adipose tissue and stimulates glucose uptake into target cells (muscle and fat) by mechanisms such as the translocation of vesicles that contain glucose transporters to the plasma membrane [7].

In type 1 diabetes mellitus a severe insulin secretion deficit exists thus the only treatment, at present, is the administration of insulin or insulin analog. However, Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure [8, 9]. This leads to a decrease in glucose transport into the liver, muscle cells, fat cells and an increase in the breakdown of fat with hyperglycemia. Recently, impaired alpha-cell function has been recognized in the pathophysiology of type 2 DM [10]. The therapeutic approach of type 2 DM is dependent on the stage of the disease and characteristics of the patient [11].

Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome.

Definition and Types

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels [12].

There are three main types of diabetes:

- Type 1 diabetes
- Type 2 diabetes
- Gestational diabetes

Type 1 Diabetes Mellitus (T1DM)

Type 1 diabetes mellitus is a chronic condition usually characterized by an autoimmune destruction of β-cells in the pancreas. As a result, the body can no longer produce the insulin it needs which leads to absolute insulin deficiency. T1DM is due to a combination of genetic and environmental factors.

The long-term complications of T1DM can be severe and include micro vascular complications, such as retinopathy, neuropathy and nephropathy, as well as macro vascular complications, including cardiovascular disease, stroke/transient ischemic attack, and peripheral vascular disease [12]. Since T1DM is caused by insulin deficiency, the treatment of this condition requires the use of insulin. Basal insulin replacement can be achieved with human or purified porcine intermediate-acting insulin, including isophane insulin (Neutral Protamine Hagedorn; NPH) and zinc insulin (lente). Long-acting insulin analogues such as glargine and detemir are more expensive than intermediate-acting insulin analogues [13, 14].

Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes is the most common type of diabetes. It usually occurs in adults, but is increasingly seen in children and adolescents. T2DM is a complex metabolic disorder resulting from relatively decreased pancreatic insulin secretion and variable contributions of decreased insulin action, or insulin resistance, in target tissues, mainly muscle and the liver. Insulin resistance is first demonstrated in skeletal muscle, in which higher concentrations of insulin are necessary to allow glucose to enter cells. Peripheral insulin resistance predicts the development of T2DM [15-17].

As the disease progresses, insulin production gradually diminish, leading to progressive stages of hyperglycemia. Hyperglycemia is first exhibited in the postprandial state, since uptake by skeletal muscle is the metabolic fate of the majority of ingested carbohydrate energy, and then during fasting [18, 19].

T2DM is due primarily to lifestyle and genetic factors [20]. A number of lifestyle factors are known to be important to the development of T2DM [21]. These include:

- Physical inactivity
- Sedentary lifestyle
- Cigarette smoking
- Generous consumption of alcohol.
- Obesity
- Advancing age
- Family history of diabetes
- Ethnicity
- High blood glucose during pregnancy affecting the unborn child.

In contrast to people with type 1 diabetes, the majority of those with type 2 diabetes usually do not require daily doses of insulin to survive. Many people are able to manage their

conditions through a healthy diet and increased physical activity or oral medication. However, if they are unable to regulate their blood glucose levels, they may be prescribed insulin.

The number of people with type 2 diabetes is growing rapidly worldwide. This rise is associated with economic development, ageing populations, increasing urbanization, dietary changes, reduced physical activity, and changes in other lifestyle patterns.

Gestational Diabetes

Women who develop a resistance to insulin and subsequent high blood glucose during pregnancy are said to have gestational diabetes. Gestational diabetes tends to occur around the 24^{th} week of pregnancy.

The condition arises because the action of insulin is blocked, probably by hormones produced by the placenta. Poorly managed blood glucose during pregnancy can lead to a significantly larger than average baby (a condition known as fetal macrosomia), which makes a normal birth difficult and risky and a caesarean section will be necessary in this case. Gestational diabetes in mothers normally disappears after birth.

However, women who have had gestational diabetes are at a higher risk of developing gestational diabetes in subsequent pregnancies and of developing type 2 diabetes later in life. Babies born to mothers with gestational diabetes also have a higher lifetime risk of obesity and developing type 2 diabetes.

Prevention and Treatment of Diabetes

The approach to the prevention and treatment of diabetes has been transformed since the discovery of insulin, which led to the rapid development of a widely available and lifesaving new treatments and initiated a series of advances that have fundamentally enhanced the daily lives of patients with diabetes and dramatically extended their life expectancy. The general goals of the treatment of diabetes are to avoid acute decompensation, prevent or delay the appearance of late disease complications, decrease mortality, and maintain a good quality of life. Good control of glycaemia makes it possible to reduce the incidence of micro vascular complications (retinopathy, nephropathy and neuropathy) [22, 23].

Diet and exercise are fundamental in the treatment of diabetes. Dietary recommendations must be customized for each individual to achieve the general objectives of treatment. Obesity is common in type 2 diabetics so one of the main objectives should be weight reduction [24]. Glycosylated hemoglobin (HbA1c) is the best index of the control of diabetes, since it provides information about the degree of glycemic control in the last two to three months and should remain below 7% [11].

Treatment of Type 1 Diabetes Mellitus

As mentioned before, insulin administration is the fundamental treatment of type 1 diabetes mellitus. Although insulin has been available for more than 75 years, in the last two

decades there have been important changes due to the generalized use of reflect meters by patients to self-monitor capillary blood glucose.

Control of blood glucose levels by patients includes adjustment by the patient of insulin doses based on algorithms prepared by the endocrinologist and allows patients more flexibility in their habits and, without a doubt, an improved quality of life [11].

Insulin Chemistry, Biology and Physiology

Insulin is a hormone produced in the pancreas that allows glucose from food to enter the body's cells where it is converted into an energy needed by muscles and tissues to function. A person with diabetes does not absorb glucose properly, and glucose remains circulating in the blood (a condition known as hyperglycemia) damaging body tissues over time. This damage can lead to disabling and life-threatening health complications. People with type 1 diabetes cannot survive without daily insulin doses. Some people with type 2 diabetes or gestational diabetes also need doses of insulin together with other medications.

The dramatic discovery of insulin and the rapid demonstration that it is essential for human health stimulated intense interest in its chemistry and biology. A number of landmark discoveries resulted, some of which reached beyond diabetes research. The sequence of the amino acids of insulin was determined by Frederick Sanger who was awarded a Nobel Prize in chemistry for developing methods to sequence the amino acids of proteins, and he used insulin as an example of his approaches [25]. Donald Steiner's demonstrated that the two-polypeptide insulin molecule is derived from a single-chain precursor proinsulin [26]. This was important not only for understanding the biochemistry of insulin but also because it applies to other peptide hormones that are transcribed as single-chain precursors. Insulin was the first hormone to be cloned [27] and then produced for therapeutic use by means of recombinant DNA technology, which provided an unlimited supply of this important molecule and laid the foundation for the biotechnology industry.

Insulin is a monomer with a molecular weight of 5802 and an isoelectric point of pH 5.5 (Figure 1). It is consisting of two chains, an A chain of 21 amino acids and a B chain of 30 amino acids (in man), linked by two disulfide bridges, A7-B7 and A20-B19. The A chain contains an intra-chain disulfide bridge between A7 and A11 [28, 29].

Types of Insulin and Adminstration Pathways

At present, the insulin used is obtained by genetic recombination techniques from cultures of bacteria or yeasts. Insulin is administered subcutaneously using pen syringes with refillable cartridges, disposable pens, or infusion pumps. Nevertheless, in situations of severe metabolic decompensation insulin can be administered intramuscularly or intravenously. In recent years, fast-acting insulin analogs have begun to be used (lispro insulin), which are obtained by changing an amino acid in the insulin sequence [30].

Insulin preparations are characterized by the onset of action, peak effect and duration of action. The current classification includes rapid, short, intermediate and long-acting products. The insulin's source determines its pharmacokinetic characteristics.

1. Rapid and Short–Acting Insulin Analogues

1.1. Insulin Lispro

It is the first genetically engineered rapid-acting insulin analogue. Its structure differs from human insulin in the B-chain where proline at position 28 and lysine at position 29 are reversed (Figure 2A), leading to a molecule with reduced capacity of self-association in solution (therefore faster absorbed, with higher peak serum levels and shorter duration of action in comparison to regular insulin) [31, 32].

1.2. Insulin Aspart

Insulin Aspart (Figure 2B) structure differs from human insulin at position 28 where a proline is substituted with a charged aspartic acid, allowing it to be absorbed twice as fast as human insulin. It causes better glycemic control when administered directly before a meal [31, 33].

1.3. Insulin Glulisine

Insulin Glulisine (Figure 2C) is the most recent rapid-acting analogue. Its structure differs in two points from human insulin; asparagine at position 3 is substituted by lysine and lysine at position 29 by glutamic acid. These alterations reduce hexamers formation and enhance absorption from subcutaneous depots [34, 35].

The insulin analogues (Lispro, Aspart and Glulisine) dissociate into monomers almost instantaneously following injection. This property results in rapid absorption and shorter duration of action compared to regular insulin [36].

1.4. Regular Insulin (Crystalline Zinc Insulin)

It has the most rapid and the shortest duration of action among other insulin analogues. It is the only insulin given IV and it can be given IM and SC.

2. Intermediate-Acting Insulin Analogoues

NPH insulin preparations are suspensions of small insulin protamine crystals of the same size. The crystals are suspended in a phosphate buffer at neutral pH. The lente insulin preparations are suspensions of about 70% large rhombohedra beef zinc insulin crystals (ultralente) and 30% amorphous porcine zinc insulin particles (semilente).

The mixture is suspended in acetate buffer at neutral pH containing a surplus of zinc. Because the zinc insulin crystals are larger and heavier than the NPH crystals, lente insulin will sedimentate faster than NPH insulin after shaking the suspension, which might have some practical importance [37]. NPH or lente insulin can be mixed with regular insulin in the same syringe in every ratio. However, the course of the effect will change with lente/regular mixtures depending on the ratio between lente and the regular insulin in the syringe [38].

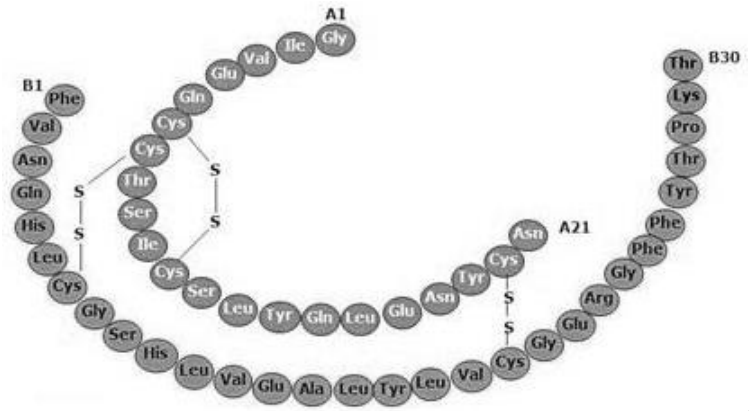


Figure 1. Primary structure of human insulin.

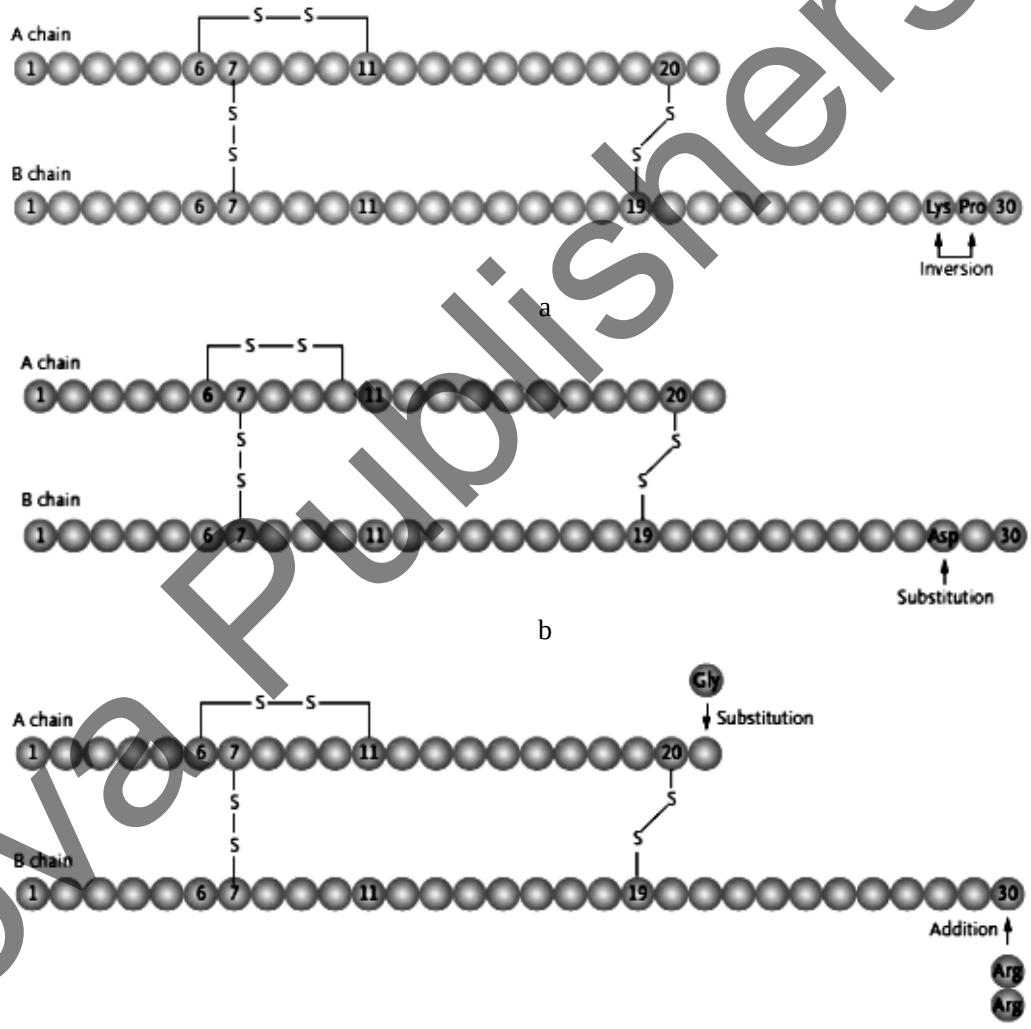


Figure 2. Schematic diagram of insulin Lispro (A), insulin Aspart (B) and insulin Glargine (C).

3. Long–Acting Insulin Analogues

3.1. Insulin Glargine

It is the first long-acting insulin analogue having amino acid modifications in both chains. In the A-chain, the asparagine at position 21 is substituted by glycine and the B-chain is elongated at the C-terminus by the addition of two arginine residues. Glargine is a molecule with a changed isoelectric point towards neutral, bearing decreased solubility at physiological pH. This causes precipitation after injection in subcutaneous tissue, stabilization of insulin hexamers, delay of their dissociation, and steady absorption into the circulation [39, 40].

3.2. Insulin Detemir

It is characterized by acylation of myristic acid to the lysine residue at position 29 in the B-chain and deletion of the last threonine in position 30 of the B-chain. Its protracted action is achieved through delayed resorption caused by the increased self-association and reversible albumin binding at the injection site as well as because albumin binding causes buffering of the insulin concentration. This results in a flat, prolonged pharmacodynamic profile which provides a metabolic effect for approximately 17 hours [39, 41].

Treatment of Type 2 Diabetes Mellitus

Treatment of diabetes with pharmacologic therapy is often necessary to achieve optimal glycemic control. Orally administered ant hyperglycemic agents (OHAs) can be used either alone or in combination with other OHAs or insulin. The number of these drugs has increased significantly in the last decade, which might provide better therapy.

Oral Antidiabetic Drugs

Insulin Secretagogues (Drugs That Promote the Body's Production of Insulin)

Insulin secretagogues can be divided into 2 subclasses: (I) sulfonylureas and (II) non-sulfonylureas.

I. Sulfonylureas

The sulphonylurea compounds (SUs) are effective in reducing blood glucose levels in patients with type 2 diabetes mellitus and are commonly used when conventional dietary treatment fails to normalize blood glucose levels [42, 43]. They are classified as first and second generation SUs.

The first-generation agents include long acting acetohexamide, chlorpropamide, tolazamide and tolbutamide. The second-generation agents are more potent and have better pharmacokinetic and safety profiles than first-generation SUs but essentially of equal efficacy. The second-generation SUs include glyburide (glibenclamide), glipizide, gliquidone

and glimepiride. The different drugs in this generation vary in their duration of action. Glimepiride and glyburide are longer-acting agents than glipizide (Figure 3) [19, 44-49].

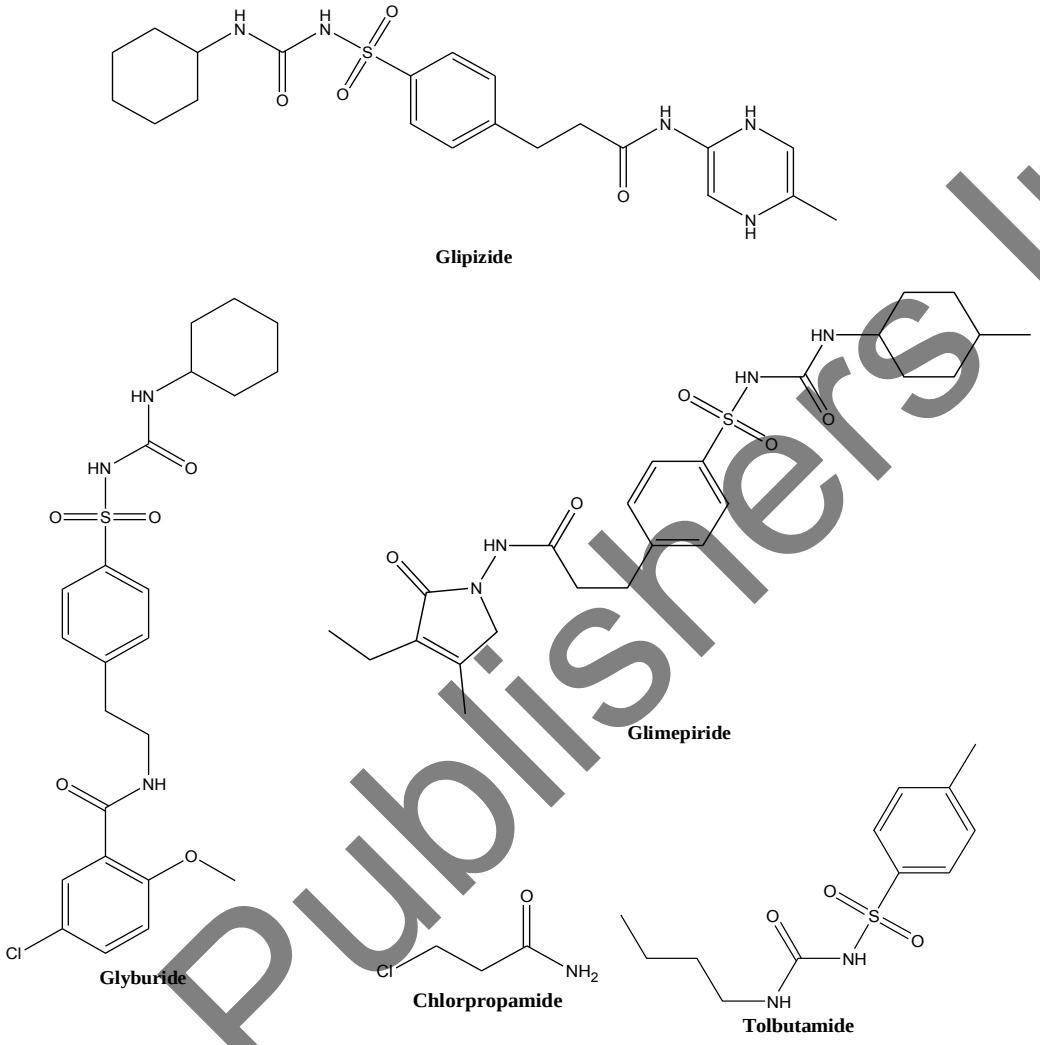


Figure 3. Chemical structures of sulphonylurea drugs.

The sulphonylurea act to enhance the sensitivity of the β-cells to glucose. This mechanism involves sulphonylurea interaction with specific receptors at the plasma membrane of the insulin-releasing pancreatic β-cells where they inhibit adenosine triphosphate (ATP)-sensitive K^+ channels resulting in depolarization of the cell membrane, opening of voltage-sensitive Ca^{2+} channels, increase in intracellular calcium levels and subsequent insulin release. Thus, endogenous insulin secretion is stimulated but insulin synthesis is unaffected. Insulin production is only stimulated by sulphonylurea if there is a sufficient mass of β-cells. Reductions in the available β-cells with progression of type 2 diabetes mellitus results in inadequately stimulated insulin release [50-54]. Loss of efficacy over time is a major concern with the use of sulfonylureas. This appears to be related to exhaustion of ß-cell function [52].

Sulphonylurea are well absorbed after oral administration and reach peak plasma concentrations within 2-4 hours [55]. Food ingestion appears to have very little effect on their efficacy, but it is nevertheless advised that they be taken at least 15-20 minutes before a meal, since all sulphonylurea are highly bound to plasma proteins, they can potentially interact with other protein-bound drugs, e.g., warfarin.

Displacement from plasma proteins because of drug interactions has been implicated as a cause of severe SU-induced hypoglycemia [56]. Sulfonylureas are predominantly metabolized by the liver and cleared by the kidneys. Therefore, they must be used cautiously in patients with advanced forms of either hepatic or renal impairment. The last two conditions drastically alter the half-life of these drugs and can increase the plasma concentrations up to 3 times, which contributes greatly to increased risk of hypoglycemic events [57, 58].

Glibenclamide is considered an intermediate-acting drug (12-24 hours) with active metabolites of which approximately 50% are eliminated by the liver [57, 59]. Gliclazide also has a duration of action of 12-24 hours, but up to 65% of active metabolites are excreted mainly by the kidneys [60]. Glimepiride has a duration of action of about 24 hours and is eliminated by the liver [42].

Sulfonylureas are approved for use as monotherapy and in combination with all other oral agents except other secretagogues (including the meglitinides). They can also be used in combination with longer-acting insulin as part of the day time sulphonylurea- night-time-insulin regimen [61]. Starting with a low oral dose, dosages can be up-titrated at intervals of 2-4 weeks to achieve optimal glycemic control.

Side-effects that have been reported include hypoglycemia, weight gain (1-4 kg over 6 months), skin reactions, acute porphyria and, rarely, hyponatraemia [53, 61, 62]. Hypoglycemia can occur because these drugs potentiate the release of insulin even when glucose concentrations are below the normal threshold for glucose-stimulated insulin release [58, 63]. Hypoglycemia is especially a problem with the first-generation agents because of their long half-lives. Elderly individuals, people who frequently skip meals, and people who perform frequent intense exercise are most susceptible admin [64].

Given that there is a sulfonyl component in the chemical structure of sulfonylureas, hypersensitivity can occur in people with sulfa allergies and should be prescribed to people with a sulfa allergy with caution [65]. Studies have showed that sulphonylurea are also vasoconstrictors and worsen vascular reactivity; they have been reported to increase the risk of death during long term follow-up after coronary angioplasty, and to increase the risk of in hospital mortality after angioplasty for acute myocardial infarction [66].

II. Non-Sulfonylureas (Miglitinide Analogs)

This is a new class of medications which is currently represented by nateglinide (phenylalanine derivative) and repaglinide (benzoic acid derivative) (Figure 4) [67, 68]. Those secretagogues molecules have more rapid anti-hyperglycemic action and shorter duration than sulfonylureas, thus providing better control of post-prandial hyperglycemia and reducing the risk of late hypoglycemia [69, 70].

Miglitinide analogs are considered as a first drug choice for patients with type 2 diabetes mellitus in whom glucose control cannot be improved further by diabetes education, healthy nutrition, bodyweight loss and increased physical activity, and especially in those patients in whom metformin is contraindicated [69].

They are distinguished from the SUs by their short metabolic half-lives, which result in brief episodic stimulation of insulin secretion [71].

Therefore, they need to be taken more frequently [72].

Similar to sulfonylurea (though the binding site is different) miglitinide analogs stimulate insulin secretion by inhibiting adenosine triphosphate (ATP)-dependent potassium channels in the membrane of the pancreatic β-cell.

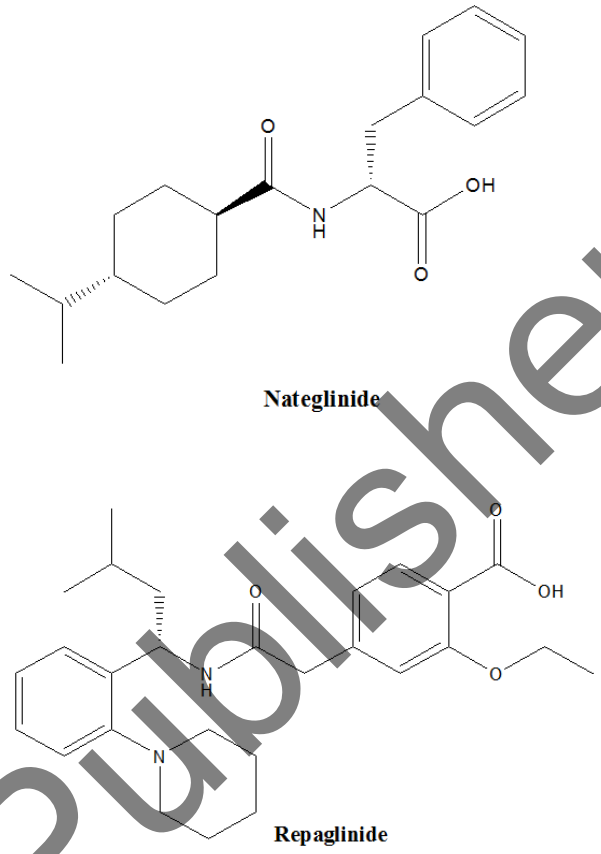


Figure 4. Chemical structures of miglitinide analogs; nateglinide and repaglinide.

This causes depolarization and gating of the voltage-sensitive calcium channels, increasing the intracellular concentration of calcium and subsequent exocytosis of insulin-containing granules [12-14, 73-75].

Pharmacokinetic profiles of repaglinide and nateglinide showed that both are rapidly absorbed from intestinal tract after oral intake and have a very rapid onset of action. Repaglinide absorption is not affected by food, the bioavailability is 63% and the half-life is 1 hour. Nateglinide absorption is dose-dependent; its bioavailability is approximately 72%. Both agents have a small volume of distribution and are extensively bound to plasma albumin. These compounds are metabolized in the liver through the cytochrome p450 system. Repaglinide is metabolized by the liver cytochrome P450 (CYP3A4) and eliminated rapidly throughout the biliary tract. Nateglinide is metabolized mainly via the hepatic CYP2C9 and CYP3A4 isoenzymes of cytochrome P450 and is eliminated primarily by the kidney. Studies

have showed that substances which inhibit the enzyme CYP3A4 may reduce repaglinide metabolism and increase its concentration, while drugs which induce CYP3A4, may accelerate its metabolism [67-68, 76-77]. Repaglinide and nateglinide are approved for use either as monotherapy or in combination with other oral anti diabetic drugs except sulfonylureas. Because of their short duration of action miglitinide analogs only stimulate insulin secretion to cover the postprandial period without causing sustained insulin release between meals, hence, they should be taken immediately before meals and be omitted if the meal is missed. The lower risk of hypoglycemia, compared with a sulphonylurea, makes these drugs an attractive choice in elderly patients; they may cause minimal weight gain [78-82].

Both nateglinide and repaglinide have a large therapeutic window with an excellent safety profile [69]. However, the main adverse effects associated with this class are hypoglycemia and body weight gain [81, 83]. The risk of hypoglycemia is lower than that with sulfonylureas [84]. This difference is due in part to the shorter duration of action and in part to the glucose-dependent insulin tropic effects of nateglinide [85].

Similarly, the amount of weight gain appears to be less than that seen with sulfonylureas, perhaps because of the limited duration of elevated insulin secretion. The nonsulfonylurea insulin secretagogues are contraindicated in patients with severe liver dysfunction, and the dose should be reduced in patients with severe kidney dysfunction [19]. Other less common side effects are itching or rashes, diarrhea, nausea and respiratory effects such as bronchitis, cough and upper respiratory infections [72].

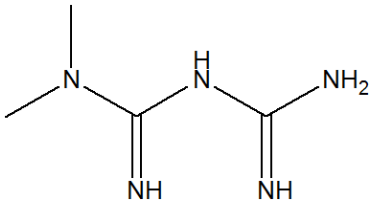
Insulin Sensitisers

I. Biguanides (Drugs That Reduce Glucose Production by the Liver)

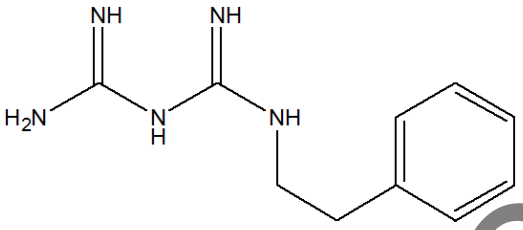
Biguanides, metformin and phenformin (Figure 5) were introduced as treatment option for hyperglycemia in patients with noninsulin-dependent diabetes mellitus (NIDDM), but phenformin was removed from the market because of a high frequency of lactic acidosis and related deaths [86]. Biguanides are generally considered the drug of choice in type 2 diabetics in whom satisfactory control of blood glucose cannot be obtained by diet alone and who have no specific contraindication to the use of these drugs. Metformin has been used as the primary agent for treatment of both non obese and obese diabetics since unlike the sulphonylurea it does not tend to promote bodyweight gain and may cause some bodyweight loss [86-88].

Other non-glycemic benefits have also been ascribed to metformin, such as the treatment of polycystic ovarian syndrome (PCOS) to improve insulin sensitivity and to lower circulating androgen levels. It also improves ovulation and menstrual cyclicity. The US's Food and Drug Administration still considers this an unlicensed indication of this drug in the absence of diabetes [89]. Metformin, therefore, may be very beneficial in NIDDM patients with associated hypertriglyceridemia and atherosclerosis [90, 91].

The proposed mechanisms that have been suggested to be responsible for biguanides effect of lowering elevated blood glucose concentrations are mainly a consequence of (1) reduced hepatic glucose output (primarily through inhibition of gluconeogenesis and, to a lesser extent, glycogenolysis) which contributes to the post-prandial plasma glucose lowering effects, (2) increased insulin-stimulated glucose uptake in skeletal muscle and adipocytes and (3) metformin also accumulates in the intestinal wall and decreases glucose absorption [83, 86].



metformin



phenformin

Figure 5. Chemical structures of biguanides; metformin and phenformin.

Metformin has an absolute oral bioavailability of 40 to 60%. It is rapidly distributed following absorption and accumulates in the esophagus, stomach, duodenum, salivary glands and kidneys. It does not bind to plasma proteins.

Because of differences in chemical structure compared with other biguanides (phenformin for instance), metformin escapes liver metabolism almost entirely, no metabolites or conjugates of metformin have been identified and 20 to 30% of an oral dose being recovered in the faces. It is eliminated by renal excretion. Hence, it accumulates only in individuals with renal impairment. Metformin has a plasma half-life about 2-5 hours, with 90% of the dose eliminated within 12 hours. Slow and incomplete absorption in combination with rapid elimination makes the rationale for sustained-release preparations of a drug less obvious [56, 92-95].

Metformin was approved for use in diabetes either as monotherapy or in combination with other oral anti diabetic drugs, as well as with insulin [96]. The starting metformin dosage is 500 mg twice daily, given with the two largest meals to minimize gastrointestinal side effects and beneficial effects can be seen within 1 week. The dose can be titrated every 2 weeks up to 2000 mg daily. The dosage should be increased by 500 mg/day every 2 weeks until the desired therapeutic goal is achieved or a maximum dosage of 2000 mg/day is reached [90, 97]. Extended-release metformin is an important addition to the formulary which reduces side effects and improves compliance with once a day dosing [64].

The most common adverse effects of metformin are gastrointestinal complaints like bloating, flatulence, diarrhea, abdominal discomfort and pain, though these may be mild and temporary, especially if dosages are brought up slowly. The frequency of these adverse effects can be minimized with food consumption and slow titration of dose; the need to discontinue therapy is uncommon [98].

Other side effects include lactic acidosis. Metformin increases lactate production in the splanchnic bed and portal venous system due to a reduction in the activity of pyruvate

dehydrogenase enzyme, thereby shifting the metabolism towards the anaerobic spectrum [99]. Metformin can interfere with vitamin B12 absorption, but this is rarely of clinical significance. Weight gain is not on the list of metformin's side effects [64], because it does not increase insulin secretion. Biochemically documented hypoglycemia is rare in diabetic patients treated with metformin alone [47]. Contraindications for this drug include evidence of kidney disease, significant liver disease, congestive heart failure, metabolic acidosis, dehydration and alcoholism [19].

Therefore, it may be used in elderly patients who do not have any of the above contraindications [28, 88]. The use of metformin for gestational diabetes seems to be safe, as indicated by a recently published MiG study [100].

II. Thizolidindiones

Currently available thiazolidinediones (TZDs) are rosiglitazone and pioglitazone (Figure 6). They act as insulin sensitizers, providing a novel means to improve glycemic control by reducing insulin resistance, they improve insulin sensitivity at peripheral tissue sites (skeletal muscle and adipose tissue) resulting in increased insulin dependent glucose disposal [101]. Troglitazone, another thiazolidinedione that was introduced in the markets in the United States. It was later removed from the market because of rare idiosyncratic hepatocellular injury [102]. Preliminary data suggest that thiazolidinediones may have beneficial effects beyond that of glycemic control. The TZDs also have certain lipid benefits.

For instance, an increase with TZD therapy results in a fall of triglyceride concentrations [103, 104]. In addition to their ability to reduce urinary albumin excretions they increase levels of high-density lipoprotein cholesterol and reduce triglyceride levels, lower blood pressure and reduce levels of plasminogen activator inhibitor [19, 105, 106].

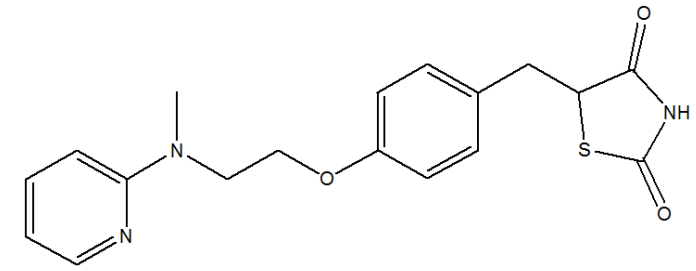
Further, they help to restore ovulation and attenuate ovarian androgen production without weight gain or other side effects [107].

The mechanism of action of the thiazolidinediones at the cellular level has not been fully elucidated [101]. The most prominent effect of TZDs is increasing the insulin-stimulated glucose uptake by skeletal muscle cells [102, 108-109].

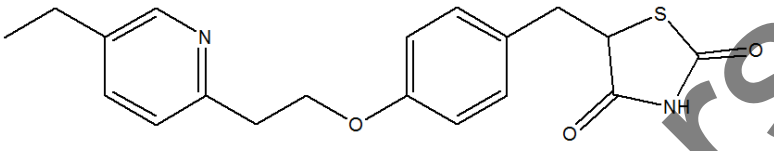
There is a variety of experimental data suggesting that the TZDs are selective and potent pharmacological ligands for a nuclear receptor known as peroxisome-proliferator-activated receptor gamma. When this receptor is activated it binds with response elements on DNA, altering transcription of a variety of genes that regulate carbohydrate and lipid metabolism [102]. Activation of peroxisome-proliferator-activated receptor gamma also reduces lipolysis and enhances adipocyte differentiation. This receptor is most highly expressed in adipocytes, while expression in myocytes is comparatively minor.

Therefore, the increase in glucose uptake by muscle may largely be an indirect effect mediated through TZD interaction with adipocytes [110]. TZDs enhance the responsiveness and efficiency of beta cells by decreasing glucose and free fatty acid levels, both of which have deleterious effects on insulin secretion [111].

Both rosiglitazone and pioglitazone are rapidly absorbed after a meal, reaching peak concentrations within 1-2 hours, and both undergo hepatic metabolism. Although rosiglitazone and pioglitazone are metabolized by CYP 2C8 and CYP 3A4 respectively, no major drug interactions have been reported. Rosiglitazone excreted mainly in urine and pioglitazone in bile [56].



Rosiglitazone



Pioglitazone

Figure 6. Chemical structures of thiazolidinediones (TZDs): rosiglitazone and pioglitazone.

Thiazolidinediones are the most expensive class of anti-diabetic medication and are indicated as monotherapy and in combination with metformin, SUs, and insulin (pioglitazone only). When monotherapy with either metformin, acarbose, a sulphonylurea or meglitinide does not achieve the required level of glycemic control, a combination therapy is advised without delay [19, 98]. TZDs have a slow onset of action, so the full effect may not be seen for up to 4 months. Rosiglitazone's starting dose is 4 mg once daily or 2 mg twice daily and is titrated up at the same interval as pioglitazone to a maximum of 8 mg/day. Pioglitazone is initiated at 15 mg daily and titrated up every 3 to 4 weeks to a maximum dose of 45 mg [47].

Edema, anemia, pulmonary edema and congestive heart failure are the major side effects of rosiglitazone and pioglitazone [112]. Bodyweight gain (in the order of 3 to 4 kg) has also been noted in the first year of treatment with thiazolidinediones. Monotherapy with thiazolidinediones has not been associated with hypoglycemia to date [113-115]. Safety of the glitazones in pregnancy and lactation has not yet been established [56, 116]. An Increase in plasma volume has been reported after administration of thiazolidinediones in healthy individuals so these agents are contraindicated in patients with moderate to severe chronic heart failure. The use of thiazolidinediones is also contraindicated in the presence of hepatic dysfunction [117].

Alpha-Glucosidase Inhibitors

α-Glucosidase inhibitors (AGIs; acarbose, miglitol, voglibose, Figure 7) are widely used in the treatment of patients with type 2 diabetes. AGIs delay the absorption of carbohydrates from the small intestine, thereby providing a unique mode of action in controlling the release of glucose from complex carbohydrates and disaccharides to reduce postprandial glucose levels [118-120]. AGIs can be used as first-line drugs in newly diagnosed type 2 diabetes

insufficiently treated with diet and exercise alone [121], as well as in combination with all oral anti diabetics and insulin if monotherapy with these drugs fails to achieve the targets for HbA1c.

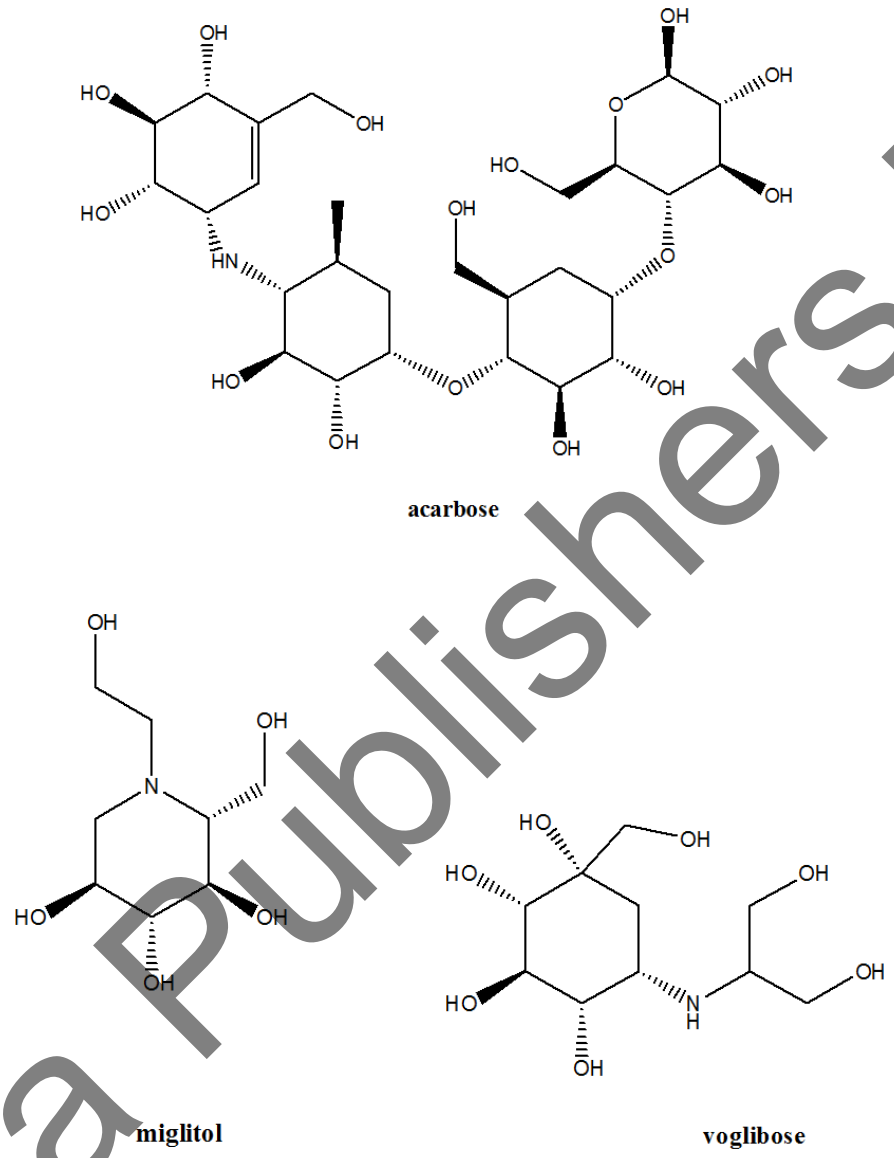


Figure 7. Chemical structures of α-glucosidase inhibitors; acarbose, miglitol and voglibose.

This class of drugs has the advantage of reducing excessive postprandial hyperglycemia without associated weight gain [56]. The blood glucose lowering efficacy of AGIs is considerably less than that of most of the other classes of oral anti diabetics like SUs or metformin [121-123].

This class acts as competitive, reversible inhibitors of α-glucosidase that present in the brush border of enterocytes in the intestinal villi and α-amylase that found in the pancreas; these enzymes are responsible for the breakdown of non-absorbable dietary oligosaccharides

and disaccharides into mono-saccharides suitable for absorption, This retards glucose entry into the systemic circulation and lowers postprandial glucose levels. α-Glucosidase inhibitors act locally at the intestinal brush border and are not absorbed, they are excreted in feces.

These agents do not affect insulin levels, so they do not cause hypoglycemia when are used alone [7, 56, 64, 124-125].

Acarbose and voglibose are not absorbed from the intestine, and have poor bioavailability. Miglitol, on the contrary, is almost completely absorbed from the upper part of the intestine. All three AGIs are distributed in extracellular space, with low tissue affinity and variable protein binding. Acarbose and voglibose are excreted through the fecal route, while miglitol is excreted by the kidneys [126, 127].

Given the relatively poor efficacy compared with other oral anti diabetic agents, α-glucosidase inhibitors are rarely used alone [7], and are most useful in combination with other drugs [119]. They should be taken with the first bite of food during a meal and not more than 15 minutes after the start of the meal [128]. The recommended doses of acarbose are 25 mg, 50 mg until a maximum dose of 100 mg three times a day. Voglibose should be orally administered in a single dose of 0.2 mg three times a day, just before each meal; if not sufficient, the dose can be up titrated to 0.3 mg three times a day. Miglitol should be started at 25 mg three times daily and then increased after four to eight weeks to 50-100 mg three times daily [129].

The major complaints of this class are bloating, flatulence, diarrhea and abdominal discomfort and pain. These effects tend to diminish with continued drug use. However, eating less carbohydrate in the diet, initiation of therapy with a low dose and slow titration may also help to minimize these adverse effects. The use of these drugs is contraindicated in pregnancy and breastfeeding and in patients with irritable bowel syndrome or severe kidney or liver dysfunction. Inflammatory bowel disease is a relative contraindication. Hypoglycemia can occur only if used in conjunction with a sulphonylurea or insulin, but does not occur when a drug in this class is used alone; if it occurs, it must be treated with glucose itself [7, 56, 124, 130-132].

Incretin Based Therapy (Dipeptidyl Peptidase-4 (DPP-4) Inhibitors)

The DPP-4 inhibitors sometimes called incretin enhancers represent the first oral therapies targeted at increasing endogenous incretin levels. As the name suggests, these agents function by inhibiting the essential enzyme DPP-4.

DPP4 is a complex molecule that exists as a membrane-spanning cell-anchored protein that is expressed on many cell types extending the physiologic half-life of endogenous GLP-1 and GIP by preventing their degradation [133].

These may be best employed early in type 2 diabetes before substantial impairments in incretin secretion become apparent [134]. DPP4 inhibitors include sitagliptin, vildagliptin and saxagliptin (Figure 8) [135, 136]. An alternative strategy has focused on supplying an exogenous, more stable molecule with the action of GLP1 (the GLP1 mimetic, exenatide, or the human GLP1 analogue, liraglutide) [137].

To understand the mechanism of action associated with the gliptin class, one must understand the function of the incretin hormones. Endogenous incretin hormones, namely glucose-dependent insulin tropic polypeptide (GIP) and glucagon like peptide 1 (GLP1), are peptide hormones secreted from endocrine cells in the small intestine in response to nutrients.

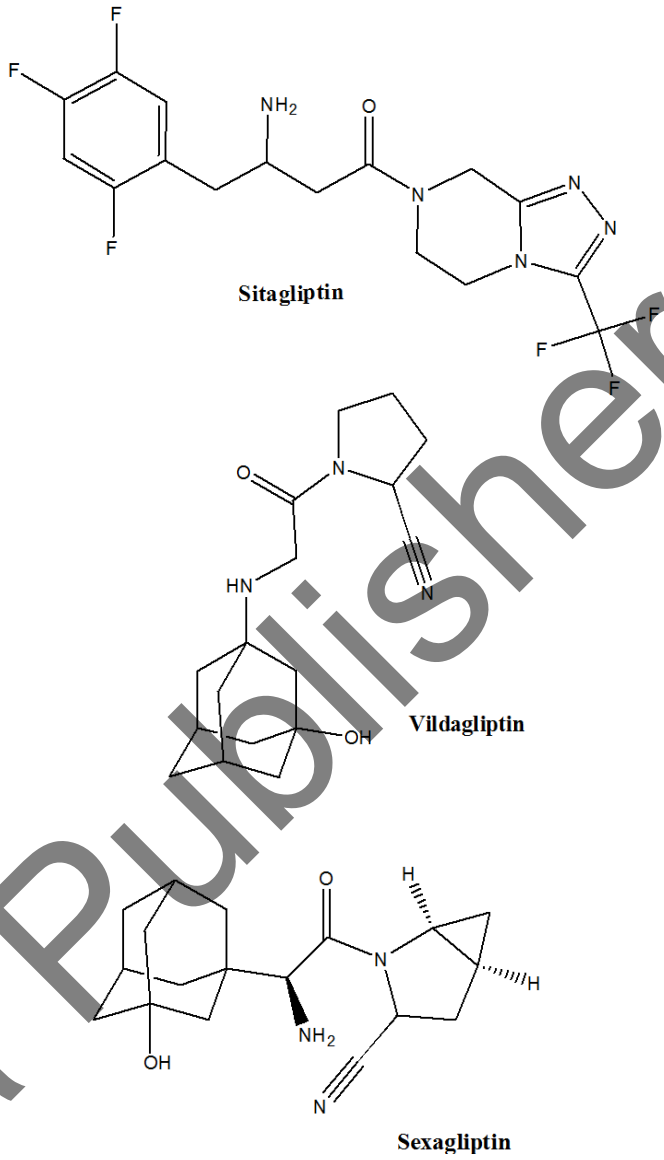


Figure 8. Chemical structures of DPP4 inhibitors; sitagliptin, vildagliptin, and saxagliptin.

In healthy individuals, both of these molecules activate insulin secretion; GLP1 also inhibits glucagon secretion and slows gastric emptying [138].

Its effects are terminated by breakdown by the enzyme dipeptidyl peptidase IV (DPP-IV). Therefore, inhibition of DPP-IV increases GLP-1 levels in the circulation and, hence, insulin is released under conditions when it is needed, i.e., after a meal but not during fasting. Consequently, inhibition of GLP-1 inactivation is an insulin tropic principle which is unlikely

to cause hypoglycemia between meals [139]. However, a key limitation to therapeutic use of the endogenous incretins is their rapid turnover (half-lives of 1 to 2 minutes), resulting from the action of the circulating enzyme dipeptidyl peptidase 4 (DPP4), which rapidly inactivates GIP and GLP1 [140]. DPP-IV is found throughout the body, however, the highest concentrations are found in the kidneys, intestines, and bone marrow [141, 142].

All together gliptins have a good oral bioavailability which is not significantly influenced by food intake. PK/pharmacodynamics characteristics, that is, sufficiently prolonged half-life and sustained DPP-4 enzyme inactivation, generally allow one single oral administration per day for the management of T2DM; the only exception is vildagliptin for which a twice-daily administration is recommended because of a shorter half-life. DPP-4 inhibitors are in general not substrates for cytochrome P450 (except of saxagliptin which is metabolized via CYP 3A4/A5) and do not act as inducers or inhibitors of this system. Several metabolites have been documented but most of them are inactive; however, the main metabolite of saxagliptin also exerts a significant DPP-4 inhibition and is half as potent as the parent compound. Renal excretion is the most important elimination pathway, except for linagliptin whose metabolism in the liver appears to be predominant. The PK characteristics of DPP-4 inhibitors suggest that these compounds are not exposed to a high risk of drug-drug interactions. However, the daily dose of saxagliptin should be reduced when co-administered with potent CYP 3A4 inhibitors [143].

Gliptins can be used as monotherapy or in combination with other anti-diabetic compounds. Sitagliptin, vildaglipin and saxagliptin are already on the market in many countries, either as single agents or in fixed-dose combined formulations with metformin. Other DPP-4 inhibitors, such as alogliptin and linagliptin, are currently in late phase of development [143]. Sitagliptin is commercially available in 25-mg, 50-mg, and 100-mg tablets [144]. The recommended dose of sitagliptin is 100 mg once daily; and this is the most effective dose for various glycemic parameters. In patients with moderate or severe renal insufficiency, the dose must be reduced to 50 mg and 25 mg once daily, respectively. The administration of sitagliptin is independent of meals [145, 146]. The recommended dosage of saxagliptin is 2.5 or 5 mg once daily administered orally regardless of meals. Dose should be reduced to 2.5 mg daily in patients with moderate to severe renal impairment or end-stage renal disease (CrCl < 50 ml/min) as well as with concurrent administration of strong CYP3A4/5 inhibitors (ketoconazole, clarithromycin, atazanavir, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir and telithromycin) [147].

In clinical studies, agents of the gliptin class were well tolerated, although infections, including nasopharyngitis, upper respiratory tract infections, and urinary tract infections, were significantly increased with sitagliptin. Headache was reported for both drugs but was more common in patients taking vildagliptin [148]. Sitagliptin is a pregnancy risk Category B agent and should only be used during pregnancy if deemed necessary. Caution is also advised in women who are nursing [144]. Sitagliptin is contraindicated in patients with type 1 diabetes and is not intended for use in the treatment of diabetic ketoacidosis. Drug–drug interactions were not observed with the use of sitagliptin, and especially no such interactions were found with other anti-hyperglycemic agents in type 2 diabetic patient [149].

Conclusion

Diabetes mellitus is a complex disorder associated with significant health and economic burdens. Keeping blood glucose levels near the normal range lowers the risk of complications and is an important therapeutic goal.

As the number of people with diabetes and the cost of treating diabetes continue to increase the challenge of treating this disease grows by the day, hence, a good understanding of the available treatment modalities is of great value. As the pathogenesis of diabetes becomes much understood, exciting new targets for drug therapy will be identified and the number of oral ant hyperglycemic agents will continue increasing, each with its own mode of action. Thus providing physicians with more 'fire power' and treatment options in the fight against this disease.

The choice of treatment should be individualized and based on the risk-benefit balance, taking into account the potential for hypoglycemia, and the weight and HbA1c concentration targets that are needed be achieved for a particular patient. Most patients will require combination therapy as their disease progresses.

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Chapter 6

Anti-Hemorrhagic Agents

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Abstract

Bleeding disorder is defined as inability to form a normal clot after an exposure to trauma, injury, surgery or menstruation which leads to extensive bleeding and might be a life threatening condition. The treatment of bleeding disorders depends on the type and severity of the bleeding. Anti-hemorrhagic agents are used to stop bleeding; they are also known as hemostatic agents.

This chapter describes the two different classes of anti-hemorrhagic agents (hemostatic agents): the first class includes systemic drugs such as tranexamic acid, ω-aminocaproic acid, anti-inhibitor coagulant complex-heat treated, anti-hemophilic factor, factor IX, carbazochrome, fibrinogen concentrate, oprelvekin and phylloquinone and the second class of hemostatic agent is the local acting agents such as cellulose, collagen, gelatin, thrombin and thrombin combination products.

Keywords: Anti-bleeding agents, tranexamic acid, ω-aminocaproic acid, anti-inhibitor coagulant complex-heat treated, anti-hemophilic factor, factor IX, carbazochrome, fibrinogen concentrate, oprelvekin, phylloquinone

Abbreviations

F	Factor
TF	Tissue factor
TA	Tranexamic Acid

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ACA	Aminocaproic acid
R	Recombinant
IV	Intravenous
SC	Subcutaneous

Background

Bleeding disorder is the inability to form a normal clot after exposing to trauma, injury, surgery or menstruation which can lead to extensive bleeding and consequently this condition may be a life threatening. Bleeding disorder maybe occur due to a defect or a deficiency in the blood clotting factors.

There are 13 different clotting factors used in clotting process when the body is exposed to injury, the clotting cascade will be activated using these factors so if one of them works in an improper way the body will have a mild, moderate or severe bleeding condition.

The majority of defects in these factors are inherited and other defects occur due to medical conditions as liver disease, vitamin K deficiency, a low red blood count and medications side effects.

The most common bleeding disorders are:

1 **Hemophilia, which** is a bleeding disorder that is caused by a deficiency or a defect in blood clotting factors such as factor VIII (hemophilia A) or factor IX (hemophilia B), patient with hemophilia will experience an abnormal bleeding after exposing to injury, the bleeding can occur in the joints, muscles, and soft tissues. There are two main types of hemophilia: (i) Hemophilia **A also known as** factor VIII (FVIII) deficiency or classic hemophilia, it is the most common type of hemophilia, it can be caused by inherited deficiency of functional blood clotting factor VIII, or in other cases this disorder can occur due to a mutation in the gene and (ii) Hemophilia B **also known as** factor IX (FIX) deficiency or Christmas disease.
2 Von Willebrand disease, is the most common inherited bleeding disorder caused by deficiency or impairment of a protein called Von Willebrand factor (VWF); this factor plays a key role in clotting process, it binds to factor VII and helps blood platelets clump together and stick to a blood vessel wall and
3 Factor II, V, VII, X, XII deficiency which is related to blood clotting problems or abnormal bleeding problems.

The main symptoms of bleeding disorder is excessive prolong heavier bleeding after minor cuts or dental surgery, unexplained bruising, heavy menstrual bleeding and frequent nose bleeding. The treatment of bleeding disorders depends on the type and severity of the bleeding. Ant hemorrhagic agents are used to stop bleeding and they are also known as hemostatic agents. Anti-hemorrahgic agents (hemostatic agents) can be classified into two groups depending on their mechanism of action:

- Systemic drugs that inhibit fibrinolysis or prompting coagulation.
- Locally acting hemostatic agents work by causing vasoconstriction or prompting platelet aggregation.

The Biology of Hemostasis

Hemostasis is defined as tightly regulated process that limits blood loss from injured vessels. Four interrelated components participate in the hemostatic process: vascular constriction, platelet plug formation, fibrin formation and fibrinolysis. Once the vessel injured, the smooth muscle is constricted and diminish the blood loss while the exposed damaged collagen stimulates platelets adherence and platelets activation. Activated platelet releases cytoplasmic granules that contain serotonin (vasoconstrictor), ADP and thromboxane A2 which lead to more platelets adhesion and activation to form a platelet plug. Von Willebrand is a glycoprotein which stimulates the platelets to adhere, stick to each other and form the plug which is followed by an initiation ofthe coagulation cascade.

Coagulation Cascade

Coagulation cascade (Figure 1) consists of two interrelated pathways: tissue factor pathway (extrinsic) and contact activation pathway (intrinsic). The activation of these pathways leads to fibrin formation [1].

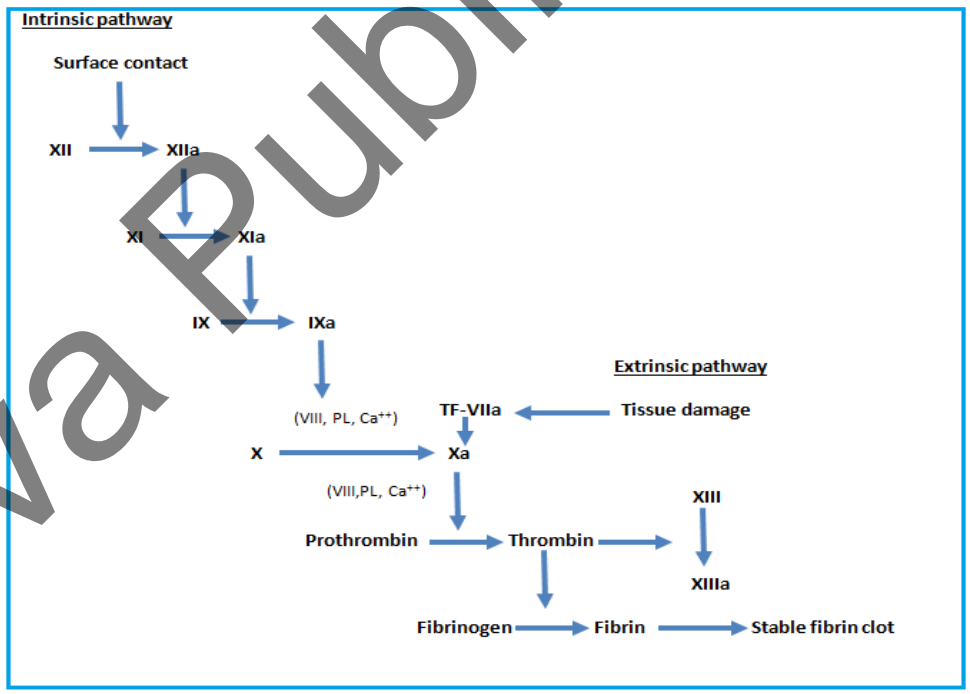

Figure 1. The coagulation cascade.

Intrinsic Pathway

The intrinsic pathway requires clotting factors VIII, IX, X, XI and XII, in addition to proteins prekallikrein (PK) and high molecular weight kininogen (HK), both proteins facilitate the activation of factor XII to factor XIIa (FXIIa). Activated factor XIIa activates factor XI (FXIa) which catalyzes the conversion of factor IX to FIXa. The latter binds with FVIII on the surface of the cell's membrane to form complex IXa-FVIIIa which binds to factor X and activated to FXa. FXa binds with FV to form complex FXa-FVa, then prothrombin binds with this complex and converts to thrombin.

Extrinsic Pathway

As the tissue factor (TF) is released after the tissue is damaged, it binds with factor VIIa (FVIIa) that is circulated within the blood and forms an activated complex, TF-FVIIa, which in its turn activates FIX and FX. The activated form of FX (FXa) activates the conversion of prothrombin (FII) to thrombin (FIIa). The production of thrombin is needed for the conversion of fibrinogen to insoluble fibrin. The insoluble fibrin aggregates to form clots that gather with aggregated platelets of the damaged blood vessel and prevent further bleeding [2].

Fibrinolysis Inhibitors

Two synthetic lysine derivatives are used as fibrinolytic inhibitors named ω-aminocaproic acid (ACA) and tranexamic acid (TA) and there is a naturally occurring inhibitor called aprotinin which was approved but it was withdrawn from the drug's market in 2008 [3].

Both, ω-aminocaproic and tranexamic acids work as competitive inhibitor of plasminogen that prevents the activation of plasminogen to plasmin; plasmin is an enzyme used to degrade fibrin clot.

Tranexamic Acid

Tranexamic acid (trans-4 (aminomethyl) cyclohexanecarboxylic acid) (Figure 2) is a synthetic lysine derivative. It is used as antifibrinolytic to treat excessive blood loss during surgery and in other medical conditions as hemorrhage in hemophilia patients and the bleeding in tooth extraction procedure. It is a competitive inhibitor of plasminogen that prevents the activation of plasminogen to plasmin. Tranexamic acid is an important agent in decreasing mortality rate due to bleeding in trauma patients; this can be evident from CRASH-2 study which revealed that all caused mortality, relative risk and relative death due to bleeding were reduced with a tranexamic acid group compared to a placebo group [4].

Tranexamic acid can be used safely in women who undergo lower segment cesarean section; in this operation, it was found that tranexamic acid reduced the blood loss during and

after surgery [5]. Furthermore, it is pharmacologically active in reducing blood using in intra-operative heart, hip and knee replacement and liver transplant surgeries [6].

Tranexamic acid is considered as an effective medication and safe non-hormonal therapy for the management of heavy blood loss during menstrual cycle and hence it improves women`s life quality during menses [7]. In a randomized controlled trial it was concluded that oral tranexamic acid is effective in decreasing blood loss during menstrual cycle by 40%. The total oral dose recommended in women with heavy menstrual bleeding was two 650 mg tablets three times daily for 5 days [8].

It was demonstrated that tranexamic acid is effective in inhibiting the activity of urokinase in urine [9]. Therefore, it is safe and effective to treat severe hematuria in patient with chronic renal impairment that are poorly respond to conventional therapy [10].

Further, it was reported that tranexamic acid inhibits the ultraviolet radiation induced pigmentation activity hence it can be used as a bleaching agent. Oral tranexamic acid is effective and safe in treating malesma which is a hypermelanosis disease that occurs in Asian women and it is a non-invasive and non-irritating treatment for this disease [11].

Pharmacokinetics of Tranexamic Acid

Studies on healthy individuals using an intravenous injection of tranexamic acid with a dose of 10mg per kg of body weight showed that the highest plasma concentration was reached within one hour after the injection [9]. After 24 hours, 90% of the dose was excreted in the urine with reported elimination half-life of 80 minutes. After an oral doses of 10 to 15mg per kg body weight, the maximum plasma concentration was reached after 3 hours [12]. Absorption of tranexamic acid was shown not to be affected with the presence of food in the stomach [13]. It was found that tranexamic acid has the ability to cross the placenta to the fetus [14] without teratogenic effect, and it can be found in breast milk with a concentration 100 times lower than its concentration in the serum [15].

Side Effects of Tranexamic Acid

The side effects of using tranexamic acid are diarrhea, nausea, vomiting, headache, fatigue, and low blood pressure and blood clot events.

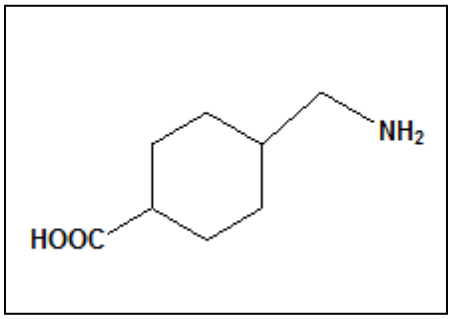

Figure 2. Chemical structure of tranexamic acid.

Ω-Aminocaproic Acid

Ω-Aminocaproic acid (Figure 3) used to control bleeding during or after heart surgery, in people who have certain bleeding disorders, prostate, lung, stomach, or cervical cancer, and in pregnant women when the placenta separates from the uterus before the baby is ready to be born. It is also used to control bleeding in the urinary tract that may occur after prostate or kidney surgery [16]. ω-Aminocaproic acid is effective in decreasing mortality and morbidity in many traumatic cases and different types of surgery like coronary artery bypass grafting in which its administration results in a significant decrease in blood loss, and blood transfusion requirements are significantly reducedespecially in patients undergo hip replacement [17].

In addition, ω-aminocaproic acid can reduce the incidence of secondary hemorrhage following traumatic hyphema [18], and it plays an important role in dental extraction in patients with hemophilia [19].

Pharmacokinetic of Ω-Aminocaproic Acid

Peak plasma concentration of ω-aminocaproic acidis reached within 1.2 hours after an administration of a single dose of 5 g. The drug is distributed through extravascular and intravascular compartments and excreted in the urine with an elimination half-life of 2 hours.

Side Effects of Ω-Aminocaproic Acid

The major side effects of ω-aminocaproic acid are slow heart rate, low blood pressure, peripheral ischemia, thrombosis, dizziness and headache, hallucination, ringing in the ear, decrease vision and watery eye, nausea and vomiting.

Ways to Improve the Bioavailability of Tranexamic and ω-Aminocaproic Acids

At physiological pH of the intestine, tranexamic and ω-aminocaproic acids exist mainly in their ionized forms. This ionization decreases the ability of these two anti-bleeding agents to be absorbed to the systemic blood circulation and hence only 34% of tranexamic acid and 24% of ω-aminocaproic acid are available in the systemic circulation [13, 20].

A bioavailability is known as the rate at which the active drug reaches the systemic circulation. Low bioavailability of drugs occurs as a result that the resident time of the drug in the stomach is too long or the drug has an insufficient solubility in the blood.

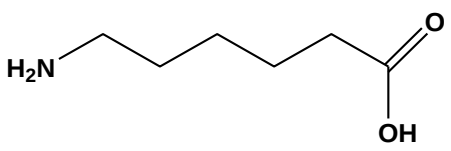

Figure 3. Chemical structure of ω-aminocaproic acid.

The bioavailability can be improved by a variety of techniques such as a solid dispersion, nanonisation and synthesis of prodrug.

A prodrug is a chemical entity in which the drug is covalently linked to a chemical moiety; this alteration temporarily affects the physicochemical properties of the drug for the purpose to increase its usefulness or decreasing its toxicity. The prodrug should be converted to its active form by metabolic or/and chemical processes. The metabolic conversion process involves catalysis by enzymes distributed throughout the body. These enzymes might decrease the drug's bioavailability and their genetic polymorphisms might lead to variability in prodrug activation and thus affect the efficacy and safety of the prodrug.

In the past few decades computational chemistry methods have been utilized in calculating physicochemical and molecular properties of variety of compounds. This tool can be used to design prodrugs that chemically (intramolecular processes) interconvert to their parent drugs without any involvement of enzyme catalysis. The release of the active drug is solely dependent on the rate limiting step of the intramolecular process.

Recently, Karaman's group has designed several prodrugs of tranexamic and ω-aminocaproic acids utilizing Kirby's N-alkylmaleamic acid linkers [21]. In vitro kinetic studies of the prodrugs shown in Figure 4 revealed that the conversion rate of the acid-catalyzed hydrolysis of these prodrugs to their corresponding drugs are largely affected by the nature of the linker and the reaction medium (Table 1).

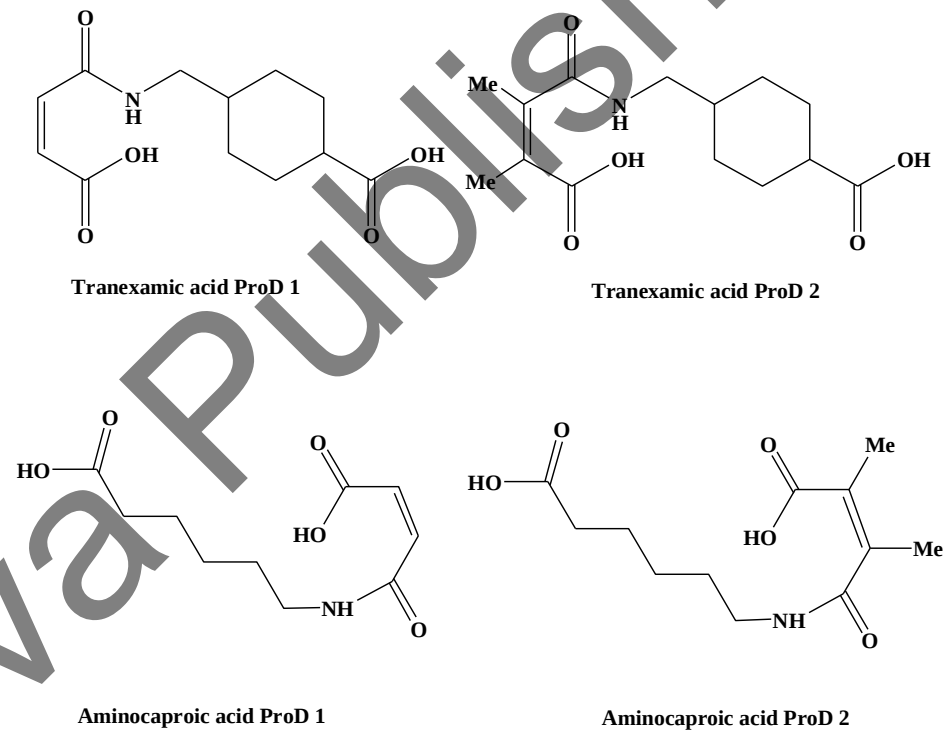

Figure 4. Chemical structures of tranexamic acid and ω-aminocaproic acid prodrugs.

Table 1. Half-life ($t_{½}$) values for the conversion of tranexamic acid and ω-aminocaproic acid prodrugs to their parent drugs in different media

Prodrug system	$t_{1/2}$ (h)	
Tranexamic acid ProD 1	1N HCl	0.9
	pH 2	23.9
	pH 5	270
	pH 7.4	No reaction
Tranexamic acid ProD 2	1N HCl	Fast intraconversion
	pH 2	Fast intraconversion
	pH 5	No reaction
	pH 7.4	No reaction
ω-aminocaproic acid ProD 1	1N HCl	11
	pH 2.5	20.6
	pH 5	23.4
	pH 7.4	No reaction
ω-aminocaproic acid ProD 2	1N HCl	Fast intraconversion
	pH 2.5	15
	pH 5	19.5
	pH 7.4	No reaction

Anti-Inhibitor Coagulant Complex-Heat Treated

Anti-inhibitor coagulant complex-heat treated is a sterile human plasma fraction containing anti-inhibitor coagulation complex and active coagulation factor VIII (FVIII). It is effective as a treatment for bleeding episode in patients with hemophilia A and patients having inhibitors to factor VIII. It is available as an IV injection that should be given by a health care provider. Anti-inhibitor coagulant complex-heat treated is a second generation of this kind of complexes. It is vapor-heated for 10 hours at a temperature of 60°C and a pressure of 1190 millibar (mbar) and for 1 additional hour at 80°C and 1375 mbar. This heating step is designed to reduce the risk of transmission of hepatitis and other viral diseases such as HIV. A study was performed to evaluate if the heating process affects the efficacy of anti-inhibitor coagulant complex-heat treated compared with the unheated anti-inhibitor coagulant complex and it was concluded that the heated complex was at least as effective as the unheated complex in controlling bleeding episodes and can be compared favorably to any reported treatment of bleeding episodes in hemophilia, and no toxicity was reported upon its use [22].

Side Effects of Anti-Inhibitor Coagulant Complex-Heat Treated

The side effects accompanying the use of this method are headache, fever, chills, flushing, easy bruising, unusual bleeding (nose, mouth, vagina, or rectum), pass out feeling, runny nose, drowsiness, followed by rash and joint pain about 2 weeks later, sudden numbness or weakness, confusion, problems with vision, speech, or balance and changes in pulse rate and blood pressure due to too rapid administration.

Anti-Hemophiliac Factor

This medication is used to control bleeding episodes in patient with deficiency of factor VIII and hemophilia type A; it contains factor VIII, and there are two forms available from this product: plasma anti-hemophilic factor and human recombinant factor (man-made factor VIII).

The development of recombinant factor VIII (rFVIII) therapy was an important advance in the treatment of hemophilia, and it is superior than plasma anti-hemophilic factor because the use of plasma anti-hemophilia factor associated with virus transmission such as hepatitis A, B, C and human immunodeficiency virus (HIV) [23-25]. Therefore, the use of rFVIII is safe and efficacious treatment in hemophilia A patients [26].

A long term study was performed to assessthe efficacy and safety of rFVIII treatment in patients with hemophilia A and it was found that 82% of the bleeding episode was controlled by using only single infusion treatment and no viral infections were observed [27].

Side Effects of Anti-Hemophiliac Factor

The main side effects in using this medication are dizziness, headache, face, lips, tongue or throat swelling, flushing, burning, irritation and redness at the site of injection, fever, chills, loss of appetite, and difficulty of breathing and fast heart beat.

Factor IX

A recombinant factor IX (rFIX) is available to control bleeding episode in patients with factor IX deficiency as hemophilia B and it is available as intravenous injection.

A study was conducted to evaluate the effect of rFIX on previously untreated hemophilia B patients and it was shown that one infusion of rFIX can control 75% of hemorrhages, 94% of patients have shown a good response, rFIX was well tolerated and no viral transmission was observed [28].

It was found that rFIX can be used as prophylaxis in children with age of less than 6 years having a sever hemophilia B. Using 1 to 2 infusion of this medication per week for six months has proved to be effective and safe to prevent breakthrough hemorrhage [29].

Side Effects of Factor IX

The side effects accompanied with the use of this medication include headache, fever, chills, flushing, nausea, vomiting, lethargy and allergic reaction.

Taste perversion, injection site pain, burning sensation in jaw and skull are also adverse effects that were reported upon the use of this medication.

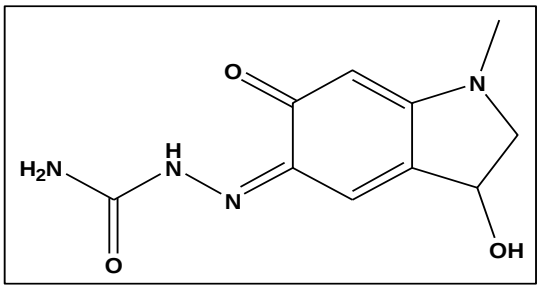

Figure 5. Chemical structure of carbazochrome.

Carbazochrome

Carbazochrome (Figure 5) is an anti bleeding agent used to stop blood flow from wound by increasing platelets aggregation and inducing platelet to form a plug. It is used to control bleeding in case of trauma, surgery and intestinal bleeding.

It acts as anti-bleeding agent by interacting with adrenorecptora that is located on platelet. The latter is a G-coupled protein binding that leads to an increase in intracellular calcium concentration which causes platelet to release factors such as serotonin, ADP, Von Willebrand and platelet activating factor that induce aggregation and platelet adherence.

It has been concluded that a combination between a fixed dose of carbazochrome with flavonoids, troxerutin, is a good and an efficacious treatment for acute uncomplicated hemorrhoids, and this combination is effective and well tolerated in the treatment of post hemorroidaectomy status [30].

Carbazochrome is available as capsules to be given with or without meal and as solution for injection under the skin to be given with the aid of a health care provider.

Side Effects of Carbazochrome

The side effects of carbazochrome are hypersensitivity and gastrointestinal disturbances.

Fibrinogen Concentrate

It is plasma derived purified fibrinogen and is indicated for acute bleeding in patients with congenital fibrinogen deficiency (a fibrinogenemia, hypofibrinogenemia). Fibrinogen is a protein synthesized in the liver and plays an essential role in hemostasis. It is available as intravenous injection that should be given by a health care provider.

Pre-clinical studies showed that the use of fibrinogen concentrate in hypofibrinogenemia may reverse the dilution coagulopathy by replacing the missing factor (factor I) and restoring the production of fibrin and clot formation [31]. It can also improve the whole blood clot firmness and reduce the postoperative blood transfusion needed in patient with severe bleeding [32]. The use of fibrinogen concentrate also reduces the transfusion of blood products in patients undergoing aortic surgery [33].

Side Effects of Fibrinogen Concentrate

The adverse effects of the use of fibrinogen concentrate are nausea, vomiting and headache.

Oprelvekin

Oprelvekin is a man made interleukin 11 (IL-11) used for sever thrombocytopenia in patients using certain chemotherapy drugs that inhibit platelets production from bone marrow. It works by inducing production, differentiation and maturation of body platelets. Oprelvekin is available as subcutaneous injection and it is used only for adult patients.

Evidence suggests that oprelvekin reduces severe thrombocytopenia, accelerates platelet recovery and reduces the need of platelet transfusion in patients treated with chemotherapy [34].

Side Effects of Oprelvekin

The side effects accompanied the use of oprelvekin are fluid retention, difficulty in breathing, fast heart rate, palpitation, abnormal heart rhythm, lung infections, fever, headache, chills, dizziness, sleeplessness, nervousness, rash, hair loss, skin discoloration, blurred vision, eye bleeding, muscle pain and bone pain.

Phylloquinone

Phylloquinone known as vitamin K1 (Figure 6) is used to treat bleeding disorders in patient with vitamin K deficiency. Vitamin K is a fat soluble vitamin needed by humans for a vital function in the blood clotting process.

Vitamin K is involved in the carboxylation of certain glutamate residues in protein to form gamma-carboxyglutamate residues (Gala-residues).

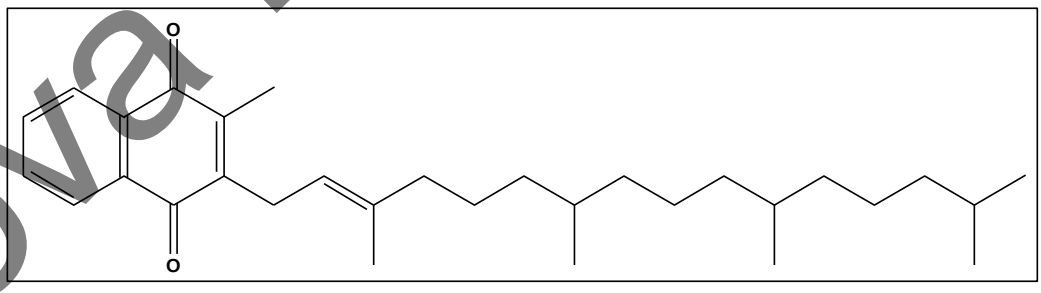

Figure 6. Chemical structure of phylloquinone.

Gala residues are usually involved in calcium binding and play important roles in the regulation of:

- Blood coagulation (prothrombin (factor II), factors VII, IX, X, protein C, protein S and protein Z).
- Bone metabolism
- Vascular biology.

Any deficiency of vitamin K which may occur as a result of malnutrition or due to therapeutic intake of vitamin K antagonist will lead to massive uncontrolled bleeding, cartilage calcification and severe developed bone malformation.

Vitamin K deficiency bleeding disorder in neonate may occur after four weeks of the neonatal period which leads to bleeding due to inadequate activity of vitamin K dependent coagulation factors (II, VII, IX, X) and it can be prevented by using one intramuscular or multiple oral vitamin K supplement [35].

Warfarin is used as an effective anticoagulant. It acts by inhibiting vitamin K epoxide reductase enzyme which is needed for the synthesis of vitamin K in the liver but patients treated with warfarin are at significant risk of bleeding. Vitamin K can be used to reverse the effect of warfarin in patients who have taken warfarin and need surgery, however it takes four to six hours for vitamin K to reverse the anticoagulation of warfarin [36].

Side Effects of Phylloquinone

The side effects of phylloquinone include severe life threatening allergic reactions, pain, swelling, and tenderness at site of injection, dizziness, difficulty in breathing, sweating and low blood pressure.

Locallyacting Hemostatic Agents

Topical local hemostatic agents are used in emergency bleeding control and applied directly to the site of injury to prevent continuous bleeding during surgery procedure and into postoperative recovery period. They can be divided into two categories, passive and active hemostatic agents.

Passive Hemostatic Agents

The basic mechanism of action of passive hemostatic agents is to provide a structure for platelets to be aggregated and form clots. The passive hemostatic agents include collagen, cellulose and gelatin. Collagen based agents can be applied to the bleeding site as powder, paste and sponge. They can control the bleeding by making direct contact between collagen and blood which stimulates platelet aggregation [37]. Bovine derived collagen has a potential to cause allergy in 2-4% of the population [38].

Cellulose based agents contain regenerated oxidized cellulose and it can be cut to the size that fits the wound. The mechanism of these agents is via contact activation [39].

A minimum amount of the agent should be applied to the site of injury and should be removed when hemostasis is achieved [40].

Gelatin based agents can control bleeding by contact activation. Gelatin has the ability to conform to irregular wounds and swell, the swollen gelatin will then restrict the blood flow and provide a stable matrix that can form a surface to initiate clot formation [41]. Gelatin sponge do not form a tight bond with the bleeding site [40].

Active Hemostatic Agents

Active hemostatic agents have a biological activity on coagulation cascade to induce clot formation at the site of bleeding. They include thrombin and thrombin combination products [42].

Thrombin Products

Three types of the active hemostatic agent thrombin are available, thrombin- bovine origin, thrombin- man made and recombinant thrombin.

The active hemostatic agents (thrombin) exert their effect on the last step on the coagulation cascade, the conversion of fibrinogen to fibrin [41]. Thrombin products can be used as adjunct therapy in the presence of anti-coagulant or anti-platelet therapy [41, 43].

Thrombin Combination Products

Thrombin can be used in a combination with passive hemostatic agent, gelatin, in order to increase effectiveness, more bleeding control, and greater reduced blood loss than using thrombin alone [44]. The combination consists of cross-linked bovine gelatin and thrombin.

Fibrin Sealant

Fibrin sealant is a fibrin glue product used to simulate the last step in the coagulation cascade. It contains a combination of two component systems, solution of concentrated fibrinogen and factor XIII combined with a solution of thrombin and calcium in order to form a clot. Once the thrombin and calcium are combined with the fibrinogen/factor XIII, a fibrin clot is formed in seconds [45, 46].

Conclusion

Bleeding disorder is the inability to form a normal clot after exposing to trauma, injury, surgery or menstruation which will lead to extensive bleeding and consequently this condition may be a life threatening.

The treatment of bleeding disorders depends on the type and severity of the bleeding conditions. Anti-hemorrhagic agents are used to stop bleeding. Fibrinolysis inhibitors as tranexamic and ω-aminocaproic acids are used to treat bleeding disorder by acting as a competitive inhibitor of plasminogen that prevents the activation of plasminogen to plasmin. Both tranexamic and ω-aminocaproic acids have a low bioavailability due to their amino acid nature. In addition, several other anti-hemorrhagic agents are used to treat bleeding disorders such as anti-inhibitor coagulant complex-heat treated, anti-hemophilic factor, factor IX, carbazochrome, fibrinogen concentrate, oprelvekin and phylloquinone. Furthermore, a number of topical anti-hemorrhagic agents are used to control emergency bleeding and prevent continuous bleeding during surgery such as cellulose, collagen, gelatin, thrombin and thrombin combination product.

In the past few years Karaman's group have used a novel prodrug approach to increase the bioavailability of some commonly used anti-bleeding agents such as tranexamic and ω-aminocaproic acids. The success of this chemically driven prodrug approach will open the door widely for improving the bioavailability of anti-bleeding agents suffering from poor permeation due to their polar nature.

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Chapter 7

Osteoporosis Drugs

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Abstract

Osteoporosis is a progressive bone disease that is characterized by a decrease in bone mass and density and deterioration of bone structure which can lead to bone fragility which might increase the risk of fracture. Fractures can be prevented by using osteoporosis drugs. This will save society from accommodation expenses in the hospital, nursing homes and save patients from the loss of quality of life and premature death.

Various therapies are available for osteoporosis. The most common are bisphosphonates, raloxifene, calcitonin, teriparatide and denosumab.

Bisphosphonates are a widely utilized class of drugs used in the management of disorders of calcium and bone metabolism. The major disadvantage concerning clinical use of bisphosphonate drugs is their poor and variable absorption after oral administration. Therefore, several strategies have been developed to increase their intestinal absorption either by changing the permeability properties of the intestinal absorptive cells or by modifying the structure of the drug through altering the physicochemical properties of the drug itself.

Raloxifene is the only selective estrogen receptor modulator that was approved worldwide for the prevention and treatment of postmenopausal osteoporosis, but its low bioavailability limited its use. It has been well established that calcitonin when administered by parental or intranasal routes are effective in preventing postmenopausal bone loss. Recently, oral formulation of calcitonin has been developed to enhance its clinical usefulness and many attempts have been made to enhance its oral bioavailability.

The recombinant human parathyroid hormone fragment, rhPTH(1-34) (teriparatide), is a potent anabolic agent used in the treatment of postmenopausal with severe osteoporosis, as well as for persons with established glucocorticoid-induced osteoporosis who are receiving long term glucocorticoids. Teriparatide was shown to reduce fracture

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risk and is now available for the treatment of patients with osteoporosis who are at high risk of fracture due to its ability to stimulate osteoblast activity to a greater extent than osteoclast.

Denosumab offers an alternative approach for the treatment of osteoporosis by decreasing bone resorption and increasing bone mineral density through the inhibition of receptor activator of nuclear factor kappa-B ligand (RANKL).

Keywords: Osteoporosis, osteoporosis drugs, bioavailability, bisphosphonates, raloxifene, calcitonin, selective estrogen receptor modulator, teriparatide, denosumab

Abbreviations

RNA	Ribonucleic Acid
ATP	Adenosine triphosphate
FDPS	Farnesyl diphosphate synthase
PCC	Palmitoyl carnitine chloride
TMC	*N*-trimethyl chitosan chloride
EGTA	Ethylene glycol-bis (β-aminoethyl ether)-*N*, *N*,*N*',*N*'-tetraacetic acid
EDTA	Ethylenediaminetetraacetic acid
BP	Bisphosphonate
PEPT1	Intestinal mucosal cell peptide transporter 1
ACE	Angiotensin converting enzyme
ODDS	osteotropic drug delivery system
CF-BP	carboxy-fluorescein, disodium (fluorescein-6-carbonyloxy) acetoaminomethylene BP
SERMs	Selective estrogen receptor modulators
HPMC	Hydroxypropylmethylcellulose
GI	Gastrointestinal
TDC	Sodium taurodeoxycholate
STC	Sodium taurocholate
LCC	Lauroylcarnitine chloride
MCC	Myristylcarnitine chloride
CPC	Cetylpyridinium chloride
rhPTH	Recombinant human parathyroid hormone
RANKL	Receptor activator of nuclear factor kappa-B ligand
BMD	Bone mineral density
GCTB	Giant cell tumor of bone

Introduction

Osteoporosis is the most common bone disease [1], which is characterized by low bone mass and deterioration of bone structure that causes bone fragility and increases the risk of fracture [2].

The disease may be classified as primary or secondary. Primary osteoporosis is a bone loss that occurs with aging. It is most common in women after menopause and may be diagnosed in elderly males [3, 4]. Secondary osteoporosis is a bone loss resulting from chronic predisposing medical problems (e.g, hypogonadism), diseases (e.g, malabsorption) or prolonged use of medications (e.g, glucocorticoids) [5, 6].

In the United States, it is estimated that more than 9.9 million people have osteoporosis and an additional 43.1 million have low bone density [7]. In 2005, the total cost of treating patients with osteoporosis including prevalent fractures was more than $19 billion and this number is expected to rise to $25.3 billion by 2025 [8].

Osteoporotic fractures are mainly occurring in the spin, hip, and wrist [3]. These fractures may be followed by full recovery or by chronic pain, disability and death [9]. Osteoporotic fractures occur in elderly people of both males and females; however, they are prevalence in postmenopausal women [10].

Treatment of osteoporosis may involve life style changes, such as diet, exercise, cessation of smoking, and administering calcium, vitamin D and other medicines [10].

Prevention of these fractures can save society from accommodation expenses in the hospital, nursing homes and save patients from the loss of quality of life and premature death [11].

In this chapter we present the most drugs that have been used to treat osteoporosis indicating their therapeutic uses, mechanism of action, side effects, pharmacokinetics properties, bioavailability and approaches to improve their bioavailability.

Bisphosphonates (BPs)

Bisphosphonates are a widely utilized class of drugs used in the management of disorders involving calcium and bone metabolism [12]. They are named bisphosphonates because they possess two phosphonate (PO3) groups similar to that in pyrophosphate. However, the oxygen atom in pyrophosphate is replaced with a carbon atom in bisphosphonate which allows a great number of possible variations (Figure 1) [13].

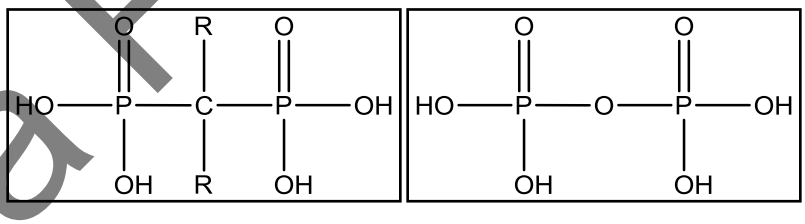

Figure 1. Chemical structures of bisphosphonates and pyrophosphate.

Bisphosphonates History

Bisphosphonates were first synthesized in 1897 by Hans von Baeyer and Karl Andreas Hofman; however, their clinical uses in the disorders of bone metabolism were commenced only 50 years later [14].

Bisphosphonates were early used in industry for manufacturing of soaps, detergents, fertilizers, water softeners, cosmetics and in the oil and gas industry because of their ability to inhibit crystallization and to form complexes with metals in solution [15].

Earlier studies on inorganic pyrophosphate found that pyrophosphate inhibited in vitro calcium phosphate precipitation and dissolution. Whereas, *in vivo*, pyrophosphate prevented ectopic calcification but had failed to influence normal mineralization and bone resorption, possibly due to its enzymatic cleavage locally by phosphatases. This encouraged scientists to look for analogs of pyrophosphate that has similar properties but with high resistance to enzymatic hydrolysis. The extensive investigations have led to the discovery of the bisphosphonates which have a stable P-C-P bond instead of the labile P-O-P bond in pyrophosphate [16, 17].

Generations of Bisphosphonate

The length and substitution on the aliphatic carbon of bisphosphonate skeleton structure led to a variety of bisphosphonate analogs having different potency and pharmacological properties [18]. Table 1 lists a number of bisphosphonate derivatives.

The first-generation bisphosphonates, such as clodronate and etidronate, are characterized by their alkyl or halide side chains while the second generation derivatives, such as tiludronate and pamidronate, containing either a sulfur- side chain or an amino terminal group while the third generation bisphosphonates such as ibandronate and zoledronate have an imidazole group (cyclic side chain) instead of aliphatic side chain which resulted in an increase in the potency of these derivatives [18-20]. Inhibiting bone resorption potency varies between the three generations. The antiresorptive potency is decreased in the following order: etidronate < tiludronate < clodronate < pamidronate < alendronate < risedronate [21, 22].

Table 1. Generations of bisphosphonate with their potencies*

Chemical modifications	**examples**	**antiresorptive potency**
First generation	Etidronate	1
Short alkyl or halide chain	Clodronate	10
Second generation	Tiludronate	10
Amino terminal group	Pamidronate	100
	Alendronate	100-1000
Third generation	Risedronate	1000-10,000
Cyclic side chain	Ibandronate	1000-10,000
	Zoledronate	More than 10,000

* Data from references 12, 19, 20.

Therapeutic Applications of Bisphosphonates

Bisphosphonate have been used as the treatment of choice for different clinical conditions associated with excessive bone resorption including Paget's disease [23, 24], hypercalcemia [12, 23], tumor-induced hypercalcemia [23], postmenopausal and glucocorticoid induced

osteoporosis [24, 25], primary and secondary hyperparathyroidism [12] and bone metastases [25].

Some bisphosphonates have been shown direct antitumor effect [22, 26]. The bisphosphonates available for oncological treatments are in order of increasing potency: etidronate, clodronate, pamidronate, alendronate, ibandronate and zoledronate [18, 22]. In one randomized control trial, women with breast cancer who received zoledronic acid had increased the rate of disease free survival and had a 36% reduction in risk for a recurrence of breast cancer or metastasis to bone compared to women who had been treated with placebo [27].

A number of studies revealed that bisphosphonates, particularly pamidronate and clondronate have shown analgesic effect and thus these drugs can be used in the management of pain and to improve the quality of life, in patients with osteolytic metastases [18, 28].

Mechanism of Action of Bisphosphonates

There are two classes of bisphosphonates which have different mode of action: the N-containing and non-N-containing bisphosphonates.

The non-nitrogenous bisphosphonates (e.g clodronate, etidronate, tiludronate) are metabolized in the cell by class II aminoacyl–transfer RNA synthetases to a non-hydrolysable analogue of ATP. Accumulation of this cytotoxic metabolite interferes with mitochondrial function and ultimately causes osteoclast cell death, leading to an overall decrease in the breakdown of bone [25, 29-33]. Overall, the action of this class appears to be as a prodrug, because after intracellular uptake by osteoclasts it converts to its active metabolite [31].

In contrast, the newer, more potent N-containing bisphosphonate (e.g., pamidronate, alendronate, ibandronate, risedronate, and zoledronate) are not metabolized [30] and lead to osteoclast apoptosis by different mode of action [25].They inhibit bone resorption by inhibiting farnesyl diphosphate synthase (FDPS) in the mevalonate pathway resulting in the prevention of prenylation and loss of function of the small GTPases [25, 29, 31, 34-36] which play a central role in the regulation of osteoclast function [37].

Pharmacokinetic Properties of Bisphosphonates

Bisphosphonates have unique pharmacokinetic properties because of their highly polar chemical structures [38]. Alendronate, risedronate, and ibandronate are orally administered drugs used for osteoporosis [39]. They are characterized by low oral bioavalability (less than 1%) due to poor absorption in the gastrointestinal tract [38-41].

Orally administered drugs can cross the gastrointestinal epithelium by either the transcellular, in which the drug molecules have to pass through epithelial cells to reach the blood circulation or paracellular pathway, in which drugs reach systemic circulation via the tight junctions between the epithelial cells [40, 42]. Water, electrolytes, and small molecules up to a certain size (molecular weight <150) can travel via these junctions [40, 43].

The poor absorption of bisphosphonates is a result of their poor lipophilicity, which prevents diffusion across the gastrointestinal epithelium through the transcellular route [40,

43]. The molecular weight of alendronate is 249 and its partition coefficient is 0.0017 which is independent of pH values ranging from 2 to 11 [40, 43, 44]. Thus, alendronate has to utilize the paracellular route in order to be absorbed. However, since its large molecular size hampers its movement through tight junctions in the gastrointestinal epithelium its absorption to the blood circulation is negligible [40, 43]. The other bisphosphonates behave similarly due to their relatively high molecular weights; MW of 235 for pamidronate, 233 for Clodronate and 206 for etidronate [34].

Additionally, all bisphosphonates are expected to be completely ionized and possess negative charge at the physiological pH of the small intestine (6-8). The brush-border membrane is negatively charged and will often repel negatively charged phosphate groups of the bisphosphonate from the epithelium and tight junctions [40, 43]. Furthermore, bisphosphonate can complex with calcium or magnesium or other divalent cations in the lumen of the gastrointestinal tract, resulting in poor absorption [40, 43].

Bisphosphonate absorption takes place by passive diffusion [40] partly in the stomach and mostly in the upper part of the small intestine in the order of: jejunum > duodenum > ileum > gavage [22, 40, 44].

Bisphosphonates bioavailability was found to be lower when the drugs were given with food, especially with calcium and iron containing food or supplements [40, 43, 45], or with beverages other than water [20, 22, 46]. Therefore, oral bisphosphonates must be taken in the morning, before eating or drinking with full glass of plain water [20]. After the administration of bisphosphonates, patients must not take anything else by mouth (food, drink or other medications) for at least 30 minutes [41, 45].

Patients take bisphosphonate tablet are advised to remain upright or stand and should not lie down after swallowing the drug for at least 30 minutes for alendronate and risedronate, and for 60 minutes in the case of ibandronate [41].

It should be indicated that some studies have found that an elevation in the gastric pH would increase bisphosphonates bioavailability [22, 45, 46].

Bisphosphonates are rapidly transferred from the systemic circulation to the bone [39]. Approximately 20-80% of absorbed dose are accumulated in the bones and the remainder excreted in the urine [47-49]. Once bound to bone, they are removed over a period of hours to years [39]. Bisphosphonates are not metabolized [20, 50] and their only route of elimination is via renal excretion. Therefore, they should not be given to patients with renal insufficiency [20, 39].

Intravenous bisphosphonates have been developed to allow long dosing regimens and to avoid the gastrointestinal problems associated with oral bisphosphonates [51, 52]. These preparations ensuring full compliance, particularly, for patients who cannot tolerate oral bisphosphonates [39, 51, 52] or have contraindications to their use [52]. Intravenous ibandronate is given once every 3 months, and zoledronic acid is given once yearly [39, 41].

Side Effects of Bisphosphonates

Bisphosphonates are generally well tolerated by the majority of patients, but serious adverse effects have been documented in certain cases [53].

Oral bisphosphonates can cause upper gastrointestinal adverse effects which are considered as the main problem of oral N-containing preparations and the most common

reason for treatment discontinuation [53, 54]. This can be prevented by taking the medication with an adequate quantity of water and remaining seated upright for 30 to 60 minutes after the drug administration [20, 55].

Gastrointestinal adverse effects that may occur in patients taking oral bisphosphonates include esophagitis, gastritis, dyspepsia, esophageal reflux, nausea, abdominal pain, and diarrhea [41]. Impaired mineralization is observed with etidronic acid at dose higher than 800 mg/day, but none of the bisphosphonates have been reported to impair mineralization at doses used for the treatment of osteoporosis [56]. Intravenous bisphosphonates can cause fever and flu-like symptoms after the first infusion which is thought to occur as a result of an increase in cytokine release from macrophages and monocyte [54, 57]. These symptoms do not recur with subsequent infusions [54]. Osteonecrosis of the jaw has been reported with bisphosphonates administered intravenously in cancer treatment [58, 59]. It is rarely, that bisphosphonates can cause serious ocular side effects such as ocular inflammation and ocular pain [60, 61], but high risk of this side effects can occur with intravenous administration more than with the oral medication [61, 62].

Other adverse effects that have been associated with the use of bisphosphonates including severe musculoskeletal pain, hypocalcaemia, secondary hyperparathyroidism [63], sever over suppression of bone turnover [53], sub trochanteric femoral fractures [55, 64] and renal frailer associated with zoledronic acid [57].

Strategies for Enhancing Bioavalability of Bisphosphonates

The major disadvantage concerning clinical use of bisphosphonates is their poor and variable absorption after oral administration. Therefore, several strategies have been developed to increase their intestinal absorption either by changing the permeability properties of the intestinal absorptive cells or modifying the structure of the drug by altering the physicochemical properties of the drug itself [40].

1-Absorption Enhancers

In order to lower the physical barrier function of biological membranes toward poorly absorbed bisphosphonates, the potency of co-administration of absorption enhancers have been extensively studied in the past years [40, 65, 66].

The main families of absorption enhancing agents are surfactants, bile salts, chelating agents and salicylates [40, 66].

The transport of clodronate through Caco-2 cells can be significantly promoted by the absorption enhancers palmitoyl carnitine chloride (PCC), *N*-trimethyl chitosan chloride (TMC), and ethylene glycol-bis (β-aminoethyl ether)-*N*,*N*,*N′*,*N′*-tetraacetic acid (EGTA). These agents cause widening of the tight junctions and thus, increase the permeability of the paracellular route [67].

It was investigated whether the intestinal absorption of two bisphosphonates, alendronate and clodronate can be improved when they co-administered with sodium EDTA [40, 68]. The absorption of alendronate without EDTA was in the range of 1–3%. An addition of EDTA led to an increase in the absorption of ten-fold at alendronate dose of 0.6 mg/kg and about two-fold at lower doses, with a minimal effective dose of EDTA being 10 mg/kg. The absorption of clodronate was also increased by EDTA, although to a lesser degree with the lowest

effective dose being 100 mg/kg EDTA. Thus, EDTA can, in certain situations, increase the intestinal absorption of bisphosphonates [40, 68].

It is believed that the addition of EDTA increased the intestinal absorption of bisphosphonates by two possible mechanism of actions, either by improving the absorption of these medications by directly enhancing intestinal permeability or by reducing the formation of un-absorbable complexes with calcium and hence, to a better absorption of the bisphosphonates [40, 68].

Despite the strong effect of EDTA as absorption enhancer for increasing the absorption of bisphosphonates, it has been shown that the absorption remains variable and occurs only at EDTA concentrations that make this chelating agent incompatible for clinical use [40, 68].

2-Novel Bisphosphonate with Better Bioavailability

Researchers suggested that a bisphosphonate having a nitrogen-containing heterocyclic ring on the side chain, and lacks the geminal hydroxyl group would contribute to high activity and better oral bioavailability due to better solubility of its calcium complexes/salts and poor calcium chelating characteristics. 2-(2- Aminopyrimidinio) ethylidene-1,1-bisphosphonic acid betane (ISA-13-1), a novel synthesized nitrogen-containing heterocyclic bisphosphonate with no hydroxyl on its germinal carbon was shown to have similar potency with 1.5-1.7 times better oral absorption than the other clinically used bisphosphonates [69].

3-Prodrug Approaches

Several prodrug approaches have been developed for enhancing the absorption of poor bioavailable compounds based on either increasing the lipophilicity of bisphosphonates promoieties bound to phosphorus atoms or using the active peptide transporter [19, 40].

I-Lipophilic Prodrugs

Masking one or more of the bisphosphonate ionizable groups would increase the lipophilicity of the drug and could decrease the chelation of the drug by Ca^{2+} or other divalent metal cations in the intestinal lumen [40, 70, 72].

Novel partial amides of clodronic acid were synthesized and their in vitro physicochemical properties were evaluated as potential bioreversible prodrugs of clodronate. The hydrolysis studies on these prodrugs indicated a release of clodronic acid via chemical hydrolysis, which limits the use of this approach [70, 73].

Several methods have been developed to prepare acyloxyalkyl and anhydride derivatives of clodronic acid. The first derivative, tris (pivaloyloxymethyl), is significantly more lipophilic than clodronate however its degradation in human serum was shown to be mostly due to chemical hydrolysis [19, 70]. The same promoiety is also active in the case of editronate [19, 72]. Synthesized anhydride derivatives of clodronic acid, were found to be sufficiently stable toward chemical hydrolysis in aqueous solutions (pH 7.4 and 2.0) and they rapidly undergo complete enzymatic hydrolysis to clodronic acid in human serum [19, 74].

II-Prodrugs for Carrier-mediated Transport Systems

The carrier systems of the brush-border membrane of intestinal mucosa have been used to improve the oral bioavailability of poorly absorbed drugs [75, 76]. It has been recognized that the intestinal mucosal cell peptide transporter (PEPT1) has a major influence on di/tri peptide

absorption [77] and on absorption of β-lactam antibiotics [78], renin inhibitors [79], and angiotensin-converting enzyme (ACE) inhibitors [80, 81].

It was found that the intestinal permeability of the parent drug L-methyldopa, a polar amino acid, that is poorly transported by the amino acid transporter is 10 times lesser than the dipeptide prodrugs: Phe-R-methyldopa, R-methyldopa-Phe, and R-methyldopa-Pro [82].

This result suggests that the peptide prodrug approach could be applied for improving the intestinal absorption of oral bisphosphonates [77, 83]. Studies revealed that the dipeptidyl prodrugs of alendronate (Pro-Phe-alendronate) and pamitronate (Pro-Phe-pamitronate) resulted in a 3-fold increase in drug absorption following oral administration in rats [77, 83], and the bioavailability of Pro-Phe-alendronate was 3.3 in the tibia and 1.9 in the urine times higher than that of the parent drug. Further, following oral administration of 20 mg/kg Pro-[3H] Phe-[^{14}C] pamidronate (equivalent to 10 mg/kg pamidronate) the urine amount of ^{14}C (bisphosphonate moiety) was 3 times higher than that found following pamidronate administration, and the levels of ^{14}C in the tibia, resulting from the administration of prodrug, were 4.8 times higher than those found following the parent drug administration [77].

Using Other Routes for Bisphosphonates Administration

Due to the poor GI absorption, attempts have been made to enhance the absorption of BPs by other routes such as nasal delivery [84] and subcutaneous or intramuscular injection [85].

An osteotropic drug delivery system (ODDS) based on a bisphosphonic prodrug was designed as a novel method for site-specific and controlled delivery of drugs to the bone. This approach is based on the chemical adsorption of the prodrug to the mineral component, hydroxy apatite in the bone, through the bisphosphonic promoiety. To verify this concept, the bisphosphonic prodrug of carboxy-fluorescein, disodium (fluorescein-6-carbonyloxy) acetoaminomethylene BP (CF-BP), was synthesized as a model compound, and the disposition after intravenous injection was studied in rats. CF-BP was efficiently absorbed by the skeleton (62.1% of dose), and the reminder was excreted in the urine (35.9% of dose). Regeneration of CF by hydrolysis of CF-BP in the bone was observed. Thus, it was suggested that ODDS has a potential to achieve osteoclast-specific or resorption surface-specific targeting of the drugs [86].

Local implantation or injection of microspheres containing bisphosphonates for site-specific therapy was successfully aided in treating several pathological conditions associated with bone destruction [87].

Nasal administration and subcutaneous or intramuscular injection have been used to improve bisphosphonates absorption [40]. It was found that the levels of alendronate in the tibia and in the femur after nasal administration were only two times higher compared with those following oral administration [40].The pharmacokinetics of clodronate was studied in rats after single intravenous, intramuscular and subcutaneous doses of clodronate. It was found that the concentrations of the drug in bone after 2 hours were about equal and the bioavailability after intramuscular and subcutaneous administrations were 105% and 89%, respectively [85]. Despite a rapid and good absorption of clodronate after intramuscular administration, in situ pain may preclude its extensive use [88].

1-Positively Charged Microemulsion

It was found that oral bioavailability of alendronate could be improved by the positively-charged microemulsion by 2.82 fold compared with the commercially available tablets (Fosamax), which is believed to widen the tight junctions and thus to increase the absorption through the paracellular route [89].

2-Bisphosphonate Having Phytic Acid Content

Oral bisphosphonate formulations having a low chelating agent, phytic acid content, could improve the clinical bioavailability of bisphosphonates by inhibiting their activity to react with minerals (calcium, magnesium, etc.) in the gastrointestinal tract and form insoluble complexes.

In vivo assays that have examined the effects on intestinal mucosa in rabbits showed that various absorption enhancers such as sodium lauryl sulfate, EDTA, etc., irritate the intestinal mucosa to cause, for example, the delamination of the intestinal mucosa and the edema of sub-mucous layers, but a low phytic acid content is improbable to irritate the intestinal mucosa, with the warranty of high safety to the patient [90].

Moreover, comprising bisphosphonate and phytic acid in combination with a delayed release of the bisphosphonate in a lower gastrointestinal tract was designed to allow patients to take bisphosphonates, together with food intake, at a bioavailability as high as that of an empty stomach, thus improving the convenience of drug administration to the patient [90].

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) are a family of compounds that interact with intracellular estrogen receptor in different various tissues as estrogen receptor agonists or antagonists [91-93].

SERMs have been developed for a variety of clinical conditions, including prevention and treatment of osteoporosis [94-96], and estrogen-regulated cancers [95, 97], and even for hormone replacement therapy [95, 98].

Postmenopausal osteoporosis is mainly due to estrogen deficiency after menopause. Hence, the estrogen agonistic effect of the selective estrogen receptor modulators on bone can prevent bone loss in postmenopausal women [93].

A number of new generations of SERMs, including ospemifene [99], bazedoxifene [100], lasofoxifene [101] and arzoxifene [102], are currently under investigation to be used in the treatment and prevention of osteoporosis, but the only SERM that was approved worldwide for the prevention and treatment of postmenopausal osteoporosis is raloxifene (Figure 2) [93, 103, 104].

Raloxifene has been found to reduce levels of both bone formation and bone resorption markers in postmenopausal women [105]. Moreover, it increases the bone mineral density without increasing the risk of endometrial cancer [10]. Raloxifene reduces the serum concentration of low-density lipoprotein cholesterol and total cholesterol [10, 105]. In breast tissue, raloxifene is an estrogen antagonist, this clarify its role in the prevention of breast cancer in postmenopausal women [106, 107], but it was slightly less effective compared with tamoxifen at preventing breast cancer [108].

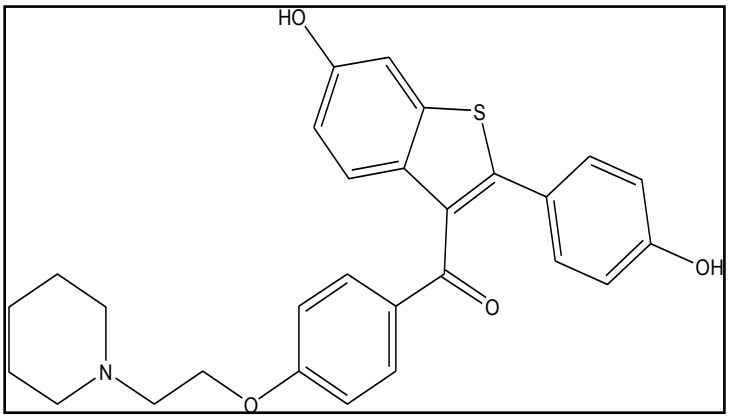

Figure 2. Chemical structure of raloxifene.

Raloxifene is administered orally at dosage of 60 mg/day [109, 110].despite the rapid absorption of raloxifene from the gastrointestinal tract, with t_{max} reached in 0.5 hour and 60% of the oral dose is absorbed [105, 109], its bioavailability is significantly less than 2% due to extensive first-pass glucoronidation [109-112]. Raloxifene is very highly bound to plasma proteins (>95%) and its apparent volume of distribution is 2,348 l/kg [109, 110]. The clearance is 40-60 l/kg x h [105] and its terminal elimination half-life after multiple dosing is 32.5 h [105, 109, 110]. Less than 0.2% of its oral dose is excreted unchanged in the urine and less than 6% is excreted in urine as glucuronide conjugates [105, 109].

The most common adverse events in patients receiving raloxifene are uterine polyps, hot flushes and muscle cramps [113-115]. Raloxifene was associated with a 1.7-fold increase in venous thromboembolism incidence compared with placebo [113].

Several attempts have been made to enhance the bioavailability of raloxifene including formulation of mucoadhesive microspheres using different proportions of carbopol and HPMC [116]. In addition, co-grinding with different super disintegrants has been made to reduce drug crystallinity, and increase the rate and extent of its dissolution [117].

Moreover, a two fold increase in raloxifene bioavailability could be obtained by using solid lipid nanoparticles of raloxifene hydrochloride [118], and 7-fold increase in dissolution rate via using rapid expansion of supercritical solution to reduce particle size of the drug [119]. Co- administrations of the drug with enzyme inhibitors to decrease first pass metabolism or the use of microemulsion and self-micro emulsifying drug delivery system can increase raloxifene bioavailability [120].

Calcitonin

Calcitonin is a peptide composed of 32 amino acids (Figure 3). It inhibits osteoclast-mediated bone resorption by reducing osteoclast activity [121, 122] and stimulates bone formation [123]. It has been utilized in the treatment of osteoporosis for many years [121, 122, 124], but it is less effective than bisphosphonates [10]. Calcitonin is available for administration by the subcutaneous, intramuscular, and intranasal routes (200 IU daily) which is much better tolerated and widely used [121, 122, 125]. Orally active formulation of

calcitonin has recently been developed to enhance its clinical usefulness [126]. A unique property of calcitonin is its analgesic effect which may be beneficial in patients with bone related pain [122, 127].

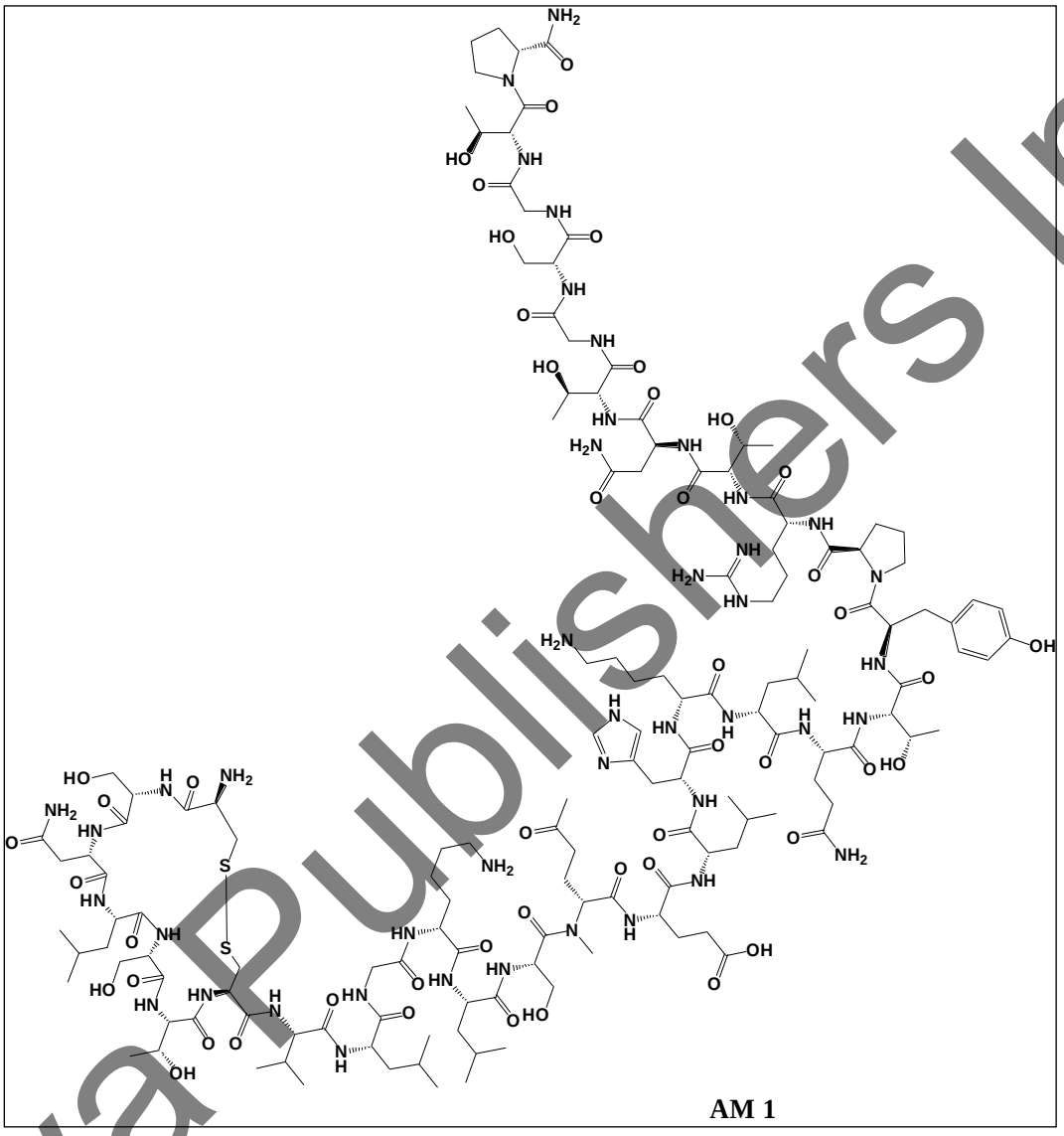

Figure 3. Chemical structure of calcitonin.

Long term administration of calcitonin in humans was shown to be safe and free of any serious or long-term side effects. However, short term administration of injectable salmon calcitonin has been associated with flushing, local irritation at injection site, nausea, dieresis, urinary urgency, headache and vomiting [128]. Studies indicated that nasal calcitonin is generally associated with mild and transient adverse events, usually involving local reactions such as nasal discomfort, rhinorrhea or rhinitis which lead to cessation of therapy in about 4% of patients [125].

The bioavailability of nasal spray relative to intramuscular administration in healthy volunteers is 3%. Intranasal spray is absorbed rapidly by the nasal mucosa with peak plasma concentration of about 31 to 39 minutes following intranasal administration. The terminal half-life of calcitonin-salmon has been calculated to be around 43 minutes [125].

The bioavailability of calcitonin following intraduodenal administration was 0.039% for ileal administration and 0.021% after intracolonic administration. This may be attributed to extensive intestinal enzymatic degradation and poor permeation across intestinal epithelial cell. Hepatic first pass elimination of calcitonin was trivial [129, 130]. Salmon calcitonin is 40-50 times more potent than human calcitonin [131].

Approaches for Enhancing Calcitonin's Bioavailability

Modulation of Intestinal Environment

The intestinal environment can be modulated to enhance oral absorption of calcitonin by several approaches including protection of calcitonin from intestinal enzyme by adding protease inhibiter [131, 132], changing intestinal pH [133] and maintaining high local drug concentrations to saturate enzyme [129].

1-Addition of Enzyme Inhibiter

Enzymatic degradation studies demonstrated that salmon calcitonin is degraded extensively by intestinal serine protease trypsin. Using ovomucoid as enzyme inhibiter can stabilize salmon calcitonin against degradation in the presence of the serine proteases for an hour [131].

2-Reduction in the Intestinal pH

Oral absorption properties of calcitonin can be modulated by the intestinal pH changes. Salmon calcitonin is a substrate for the pancreatic serine protease trypsin which has a maximal function at pH 5 to 6. Calcitonin formulations that contain various amounts of citric acid could reduce intestinal pH, thus, stabilizing calcitonin in the GI tract and enhancing its absorption [133].

3-Using absorption Enhancers

Different enhancers such as sodium taurodeoxycholate (TDC), sodium taurocholate (STC), sucrose stearate, sucrose ester-15, tween 80, lauryl carnitine chloride (LCC), myristyl carnitine chloride (MCC), cetyl pyridinium chloride (CPC) and cetrimide were evaluated for permeability of calcitonin in rat jejunum. The effective permeability was observed to increase up to 14 times over the control in the presence of TDC. The order of enhancement on the basis of EC_{50} (concentration of enhancer for 50% enhancement) was found in the order: TDC = LCC > SLC > tween- 80 > MCC > sucrose stearate > sucrose ester-15 > CPC > cetrimide [129, 131, 134].

4-Chemical Modification of Calcitonin

It is plausible that chemical modification of calcitonin to produce prodrugs and analogues may protect calcitonin against degradation by proteases and other enzymes present at the

mucosal barrier and renders calcitonin more lipophilic, resulting in an increased bioavailability. By chemical modification with fatty acids [135, 136] or N-acylated alpha-amino acids [137], a significant increase of calcitonin intestinal absorption was observed in comparison with the native calcitonin. The stability and permeability of peptides were improved by acylation with fatty acids [136], and the derivatized amino acids only weakly inhibited the activity of trypsin or leucine aminopeptidase [137].

5-Other Potential oral Delivery

Another potential approach which has been used to improve calcitonin absorption is using mucoadhesion of nanoparticles having surface hydrophilic polymeric chains. It was demonstrated that there was a good correlation between mucoadhesion and the enhancement of calcitonin absorption in rats. The gastrointestinal transit rates of nanoparticles having surface poly (N-isopropyl acrylamide), poly (vinyl amine), and poly (meth acrylic acid) chains were reduced, and calcitonin absorption was improved [138].

Encapsulation of calcitonin in liposomes to protect calcitonin from proteolytic degradation [139], and microspheres prepared from benzoylated and phenylsulfonylated amino acids [140] was another attempt made to enhance the oral bioavailability of calcitonin.

Other strategies are currently being investigated to enhance the bioavailability and effects of calcitonin, including nasal [125, 141, 142], buccal, pulmonary [143, 24], rectal [145], transdermal routes of administration [146], and novel allosteric activators of the calcitonin receptor [121].

Teriparatide

The recombinant human parathyroid hormone fragment, rhPTH (1-34) (teriparatide, Figure 4), has been approved in the United States in November 2002 for the treatment of osteoporosis in men and women [147].

Teriparatide is a potent anabolic agent used in the treatment of postmenopausal women and men with severe osteoporosis [148], as well as for persons with established glucocorticoid-induced osteoporosis who are receiving long term glucocorticoids [148-150]. Teriparatide was shown to reduce fracture risk and is now available for the treatment of patients with osteoporosis who are at high risk of fracture [148, 151].

The mechanism of action of teriparatide is distinct from that of antiresorptive drugs which increase bone mass by inhibiting osteoplastic bone resorption. Contrarily to other antiresorptive, teriparatide increases bone turnover and stimulates new bone formation by stimulating osteoblast activity to a greater extent than osteoclast activity [151].

Pharmacokinetics of teriparatide

Subcutaneous administration of teriparatide (20 μg/dose) reaches peak serum concentration in approximately 30 minutes and decreases within 3 hours [147, 151] resulting in a total duration of exposure to the teriparatide of approximately 4 hours [152]. The absolute bioavailability of teriparatide is 95% [147, 153]. The systemic clearance of teriparatide

(approximately 62 l/h in women and 94 l/h in men) exceeds the rate of normal hepatic plasma flow, consistent with both hepatic and extra-hepatic clearance [154, 155]. Volume of distribution, following intravenous injection, is approximately 0.12 l/kg and it has not been assessed for subcutaneous injection [147]. The serum half-life is approximately one hour when it is given by subcutaneous injection and 5 minutes when administered by intravenous injection [152]. Metabolism and excretion studies have not been performed with teriparatide, but the peripheral metabolism of parathyroid hormone is believed to occur by non-specific enzymatic mechanisms in the liver and excretion via the kidneys [147, 153].

Figure 4. Chemical structure of teriparatide.

Adverse Effects of Teriparatide

Teriparatide has a theoretical risk of osteosarcoma, which was found in rats' studies but not confirmed in humans. There is one case of osteosarcoma reported in a 70-years old postmenopausal woman with a complex medical history. This risk was considered by the FDA as "extremely rare" (1 in 100,000 people) and is only slightly more than the incidence in a population aged over 60 years (0.4 in 100,000). However, this has led teriparatide to be not advisable to prescribe for patients who have skeletal metastases, Paget disease, or open epiphyses [156].

Other adverse events that have been reported in patients treated with teriparatide are headache, asthenia, neck pain, hypertension, angina pectoris, syncope, nausea, constipation, dizziness, depression, insomnia, vertigo, hyperuricemia, and hypercalcemia [147].

Denosumab

Receptor activator of nuclear factor kappa-B ligand (RANKL), a protein expressed by osteoplastic stromal cells, binds to receptor activator of nuclear factor kappa-B (RANK) and is essential for osteoclast development, activation, and survival.

Denosumab (anti-receptor activator of nuclear factor κ-B ligand [RANKL] antibody) is a fully human monoclonal antibody that targets receptor activator of nuclear factor-kappa –B (RANKL) and blocks osteoclast activation. By binding RANKL, denosumab potently reduces bone resorption and turnover with an increase in bone mineral density (BMD) [157-166]

Clinical Utility of Denosumab

Denosumab was approved for the treatment of osteoporosis in postmenopausal women and also for the treatment of bone loss in men with prostate cancer [167,168]. Denosumab has also been shown to decrease bone turnover in patients with multiple myeloma [169] and bone metastases from breast cancer [169, 170]. Several studies on patients treated with denosumab have found changes in tumor composition, reduced bone destruction, and clinical benefits in cases with giant cell tumor of bone (GCTB) [171]. The drug is contraindicated for patients with hypocalcaemia [167].

Adverse Effects of Denosumab

According to a statement issued by the FDA, the most common side effects of denosumab include back pain, musculoskeletal pain, pain in the extremities, hypercholesterolemia, and infections in the urinary and bladder. Serious adverse reactions include hypercalcemia, dermatologic conditions, and infections require hospitalization [167].

Several trials showed significant increased rates of osteonecrosis of the jaw when patients were treated with denosumab [168, 172] and it is possible that such atypical fractures will also be found in patients taking long-term denosumab [168].

Pharmacokinetics Properties of Denosumab

Denosumab shows dose-dependent, nonlinear pharmacokinetics with moderate inter-individual pharmacokinetic variability [173-177]. Subcutaneous administration of denosumab (for a 60 mg/dose) reaches peak serum concentration in approximately 1 to 4 weeks and declines over a period of 4 to 5 months with a mean half-life of approximately 25 to 30 days [177]. The subcutaneous bioavailability of denosumab was 64% [178].

53% of patients had no detectable amounts of denosumab remained at 6 months after dose administration [174, 176]. Multiple-dosing of 60 mg once every 6 months did not show any accumulation and denosumab pharmacokinetics did not result in any change over 4 years of exposure [174, 176, 177].

As determined by a population analysis, age, race, and disease status (low bone mass or osteoporosis, prostate or breast cancer) did not affect the pharmacokinetics of denosumab [176].

Denosumab is expected to follow immunoglobin clearance pathways and is not eliminated via hepatic mechanisms [176, 177]. Clearance of denosumab most likely occurs by the reticula- endothelial system; it is then filtered and excreted through the kidneys [174, 175].

Summary and Conclusion

For patients with osteoporosis, therapy with bisphosphonates, raloxifene hydrochloride, calcitonin, teriparatide or denosumab should be considered.

The bisphosphonates are an important class of therapy that have been utilized in various bone and calcium related pathologies. Because of their very low lipophilicity and charge they found to be poorly absorbed from gastrointestinal tract. Various attempts have been made to improve their absorption.

Raloxifene is an oral selective estrogen receptor modulator that is used in the prevention of osteoporosis in postmenopausal women due to its estrogenic action on bone. Due to extensive first-pass glucoronidation, its bioavailability is significantly less than 2%. Therefore, several attempts have been made to enhance its bioavailability including formulation of mucoadhesive microspheres using different proportions of carbopol and HPMC, co-grinding with different superdisintegrants to reduce drug crystallinity and increase the rate and extent of dissolution, using rapid expansion of supercritical solution to reduce particle size of the drug and co- administration of the drug with enzyme inhibitors to decrease the effect of first pass metabolism.

Calcitonin inhibits osteoclast-mediated bone resorption and stimulates bone formation has been utilized in the treatment of osteoporosis and was found to be safe and free of any serious or long-term side effects. Calcitonin characterized by low oral bioavailability due to its extensive intestinal enzymatic degradation and poor permeation across intestinal epithelial cell. Therefore, the intestinal environment can be modulated to enhance oral absorption of calcitonin by several approaches including protection of calcitonin from intestinal enzyme by adding protease inhibiter, changing intestinal pH and by maintaining high local drug concentrations to saturate enzyme. Other approaches have been made such as using

absorption enhancers, mucoadhesion of nanoparticles having surface hydrophilic polymeric chains, microspheres prepared from benzoylated and phenylsulfonylated amino acids, encapsulation of calcitonin in liposomes to protect from proteolytic degradation and chemical modification of calcitonin with fatty acids or N-acylated alpha-amino acids. Other routs of administration including nasal, buccal, pulmonary, rectal and transdermal routes have been investigated to overcome its low bioavailability.

The recombinant human parathyroid hormone fragment, rhPTH(1-34) (teriparatide), is a potent anabolic agent used in the treatment of postmenopausal women and men with severe osteoporosis, as well as for persons with established glucocorticoid-induced osteoporosis who are receiving long term glucocorticoids. Teriparatide was shown to reduce fracture risk and is now available for the treatment of patients with osteoporosis who are at high risk of fracture.

Denosumab offers an alternative approach to the treatment of osteoporosis by decreasing bone resorption and increasing bone mineral density through the inhibition of RANKL.

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Chapter 8

Fumaric Acid Esters as a Treatment for Psoriasis and Multiple Sclerosis

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Abstract

Autoimmune diseases are the diseases of the modern century. Due to their complicated pathogenesis and the enrollment of many factors in disease initiation and progression, these diseases are considered uneasy to treat.

Immune cells exist normally in our bodies. They are extremely essential for our survival against many pathogenic and foreign particles. Manipulating these cells through chemical and biological drugs has tremendous effects, usually with risks outweighing the benefits, as a result of the disturbance of cellular defense mechanisms.

This chapter is devoted to the description of two different autoimmune diseases; multiple sclerosis (MS) and psoriasis. Up to date there is no known cure for MS and psoriasis. The available treatments approved by the FDA are mainly considered symptom relieving drugs and their major therapeutic action is only to slow the disease progression, and they lack the ability to eliminate the disease completely. A great devotion in this chapter was given to discuss several aspects regarding fumarate acid esters (FAEs) including; pharmacokinetics, mode of action, recommendations and specifically their potential as an effective treatment for psoriasis and MS.

Keywords: Multiple sclerosis (MS), psoriasis, fumaric acid esters, dimethylfumarate, monomethylfumarate

Abbreviations

FAEs	Fumaric acid esters
MS	Multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
SPMS	Secondary progressive multiple sclerosis
PPMS	Primary progressive multiple sclerosis
PRMS	Progressive relapsing multiple sclerosis
DMF	Dimethylfumarate
MMF	Monomethylfumarate
DEFINE	Determination of the efficacy and safety of oral fumarate in RRMS
Nrf-2	Nuclear factor E2 (erythroid-derived 2)-related factor)
PML	*Progressive multifocal leukoencephalopathy*
VCAM-1	Vascular cell adhesion molecule 1
TNF-α	Tumor necrosis factor alpha
BBB	Blood brain barrier
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
ICAM-1	Intercellular adhesion molecule-1
APCs	Antigen presenting cells

Multiple Sclerosis (MS) Preview

Multiple sclerosis (MS) is the most common neurological disease in young and middle-age adults in the Western world and it is estimated that MS affects one in every thousand [1]. It is defined as an inflammatory demyelinating disease of the central nervous system (CNS).

The World Health Organization (WHO) calculated a total cost of approximately $51,000 per patient. The prevalence of MS varies considerably by geography; northern Europe has higher incidence rates than Mediterranean countries [2]. Females are more prone to MS. The female to male ratio has increased in recent decades from 2:1 to 3:1 [3].

The clinical manifestation of multiple sclerosis is highly variable, both regarding the type and severity of symptoms and the course of the disease. The international panel of neurologists has classified four distinct subtypes of clinical disease patterns in MS: relapsing–remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS) and progressive relapsing (PRMS) [4].

RRMS affects over 80% of MS patients; approximately 50% of them will develop SPMS after 10–15 years of disease duration. Approximately 15% of MS patients develop PPMS, of which 5% will likely to develop into PRMS with time [5].

The current available treatment options for RRMS include recombinant interferons and glatiramer acetate as first-line treatment, with natalizumab and mitoxantrone as second-line therapies [6].

Multiple Sclerosis (MS) Pathogenesis

The exact mechanism of MS pathogenesis is not completely known. As MS is considered an autoimmune disease it is normal that immune cells play a central role in the disease pathogenesis. A disruption in the blood brain barrier (BBB) is thought to play a critical role in disease initiation [7].

Activated T cells crosses the BBB as a result of an interaction between their adhesion molecules and complementary receptors on endothelial cells of the vessel wall. These cells get re-activated upon exposure to their specific antigen, releasing pro-inflammatory cytokines, up-regulating the expression of adhesion molecules, and recruiting other immune cells, including B lymphocytes and macrophages [8]. Recruitment of immune cells into the brain is mainly mediated by adhesion molecules and chemokines [9]. These immune cells exacerbate the inflammatory response by releasing more inflammatory cytokines.

Oxidative stress plays a significant role in many neurodegenerative diseases including MS [10]. It results from the cellular inability to detoxify or neutralize ROS and RNS by cellular anti-oxidative mechanisms such as glutathione. These reactive species have the ability to cause damage in sub-cellular structures including proteins, lipids and DNA.

Mitochondria; the energy factory in eukaryotic cells, is an important producer of ROS as a result of the oxidative phosphorylation process. In the CNS any malfunction in the mitochondria may result in cellular stress leading to neuronal damage and death [11]. This is why MS is classified as a mitochondrial disease.

Psoriasis Preview

Psoriasis is an old known chronic inflammatory skin disease with spontaneous remissions and exacerbations. It was described by Hippocrates in Corpus Hippocraticu, using the term psora, meaning “to itch” [12]. The incidence of the disease is affected by both genetic and environmental factors [13].

Psoriasis affects 2–3% of the worldwide population [14]. Over 4.5 million patients have been diagnosed with the disease in the United States, upon which 5% of the patients have reported severe dissatisfaction with current therapy [13].

Psoriatic patients not only suffer from psoriatic lesions but nail dystrophy, psoriatic arthritis and Crohn’s disease are also very common [15]. Psoriasis also affects the daily life routine of those patients. In addition to the state of depression it causes, the disease also disrupts the patient’s ability of hands, walking, sleeping, and sexual activity [12]. At least 30% of patients diagnosed with psoriasis commit suicide [16].

Psoriasis appears usually in patients between the ages of 15 and 25 years. Nevertheless, it can occur at any age [17]. Bacterial pharyngitis, stress, HIV-1, and various medications (e.g., lithium and β -blockers) are important factors that facilitate disease initiation [12].

Psoriasis is known to have three unique features to distinguish it from other skin diseases: (a) psoriatic plaques are highly localized sites of dysregulated growth and inflammation, these sites almost never develop into malignant clones of keratinocytes, melanocytes, or T cells [18], (b) psoriatic plaques are highly resistant to bacterial, viral, and fungal infections [19]

and (c) psoriatic plaques, can disappear and revert back in to a normal symptomless healthy skin spontaneously or after various treatments.

In the past, physicians have used mostly topical treatments for treating psoriasis patients. The only systemic drugs were given are sedatives and antipruritic drugs. Among the most commonly used topical agents are coal tar, arsenic, mercury, dithranol and corticosteroids. Even that the mechanism of action for these agents was not clearly known but their use was due to the improvement in psoriatic lesions [20].

After the success of cyclosporine in the treatment of psoriasis scientists have shifted their thoughts not only to treat the hyperplastic epidermis, but to treat the underlying cause of the disease which includes immune cells specially T cells and dendritic APCs [21].

Psoriasis Pathogenesis

The cause of psoriasis remains unknown. Several hypotheses have been advanced and models proposed over the years concerning its pathogenesis. Clinical studies and translational science carried in patients with psoriasis had been used to understand disease pathogenesis [22].

The success of translational research in psoriasis was proved after the FDA approval of two biological agents: alefacept; fusion protein that binds to CD2 on T cells [23], and efalizumab; humanized antibody that binds to leukocyte function associated antigen-1 (LFA-1), an integrin expressed at high levels on T cells [24]. Thus, T lymphocytes are a major player in the disease pathogenesis.

Like other immune diseases, pathogenic process in psoriasis is not initiated by a single agent; infiltrating leucocytes, resident skin cells, proinflammatory cytokines, chemokines, and chemical mediators produced in the skin under regulation of the cellular immune system all contribute to disease initiation [22, 25].

Fumaric Acid Esters

Fumaric acid esters (FAEs) are esterification products of the unsaturated dicarbonic acid, fumaric acid. Fumaric acid (white crystalline powder) is poorly absorbed. Hence, it is supposed to have no pharmacologic effect. While fumaric acid esters; dimethylfumarate, diethylfumarate, monomethylfumarate and monoethylfumarate (Figure 1) are known to be potent agents [26]. They have been used in Europe over decades for treating psoriasis [27]. In March 2013, the FDA have approved the drug dimethylfumarate (tecfidera ®) as a treatment for RRMS [28]. Recently the fumarates role in treating many diseases such as asthma, scardiosis, annular elastolytic giant-cell granuloma and melanoma is being emphasized.

Fumaric acid is available naturally in cells; it is an intermediate in citrate cycle which constitutes a significant part in the process of cellular energy production that occurs at the mitochondria.

FAEs use was introduced by German chemist named Schweckendiek in 1959 with the assumption that any disturbance in the citrate cycle will lead to a dysregulation in the function of immune cells since they depend on mitochondrial energy supply [29].

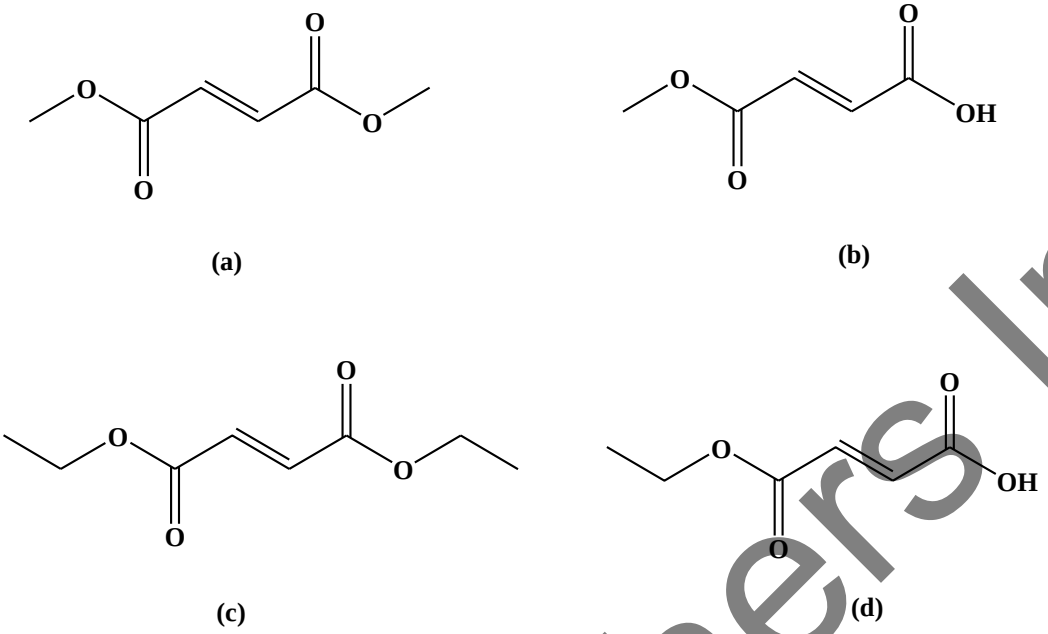

Figure 1. Fumaric acid esters: (a) dimethylfumarate, (b) monomethylfumarate, (c.) diethylfumarate and (d) monoethylfumarate.

Pharmacokinetics of FAEs

Limited information is available regarding FAEs pharmacokinetics. In vitro studies indicate that DMF is hydrolyzed by esterases into MMF at pH 8 suggesting that the hydrolysis occurs in the small intestine [30]. MMF is nearly completely absorbed from the small intestine to the blood circulation where it interacts with its immune targets.

After oral ingestion the Tmax for MMF is reached within 5-6 hours giving a maximum concentration near 20 μM. The half-life of FAE in vivo is around 90 min. There is no evidence for a cytochrome P450-dependent metabolism in the liver [31].

MMF is finally metabolized into fumaric acid which is degraded to H2O and CO2, the latter is excreted mainly through respiration. Only small amounts of intact MMF are excreted through urine or feces [32].

Contraindications

DMF use is contraindicated in patients with gastrointestinal diseases and liver or kidney diseases. Also, it should not be used for pregnant and lactating women [33].

Interactions with Other Drugs

It is not recommend in the treatment of psoriasis to combine DMF with other drugs. Concurrent use of DMF with other agents such as methotrexate and cyclosporine may exaggerate kidney and liver side effects. For psoriasis, adding topical agent like calcipotriol to DMF has shown an improvement on psoriatic lesions [34].

Teratogenicity/Pregnancy/Lactation

DMF is pregnancy category C. Data available is insufficient but it is recommended to avoid DMF use in pregnant and lactating women. Toxicological studies have given no evidence that DMF is teratogenic [35, 36].

Side Effects

Depending on phase three clinical trials in the DEFINE study it was shown that the most common adverse events associated with FAEs use that affected almost two thirds of patients are: gastrointestinal disturbances, including diarrhea, cramps and nausea, and flushing including redness and burning sensation [37, 38]. These side effects were found to be dose-dependent, tend to be high at onset of treatment then start to decrease after frequent administration.

Less common side effects were a reduction in mean white blood cells, lymphocytes and an elevation in hepatic amino transferase [26].

Dosage Regimen

In the case of treatment with FAEs a gradual increase in the dosage is recommended to reduce the severity of gastrointestinal side effects.

DMF for the treatment in MS cases is to be taken 120 mg twice daily for a week then the dose is increased to 240 mg twice daily. While for psoriatic patients the dose is adjusted according the individual response. One tablet of Fumaderm is the starting dose and it may end up to 1-2 g/day as final dose depending on the patient's status. It is important to mention that the dose is independent on the patient weight [39].

Recommendations

Patients on FAEs treatment should make a whole blood count annually. It is recommended to stop treatment if lymphocyte count is less than 500 µl.

FAEs use should be avoided in pregnant and/ lactating women and children under 18 [39].

Dimethylfumarate (Tecfidera) for MS

Unlike other oral or injectable MS treatments; DMF use is not associated with opportunistic infections, increased risk of malignancy and any other severe toxicity [28]. It was approved by FDA in March 2013 as the third oral disease-modifying treatment for RRMS. With appropriate monitoring DMF is safe and effective.

Comparison with Other Agents for MS

Efficacy

When compared to other RRMS treatments, DMF 240 mg bid have shown to reduce the annualized relapse rate more than IFN, glatiramer acetate and teriflunomide. It was similar in efficacy to fingolimod. Natalizumab was the most effective agent [40].

Safety

Along with its GI effects DMF is considered to be of the safest MS drugs.

The most effective drug natalizumab is associated with a high risk of causing PML [41]. Fingolimod was found to cause bradycardia and atrioventricular block and may cause macular edema in some patients [42]. Teriflunomide is pregnancy category X [43]. Elevation in liver transaminases is a common side effect for all of these agents including FAEs [42, 44, 45, 46].

When taking patient compliance into consideration, oral drugs are preferred over injectable ones. The FDA approved three oral disease modifying drugs for RRMS; fingolimod, teriflunomide and DMF. Although the first two are given only once daily and DMF is given twice, the associated side effects with fingolimod and teriflunomide makes DMF a more attractive drug choice.

DMF seems an attractive and more beneficial compared to other agents which overweighs its associated risks. Its effect as a neuroprotective factor is still under investigation and extensive research.

Fumaric Acid Esters Mode of Action

The exact mechanism of action of FAEs is not fully understood and still an important area for studying and investigation. Many hypotheses from the in vitro and ex vivo studies have been postulated [47].

DMF interferes with the cellular redox system by activating Nrf-2 which is responsible for up regulation of many antioxidant mechanisms in the cell including that of glutathione resulting in an inhibition of NF-κB translocation and a decrease in NF-κB-dependent genes; which regulate the expression of a cascade of inflammatory cytokines, chemokines, and adhesion molecules. It is believed that such interference affects several types of immune cells [48, 49].

Immunohistochemical analysis carried on psoriatic lesions have shown that CD4+ cells count was significantly reduced following treatment with FAEs [50]. In vitro studies have also shown that DMF in high concentrations induces T-cell apoptosis [51]

Two studies carried by de Jong et al. and Fox et al. have demonstrated a change in cytokines production upon FAEs use [52]. A shift from Th1 (proinflammatory) to Th2 (anti-inflammatory) cytokine response was observed, with an increase in IL-10, IL-4 and IL-5 production, and a decrease in IL-6, IL-1β and TNF-α expression was recognized [48, 53].

In another experiments Asadullah et al. and Vandermeeren et al. have showed that DMF have inhibited the tumor necrosis factor (TNF)-α induced expression of adhesion molecules, such as ICAM-1, VCAM-1 and Eselectin. Supposing decreased lymphocyte permeation through the BBB [53, 54].

DMF also affects astrocytes and microglia causing a decreased in proinflammatory cytokines production including; TNF-α, IL-1β, IL-6, and nitric oxide [55].

All these results have emphasized the role of DMF as a good treatment choice for MS and psoriasis. The question of whether DMF has neuroprotective tendencies is considered a critical area for research.

Problems Associated with FAEs

Gastrointestinal adverse events and flushing together lead to discontinuation of fumaric acid esters therapy in approximately 7% of patients [31]. Overall, the rate of discontinuation due to adverse events and/or noncompliance with treatment is 30-40% [56]. Other challenges for the fumaric acid esters include the inconvenience of taking up to three daily doses and the requirement for frequent laboratory monitoring.

Therefore, the need for a controlled release prodrug of fumaric acid esters is considered essential in the world of insufficiently treated MS. This can be done by chemical and or pharmaceutical manipulations of the FAEs. An extensive research and studies are to be carried to achieve this aim.

Improving Fumarates Bioavailability

One of the main ideas by Karaman et al. was to provide a therapeutic drug delivery system that releases the active fumarate ester in a controlled manner within the biological environment of the body, thus increasing bioavailability, reducing the accompanied side effects and the need of frequent dosing [57].

The mechanism of pyridine catalyzed isomerization of the inactive monomethylmaleate into the pharmacologically active monomethylfumarate was revealed to consist of four steps based on the density functional theory calculations published by Karaman et al. Step three in the reaction was found to be the rate limiting step (Figure 2).

The same group has also clarified that the rate of isomerization is affected by the solvent polarity. Polar solvents tend to accelerate the isomerization rate, while apolar solvents tend to slow it down. The basicity of the pyridine substituent used also has a significant effect. The higher the pKa value of the substituent the faster the isomerization rate [57].

These facts reflect the ability to chemically manipulate and control the isomerization process of monomethylmaleate into monomethylfumarate; thus, providing a new indirect method to administer fumarate esters with higher bioavailability and fewer side effects.

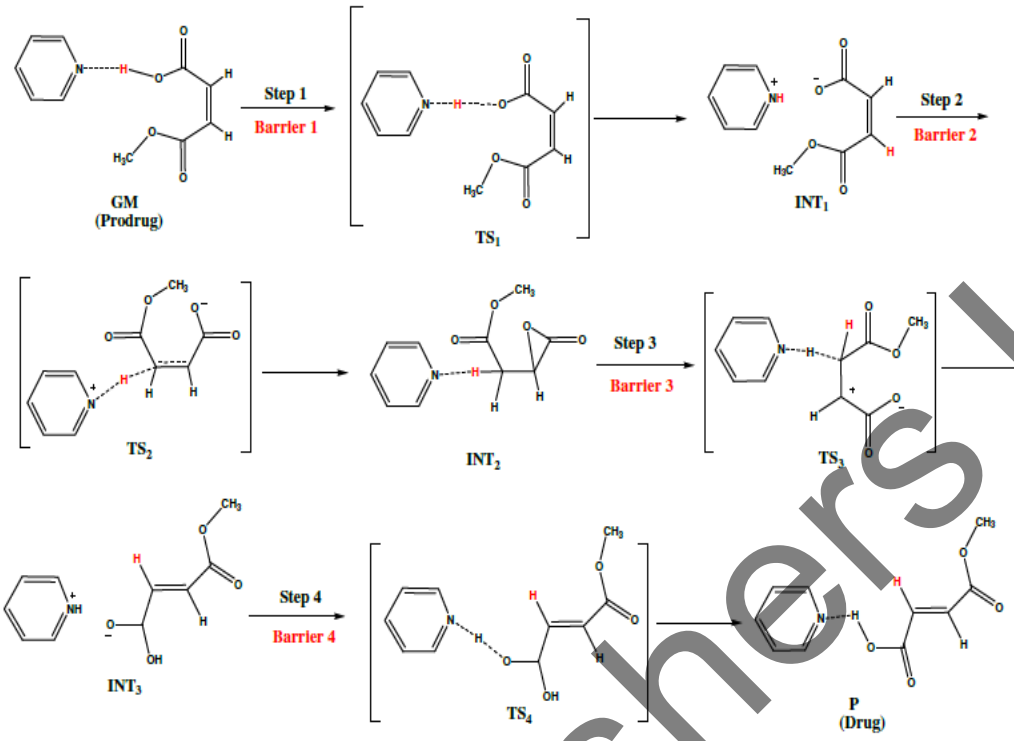

Figure 2. Mechanistic pathway for the substituted pyridine-catalyzed isomerization of monomethylmaleate into monomethylfumarate. Pyridine was chosen to represent the various pyridine derivatives.

Summary and Future Directions

- Autoimmune diseases including MS and psoriasis remain an open area for extensive research in the absence of an ultimate cure.
- The use of non-selective immune suppressant drugs should be limited due to their risks.
- From understanding of the factors that contribute to disease pathogenesis it is better to develop drugs that target these factors selectively in order to minimize side effects.
- The use of FAEs for psoriasis is not a new. It has been used in Germany for treating psoriasis for decades.
- FAEs, especially DMF, have showed a great clinical response with a good safety and tolerability profile in RRMS.
- When compared to other MS treatments, FAEs are very appealing regarding their tolerability and safety profile.
- The main problems associated with FAEs are the gastrointestinal problems, flushing and frequent dosing; they are the main cause of treatment withdrawal.
- Scientists should search for a method to provide a controlled release of DMF thus reducing the frequency of dosing and decreasing the associated side effects since they are dose dependent.

- More devotion should be given to study and declare the neuroprotective characteristics of FAEs, its exact mechanism of action and how it interacts with its targets at the molecular level.

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