REFERENCE GUIDE FOR THE PHARMACY LICENSING EXAM Theory-Fourth Edition

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Part-II

MANAN H SHROFF

PREFACE

I am very happy to introduce the FOURTH edition of the Reference Guide for the Pharmacy Licensing Exam-Theory. It is specifically written for students preparing for NAPLEX® and QCE® exams. It contains over 70 chapters and includes well organized therapeutic classifications at the beginning of each chapter, with brand and generic names of medications.

This review guide also covers over 3000 drugs; a sound knowledge of these drugs is an important factor for passing NAPLEX® and QCE® exams. I would also recommend the Reference Guide for the Pharmacy Licensing Exam - Questions and Answers (over 1200 NAPLEX-type questions) and the Reference Guide for Pharmaceutical Calculations (over 500 calculations).

I hope my efforts will help you to pass your key exams. I wish you the very best of luck, and any question or comment is always welcome.

Good luck,

Manan H. Shroff

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Definition: Benign Prostatic Hyperplasia is defined as an enlargement of the prostate gland which is often associated with urination and bladder problems.

A). 5-Alpha-Reductase Inhibitors

	Dose	Special Notes
Finasteride (Tablet)	1. B.P.H. 5 mg once a day with or without food. 2. Androgenetic alopecia 1 mg orally once daily with or without food.	1). Finasteride (Proscar) is a specific inhibitor of steroid Type II 5α-reductase; an intracellular enzyme that converts the androgen testosterone into 5α-dihydrotestosterone (DHT). The development and enlargement of the prostate gland is dependent on this potent androgen, 5α-dihydrotestosterone (DHT). 2). It is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to: i). Improve symptoms ii). Reduce the risk of acute urinary retention (AUR) iii). Reduce the risk of the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy. 3). In combination with the alpha-blocker Doxazosin, It is indicated to reduce the risk of symptomatic progression of BPH.

	Dose	Special Notes
Finasteride (Tablet)		4). Finasteride, under the brand name of Propecia, is indicated for the treatment of male pattern hair loss (androgenetic alopecia) in MEN ONLY. It must NOT be used in children or women. 5). Women should NOT handle crushed or broken Finasteride (Proscar) tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of Finasteride (Proscar) and the subsequent potential risk to a male fetus. Finasteride (Proscar) tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. 6). Finasteride (Proscar) is classified under pregnancy category X.
Dutasteride (Capsule)	1). B.P.H. a). Avodart 0.5 mg taken once daily with or without food. b). Jalyn 0.5 mg Dutasteride, 0.4 mg Tamsulosin once daily with or without food.	1). Dutasteride (Avodart) is a synthetic 4-azasteroid compound that is a selective inhibitor of both the type 1 and type 2 isoforms of steroid 5 alpha-reductase, an intracellular enzyme that converts testosterone to DHT. 2). Dutasteride (Avodart) is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to: i). improve symptoms, ii). reduce the risk of acute urinary retention (AUR), and iii). reduce the risk of the need for BPH-related surgery. 3). In combination with the alpha adrenergic antagonist, Tamsulosin, it (Jalyn) is indicated for the treatment of symptomatic BPH in men with an enlarged prostate. 4). The capsules of Dutasteride (Avodart) should be swallowed whole and not chewed or opened, as contact with the capsule contents may result in irritation of the oropharyngeal mucosa. 5). Dutasteride (Avodart) capsules should NOT be handled by a woman who is pregnant or who could become pregnant. Dutasteride (Avodart) is absorbed through the skin and could result in unintended fetal exposure. If a woman who is pregnant or who could become pregnant comes in contact with leaking dutasteride capsules, the contact area should be washed immediately with soap and water. It is classified under pregnancy category X. 6). Impotence, decreased libido, breast disorders (including breast enlargement and tenderness), dizziness and ejaculation disorders are most commonly reported side effects of Dutasteride (Avodart).

39. ERYTHROPOIESIS AND COLONY STIMULATING AGENTS

A). Erythropoiesis-Stimulating Agents (ESAs)

Epoetin alfa	=	Epogen, Procrit
Darbepoetin alfa	=	Aranesp
Epoetin beta methoxy propylene glycol	=	Mircera

B). Colony Stimulating Factors (CSF)

Filgrastim	=	Neupogen
Pegfilgrastim	=	Neulasta
Sargramostim	=	Leukine

	Dose	Special Notes
Epoetin alfa (Injection)	1. Anemia due to Chronic Kidney Disease: 50 to 100 Units/kg 3 times weekly IV or SC.	1). Erythropoietin is a glycoprotein which stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. Epoetin alfa (Epogen, Procrit), a 165 amino acid glycoprotein manufactured by recombinant DNA technology, has the same biological effects as endogenous erythropoietin.
	2. Zidovudine induced anemia: 100 Units/kg 3 times weekly IV or SC.	2). Epoetin alfa (Epogen, Procrit) is indicated for the anemia due to: a). Chronic Kidney Disease (CKD) b). Zidovudine in HIV-infected Patients c). Chemotherapy in Patients With Cancer d). To reduce the need for allogeneic blood transfusions in anemic patients who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.
	3. Chemotherapy induced anemia: 150 Units/kg subcutaneously 3 times per week until completion of a chemotherapy course.	3). In clinical studies, patients experienced greater risks for death, serious cardiovascular events, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target hemoglobin levels of 13 g/dL and above. Therefore, it is advisable to individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL or precisely 11 g/dL.
	4). Surgery Patients: 300 Units/kg per day SC for 10 days before surgery; on the day of surgery and 4 days after surgery.	4). An increased incidence of deep vein thrombosis, serious cardiovascular events and strokes (especially in chronic renal failure patients), pure red cell aplasia (PRCA), severe anemia, hypertension and seizure are reported side effects of Epoetin alfa (Epogen, Procrit).

	Dose	Special Notes
Epoetin alfa (Injection)		5). ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers. Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Epogen or Procrit to patients with cancer.
Darbepoetin Alfa (Injection)	1. Patients with CKD on dialysis: 0.45 mcg/kg IV or SC as a weekly injection OR 0.75 mcg/kg once every 2 weeks. 2. Patients with CKD NOT on dialysis: 0.45 mcg/kg IV or SC given once every 4 weeks. 3. Chemotherapy induced anemia: 2.25 mcg/kg every week SC until completion of a chemotherapy course. OR 500 mcg every 3 weeks SC until completion of a chemotherapy course.	1). Darbepoetin alfa (Aranesp) is an erythropoiesis-stimulating protein that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. 2). Darbepoetin alfa (Aranesp) is indicated for the anemia due to: a). Chronic Kidney Disease (CKD) b). Chemotherapy in Patients With Cancer 3). In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL. 4). ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers. Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Aranesp to patients with cancer. 5). An increased incidence of deep vein thrombosis, serious cardiovascular events and strokes (especially in chronic renal failure patients), pure red cell aplasia (PRCA), severe anemia, hypertension and seizure are reported side effects of Darbepoetin alfa (Aranesp).
Epoetin beta methoxy propylene glycol (Injection)	1. Anemia due to CKD: 0.6 mcg/kg body weight given as a single IV or SC injection once every two weeks.	1). Epoetin beta methoxy polyethylene glycol (Mircera) is an erythropoiesis-stimulating agent. It is indicated for the treatment of anemia associated with chronic renal failure (CRF) in adults, including patients on dialysis and not on dialysis.

	Dose	Special Notes
Epoetin beta methoxy propylene glycol (Injection)		2). Epoetin beta methoxy polyethylene glycol (Mircera) is NOT indicated for the treatment of anemia due to cancer chemotherapy. 3). Patients experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL. 4). ESAs, including Epoetin beta methoxy polyethylene glycol (Mircera), shortened overall survival and/or time-to-tumor progression in clinical studies in patients with advanced breast, head and neck, lymphoid and non-small cell lung malignancies when dose to a target hemoglobin of ≥ 12 g/dL. 5). An increased incidence of deep vein thrombosis, serious cardiovascular events and strokes (especially in chronic renal failure patients), pure red cell aplasia (PRCA), severe anemia, hypertension and seizure are reported side effects of Epoetin beta methoxy polyethylene glycol (Mircera).
B). Colony Stimulating Factors (CSF)		
Filgrastim (Injection)	1. MC: 5 mcg/kg/day, given as a single daily injection by SC bolus injection, by short IV infusion (15 to 30 minutes), or by continuous SC or continuous IV infusion. 2. BMT: 10 mcg/kg/day given as an IV infusion of 4 or 24 hours, or as a continuous 24-hour SC infusion.	1). Filgrastim (Neupogen) is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology. Filgrastim (Neupogen) is produced by Escherichia coli (E coli) bacteria into which the human granulocyte colony-stimulating factor gene has been inserted. Colony-stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation. 2). Filgrastim (Neupogen) is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, eg, febrile neutropenia, in: a). Cancer patients receiving myelosuppressive chemotherapy (MC) b). Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy (AML) c). Cancer patients receiving bone marrow transplant (BMT) d). Patients undergoing peripheral blood progenitor cell collection and therapy (PBPC) e). Patients with congenital, cyclic, or idiopathic neutropenia.

	Dose	Special Notes
Filgrastim (Injection)	3. PBPC: 10 mcg/kg/day SC, either as a bolus or a continuous infusion. 4. Congenital neutropenia: 6 mcg/kg BID SC every day. 5. Idiopathic or Cyclic Neutropenia 5 mcg/kg as a single injection SC every day.	3). A CBC and platelet count should be obtained before instituting Filgrastim (Neupogen) therapy, and monitored twice weekly during therapy. 4). For patients receiving bone marrow transplant (BMT), the first dose of Filgrastim (Neupogen) should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion. 5). Nausea, vomiting, hypertension, rash, cutaneous vasculitis, acute respiratory distress syndrome, splenic rupture, alveolar hemorrhage and hemoptysis, sickle cell crisis and sweet's syndrome (acute febrile neutrophilic dermatosis) are reported with Filgrastim (Neupogen) therapy.
Pegfilgrastim (Injection)	Febrile neutropenia: 6 mg via SC given once per chemotherapy cycle.	1). Pegfilgrastim (Neulasta) is a covalent conjugate of recombinant methionyl human G-CSF (Filgrastim) and monomethoxypolyethylene glycol. 2). Pegfilgrastim (Neulasta) is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. 3). The 6 mg fixed-dose formulation should not be used in infants, children, and smaller adolescents weighing less than 45 kg. 4). Pegfilgrastim (Neulasta) should NOT be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy. 5). Nausea, vomiting, hypertension, rash, cutaneous vasculitis, acute respiratory distress syndrome, splenic rupture, alveolar hemorrhage and hemoptysis, sickle cell crisis and sweet's syndrome (acute febrile neutrophilic dermatosis) are reported with Filgrastim (Neupogen) therapy.
Sargramostim (Injection)	250 mcg/m^2/day administered IV or SC depend on the conditon treated.	1). Sargramostim (Leukine) is a recombinant human granulocyte macrophage colony stimulating factor (Rhu GM-CSF) produced by recombinant DNA technology in a yeast (S. cerevisiae) expression system. GM-CSF is a hematopoietic growth factor which stimulates proliferation and differentiation of hematopoietic progenitor cells.

Dose	Special Notes
Sargramostim (Injection)	2). Sargramostim (Leukine) is indicated for: a). Use following induction chemotherapy in older adult patients with acute myelogenous leukemia (AML) to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death. b). The mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis. Mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment as compared with collection without mobilization. c). Acceleration of myeloid recovery in patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's disease undergoing autologous bone marrow transplantation (BMT). d). In patients who have undergone allogeneic or autologous bone marrow transplantation (BMT) in whom engraftment is delayed or has failed. 3). Headache, pericardial effusion, arthralgia, myalgia, fever, abdominal pain, nausea, vomiting, arrhythmia, fainting, eosinophilia, dizziness, hypotension, injection site reactions, pain (including abdominal, back, chest, and joint pain), tachycardia, thrombosis, and transient liver function abnormalities are reported with Sargramostim (Leukine).
Terminology:	
Neutropenia	Neutropenia is a granulocyte disorder characterized by an abnormally low number of neutrophils, the most important type of white blood cell. Neutrophils usually make up 50-70% of circulating white blood cells and serve as the primary defense against infections by destroying bacteria in the blood. Hence, patients with neutropenia are more susceptible to bacterial infections and, without prompt medical attention, the condition may become life-threatening (neutropenic sepsis).
Congenital neutropenia	Severe congenital neutropenia is a condition that causes affected individuals to be prone to recurrent infections. People with this condition have a deficiency of neutrophils, a type of white blood cell that plays a role in inflammation and in fighting infection. The deficiency of neutrophils, called neutropenia, is apparent at birth or soon afterward.

Idiopathic neutropenia	The term 'idiopathic neutropenia' describes various types of neutropenia that may occur at any point in life for unknown reasons.
Cyclic neutropenia	Cyclic neutropenia (or cyclical neutropenia) is a form of neutropenia that tends to occur every three weeks and lasting three to six days at a time due to changing rates of cell production by the bone marrow.

51. IRRITABLE BOWEL SYNDROME

A). Anticholinergic Agents

Hyoscyamine	=	NuLev, Levbid, Levsin, Levsinex, A-Spaz, Anaspaz, Colidrops, Cystospaz, Ed-Spaz, HyoMax, Spasdel, Symax
Dicyclomine	=	Bentyl

B). Anticholinergic + Antispasmodics

Atropine + Hyoscyamine + Scopolamine + Phenobarbital	=	Donnatal, Donnatal Extentab, Bellatal, Alkabel-SR, Antispasmodic, Hyosophen, Quadrapax, Servira, Spasmolin

C). Benzodiazepine + Anticholinergic

Chlordiazepoxide + Clidinium	=	Librax

D). 5-HT3 Receptor Antagonist

Alosetron	=	Lotronex

E). Chloride Channel Activator

Lubiprostone	=	Amitiza

Irritable Bowel Syndrome (IBS) is a disorder in which the nerves that control the muscles in the GI tract are too active, causing it to become sensitive to food, stool, gas, and stress. This may cause abdominal pain, bloating, constipation or diarrhea.

A). Anticholinergic Agents

	Dose	Special Notes
Hyoscyamine (Tablet) (Tablet, SL) (Tablet, ER) (Tablet, ODT) SL: Sublingual ER: Extended Release IR: Immediate Release ODT: Orally Disintegrating	IBD a). IR 1 to 2 tablets (0.125 mg each) every 4 hours as needed. Do not exceed 12 tablets in 24 hours. b. ER 1 to 2 tablets (0.375 mg each) every 12 hours. Do not exceed 4 tablets in 24 hours.	1). Hyoscyamine inhibits the action of acetylcholine. It prevents gastrointestinal propulsive motility and decreases gastric acid secretion. It also controls excessive pharyngeal, tracheal and bronchial secretions. 2). Hyoscyamine is effective as adjunctive therapy in the treatment of: a). Peptic ulcer b). Neurogenic bladder and neurogenic bowel disturbances c). Infant colic d). Along with morphine or other narcotics in symptomatic relief of biliary and renal colic e). As a "drying agent" in the relief of symptoms of acute rhinitis f). In the therapy of parkinsonism to reduce rigidity and tremors and to control associated sialorrhea and hyperhidrosis g). Irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and functional gastrointestinal disorders h). To control gastric secretion, visceral spasm and hypermotility in spastic colitis, spastic bladder, cystitis, pylorospasm, and associated abdominal cramps. 3). Hyoscyamine is available in immediate release tablet (0.125 mg, Levsin), sublingual tablet (0.125 mg, Levsin SL), extended release tablet (0.375 mg, Levbid), orally disintegrating tablets (0.125 mg, NuLev). 4). Dryness of the mouth; urinary hesitancy and retention; blurred vision; tachycardia; palpitations; mydriasis; increased ocular tension; and decreased sweating are commonly reported side effects of Hyoscyamine.
Dicyclomine (Tablet) (Capsule) (Syrup) (Injection)	IBS a). Oral 20 to 40 mg PO four times a day. b). Injection 10 to 20 mg IM four times a day.	1). Dicyclomine (Bentyl), an antispasmodic and anticholinergic agent, relieves smooth muscle spasm of the gastrointestinal tract through its anticholinergic-antimuscarinic effect. 2). Dicyclomine (Bentyl) is indicated for the treatment of patients with functional bowel/irritable bowel syndrome. 3). Dicyclomine (Bentyl) injection must be administered via intramuscular route only.

	Dose	Special Notes
Dicyclomine (Tablet) (Capsule) (Syrup) (Injection)		4). Dryness of the mouth; urinary hesitancy and retention; blurred vision; tachycardia; palpitations; mydriasis; increased ocular tension; and decreased sweating are commonly reported side effects of Dicyclomine (Bentyl).

B). Anticholinergic + Antispasmodics

Atropine, Hyoscyamine, Scopolamine, Phenobarbital (Tablet) (Tablet, ER) (Tablet, CR) (Elixir)	IBS a). Oral IR 1 to 2 teaspoonfuls 3 or 4 times a day. b). Oral ER 1 tablet every 8 or 12 hours.	1). Belladonna alkaloids (Atropine, Hyoscyamine and Scopolamine) and Phenobarbital are indicated as adjunctive therapy in the treatment of irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis. Belladonna alkaloids (Atropine, Hyoscyamine and Scopolamine) provide anticholinergic/antispasmodic action whereas Phenobarbital is included in the formulation for its mild sedative action. 2). Each 5 cc of elixir contains 6.2 mg, phenobarbital; 0.1037 mg, hyoscyamine; 0.0194 mg, atropine and 0.0065 mg, scopolamine. Each extended release tablet (Donnatal Extentab) contains 48.6 mg, phenobarbital; 0.3111 mg, hyoscyamine; 0.0582 mg, atropine and 0.0195 mg, scopolamine. 3). This drug combination should be carefully prescribed to patients suffering from glaucoma, obstructive uropathy, obstructive GI disease or paralytic ileus. Xerostomia, urinary retention, blurred vision, tachycardia, mydriasis, and headache are reported side effects of the drug.

C). Benzodiazepine + Anticholinergic

Chlordiazepoxide + Clidinium	IBS 1 or 2 capsules 3 or 4 times daily.	1). Each capsule of Librax (Chlordiazepoxide 5 mg and Clidinium 2.5 mg) contains antianxiety agent Chlordiazepoxide and the anticholinergic /spasmolytic agent Clidinium. 2). Librax (Chlordiazepoxide 5 mg and Clidinium 2.5 mg) is indicated for adjunct treatment of irritable bowel syndrome, acute enterocolitis, and peptic ulcer. 3). The drug should be carefully prescribed to patients suffering from glaucoma, prostatic hypertrophy, or benign bladder neck obstruction. Drowsiness, ataxia, confusion, dry mouth, nausea, and constipation are reported side effects of the drug.

D). 5-HT3 Receptor Antagonist

	Dose	Special Notes
Alosetron (Tablet)	Women with severe diarrhea-predominant irritable bowel syndrome (IBS) 0.5 to 1 mg twice a day with or without food.	1). Alosetron (Lotronex) is a potent and selective 5-HT3 receptor antagonist. 5-HT3 receptors are ligand-gated cation channels that are extensively distributed on enteric neurons in the human gastrointestinal tract, as well as other peripheral and central locations. Activation of these channels and the resulting neuronal depolarization affect the regulation of visceral pain, colonic transit and gastrointestinal secretions, processes that relate to the pathophysiology of irritable bowel syndrome (IBS). 2). Alosetron (Lotronex) is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have: a). chronic IBS symptoms (generally lasting 6 months or longer), and b). not responded adequately to conventional therapy. 3). Diarrhea-predominant IBS is severe if it includes diarrhea and one or more of the following: a). frequent and severe abdominal pain/discomfort b). frequent bowel urgency or fecal incontinence 4). Before receiving the initial prescription for Alosetron (Lotronex), the patient must read and sign the Patient-Physician Agreement for Alosetron. For safety reasons, only physicians who enroll in the Prometheus Prescribing Program for Lotronex should prescribe Lotronex. 5). Alosetron (Lotronex) should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice a day. 6). Infrequent but serious gastrointestinal adverse events have been reported with the use of Alosetron. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization, and rarely, blood transfusion, surgery, and death. Therefore, Alosetron (Lotronex) should be discontinued immediately in patients who develop constipation or symptoms of ischemic colitis. Patients should immediately report constipation or symptoms of ischemic colitis to their physician. The drug should not be resumed in patients who develop ischemic colitis. Patients who have constipation should immediately contact their physician if the constipation does not resolve after Alosetron is discontinued. 7). Serious GI adverse events including ischemic colitis, rectal bleeding, bloody diarrhea, abdominal pain, and severe constipation are major side effects of Alosetron (Lotronex).

E). Chloride Channel Activator

	Dose	Special Notes
Lubiprostone (Capsule)	1. Chronic Idiopathic Constipation 24 mcg PO bid with food and water. 2. IBS-C 8 mcg PO bid with food and water.	1). Lubiprostone (Amitiza) is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby facilitating the passage of stool and alleviating symptoms associated with chronic idiopathic constipation. 2). Lubiprostone (Amitiza) is indicated for the treatment of: a). chronic idiopathic constipation in adults b). irritable bowel syndrome with constipation (IBS-C) in women ≥ 18 years old 3). For patients with severely impaired hepatic function (Child-Pugh Class C), the recommended dose is 8 mcg once daily. If this dose is tolerated and an adequate response has not been obtained after an appropriate interval, doses can then be escalated to full dosing with appropriate monitoring of patient response. Dosage adjustment is not required for patients with moderately impaired hepatic function (Child-Pugh Class B). 4). It may cause fetal loss. It should be strictly avoided by pregnant women. Nausea, diarrhea, abdominal distention and flatulence are reported side effects of the drug.
Terminology		
Idiopathic constipation		It means that a particular cause for the constipation has not been found.
Chronic constipation		It means that constipation persists for a long period of time and doesn't respond to other treatments, as opposed to acute constipation, which may come on suddenly and be easily treated.

52. ENURESIS/INCONTINENCE MANAGEMENT

A). Muscarinic Antagonists

Tolterodine	=	Detrol, Detrol LA
Fesoterodine	=	Toviaz
Oxybutynin	=	Ditropan, Ditropan XL, Gelnique, Oxytrol, Urotrol, Anturol
Trospium	=	Sanctura, Sanctura XR
Darifenacin	=	Enablex
Solifenacin	=	VESIcare

B). Urinary Spasmolytic

Flavoxate	=	Urispas

C). Endocrine Hormone

Desmopressin	=	DDAVP, Stimate

D). Tricyclic Antidepressant

Imipramine	=	Tofranil

A). Muscarinic Antagonists

	Dose	Special Notes
Tolterodine (Tablet) (Capsule, ER)	Urinary Incontinence:	1). Tolterodine (Detrol), a muscarinic receptor antagonist, is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.
IR: Immediate Release	a). IR 1 to 2 mg PO bid.	2). Tolterodine is available in immediate release tablet (1 mg, 2mg - Detrol) and extended release capsule (2mg, 4mg – Detrol LA).
ER: Extended Release	b). ER 2 to 4 mg once daily with water.	3). For patients with mild to moderate hepatic impairment (Child-Pugh Class A or B) or severe renal impairment (CrCl 10-30 mL/min), the recommended dose of Detrol LA is 2 mg once daily. Detrol LA is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C). 4). For patients receiving ketoconazole or other potent CYP3A4 inhibitors such as other azole antifungals (e.g., itraconazole, miconazole) or macrolide antibiotics (e.g., erythromycin, clarithromycin) or cyclosporine or vinblastine, the recommended dose of Tolterodine (Detrol) is 1 mg twice daily and the recommended dose of Tolterodine (Detrol LA) is 2 mg once daily.

	Dose	Special Notes
Tolterodine (Tablet) (Capsule, ER) ER: Extended Release		5). Xerostomia, urinary retention, blurred vision, tachycardia, mydriasis, and headache are reported side effects of the drug. 5). Tolterodine (Detrol) is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. It is also contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients, or to Fesoterodine fumarate which, like Tolterodine, is metabolized to 5hydroxymethyl tolterodine.
Fesoterodine (Tablet, ER) ER: Extended Release	Urinary Incontinence 4 to 8 mg once daily with or without food.	1). Fesoterodine (Toviaz), a prodrug of Tolterodine, is rapidly de-esterified to its active metabolite 5-hydroxymethyl Tolterodine which is a muscarinic antagonist. 2). Fesoterodine (Toviaz) is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. 3). The daily dose of Fesoterodine (Toviaz) should not exceed 4 mg in the following populations: a). Patients with severe renal impairment (CLCR < 30 mL/min). b). Patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin. 4). Fesoterodine (Toviaz) is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. It is also contraindicated in patients with known hypersensitivity to the drug or its ingredients, or to Tolterodine. 5). Xerostomia, urinary retention, blurred vision, tachycardia, mydriasis, and headache are reported side effects of the drug.
Oxybutynin (Tablet) (Tablet, ER) (Transdermal) (Topical gel)	Urinary Incontinence 1). Oral a). 2.5 to 5 mg (Ditropan) 2 to 4 times daily. b). 5 to 30 mg (Ditropan XL) once daily.	1). Oxybutynin (Ditropan) exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. It relaxes bladder smooth muscle, increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin thus decreases urgency and the frequency of both incontinent episodes and voluntary urination. 2). Oxybutynin (Ditropan) is indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria).

	Dose	Special Notes
Oxybutynin (Tablet) (Tablet, ER) (Transdermal) (Topical gel)	2). Transdermal Apply one patch (3.9 mg/day) and replace twice weekly (every 3 to 4 days). 3). Topical gel a). Apply one sachet of (10% Oxybutynin gel) once daily. b). Apply 3 pumps of (3% Oxybutynin gel) once daily.	3). Oxybutynin is available in immediate release tablet (5 mg, Ditropan), extended release tablet (5 mg, 10 mg or 15 mg, Ditropan XL), transdermal patch (3.9 mg/day, Oxytrol), topical gel (10%, Gelnique and 3%, Anturol). 4). Ditropan XL uses osmotic pressure to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The system, which resembles a conventional tablet in appearance, comprises an osmotically active bilayer core surrounded by a semipermeable membrane. The bilayer core is composed of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice in the semipermeable membrane on the drug-layer side of the tablet. In an aqueous environment, such as the gastrointestinal tract, water permeates through the membrane into the tablet core, causing the drug to go into suspension and the push layer to expand. This expansion pushes the suspended drug out through the orifice. The semipermeable membrane controls the rate at which water permeates into the tablet core, which in turn controls the rate of drug delivery. The controlled rate of drug delivery into the gastrointestinal lumen is thus independent of pH or gastrointestinal motility. The function of Ditropan XL depends on the existence of an osmotic gradient between the contents of the bilayer core and the fluid in the gastrointestinal tract. Since the osmotic gradient remains constant, drug delivery remains essentially constant. 5). Oxybutynin transdermal system (Oxytrol) should be changed twice weekly or every 3 to 4 days. 6). Oxybutynin is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. 7). Xerostomia, urinary retention, blurred vision, tachycardia, mydriasis, and headache are reported side effects of the drug.
Trospium (Tablet) (Capsule, ER) ER: Extended Release	Urinary Incontinence a). IR 20 mg PO bid at least one hour before meals or given on empty stomach.	1). Trospium (Sanctura), a muscarinic antagonist, antagonizes the effect of acetylcholine on muscarinic receptors in cholinergically innervated organs including the bladder. Its parasympatholytic action reduces the tonus of smooth muscle in the bladder. 2). Trospium (Sanctura) is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

	Dose	Special Notes
Trospium (Tablet) (Capsule, ER) ER: Extended Release	b). ER 60 mg PO once daily in morning 1 hour before meals or on empty stomach.	3). Administration with a high fat meal resulted in reduced absorption, with AUC and Cmax values 70-80% lower than those obtained when Trospium (Sanctura) was administered while fasting. Therefore, it is recommended that Trospium (Sanctura) should be taken at least one hour prior to meals or on an empty stomach. 4). It is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions. 5). Coadministration of Trospium (Sanctura) with procainamide, pancuronium, morphine, vancomycin or tenofovir may increase the serum concentration of Trospium (Sanctura) and/or the coadministered drug due to competition to eliminate via active tubular secretion pathway. Careful patient monitoring is recommended in patients receiving such drugs. 6). Dry mouth, urinary retention, blurred vision, tachycardia, mydriasis, and headache are reported side effects of the drug.
Darifenacin (Tablet, ER)	Urinary Incontinence 7.5 to 15 mg once daily with or without food.	1). Darifenacin (Enablex) is a potent muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. 2). For patients with moderate hepatic impairment (Child-Pugh B) or when co-administered with potent CYP3A4 inhibitors (for example, ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin and nefazodone), the daily dose of Darifenacin (Enablex) should not exceed 7.5 mg. Darifenacin (Enablex) is not recommended for use in patients with severe hepatic impairment (Child-Pugh C). 3). It is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions. 4). Dry mouth, urinary retention, blurred vision, tachycardia, mydriasis, and headache are reported side effects of the drug.
Solifenacin (Tablet)	Urinary Incontinence 5 to 10 mg once daily with or without food.	1). Solifenacin (VESIcare), a muscarinic receptor antagonist, is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. 2). For patients with severe renal impairment (CrCl < 30 mL/min), a daily dose of Solifenacin (VESIcare) greater than 5 mg is not recommended.

	Dose	Special Notes
Solifenacin (Tablet)		3). For patients with moderate hepatic impairment (Child-Pugh B), a daily dose of Solifenacin (VESIcare) greater than 5 mg is not recommended. Use of Solifenacin in patients with severe hepatic impairment (Child-Pugh C) is not recommended. 4). When administered with potent CYP3A4 inhibitors such as ketoconazole, a daily dose of Solifenacin (VESIcare) greater than 5 mg is not recommended. 5). It is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions. 6). Dry mouth, urinary retention, blurred vision, tachycardia, mydriasis, and headache are reported side effects of the drug.
B). Urinary Spasmolytic		
Flavoxate (Tablet)	Urinary tract spasmolytic 1 or 2 (100 mg tablet) 3 or 4 times daily.	1). Flavoxate (Urispas), a synthetic urinary tract spasmolytic, counteracts smooth muscle spasm of the urinary tract and exerts its effect directly on the muscle. 2). Flavoxate (Urispas) is indicated for symptomatic relief of dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence as may occur in cystitis, prostatitis, urethritis, urethrocystitis/urethrotrigonitis in adults and children over 12 years of age. 3). Flavoxate (Urispas) should be given cautiously in patients with suspected glaucoma. 4). It is contraindicated in patients who have any of the following obstructive conditions: pyloric or duodenal obstruction, obstructive intestinal lesions or ileus, achalasia, gastrointestinal hemorrhage and obstructive uropathies of the lower urinary tract. 5). Nausea, vomiting, dry mouth, vertigo, headache and drowsiness are commonly reported side effects of the drug.

Enuresis Management:

C). Endocrine Hormone

	Dose	Special Notes
Desmopressin (Tablet) (Rhinal Tube) (Nasal Spray) (Injection)	1. Central diabetes insipidus or Cranial diabetes insipidus a). Tablet 0.1 to 0.8 mg in two divided doses. b). Rhinal Tube and Nasal Spray 0.1 to 0.4 ml intranasally daily, either as a single dose or divided into 2 or 3 doses. c). Injection 0.5 ml (2 mcg) to 1 ml (4 mcg) via IV or SC in two divided doses. 2. Primary nocturnal enuresis 0.2 to 0.6 mg PO at bed time. Please read special note 3). 3. Hemophilia A and von Willebrand's Disease (Type I) a). Stimate Spray 1 spray (0.1 ml) per nostril to provide a total dose of 300 mcg.	1). Desmopressin (DDAVP), a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. Desmopressin has been shown to be more potent than arginine vasopressin in increasing plasma levels of factor VIII activity in patients with hemophilia and von Willebrand's disease Type I. 2). Desmopressin (DDAVP) is indicated for the following: a). Central diabetes insipidus (Tablet and Injection) b). Primary nocturnal enuresis (patients 6 year and older) (Tablet) c). Central cranial diabetes insipidus (Rhinal tube and Nasal spray) d). Hemophilia A with factor VIII coagulant activity levels greater than 5% (Injection and Stimate Nasal Spray) e). Von Willebrand's Disease (Type I) (Injection and Stimate Nasal Spray) 3). When using for nocturnal enuresis, fluid restriction should be observed, and fluid intake should be limited to a minimum from 1 hour before desmopressin administration, until the next morning, or at least 8 hours after administration. 4). Please note Desmopressin (DDAVP) is not indicated for the treatment of hemophilia A with factor VIII coagulant activity levels equal to or less than 5%, or for the treatment of hemophilia B, or in patients who have factor VIII antibodies. 5). Headache, nausea, abdominal cramps, facial flushing, rhinitis, and nasal congestion are reported side effects of the drug.

	Dose	Special Notes
Desmopressin (Tablet) (Rhinal Tube) (Nasal Spray) (Injection)	b). Injection 0.3 mcg DDAVP/kg infused slowly over 15 to 30 minutes	

D). Tricyclic Antidepressant

Imipramine	Please Refer To Page 106 (Part 1) of Chapter 14-AntiDepressant

Terminology:

Central cranial diabetes insipidus or central diabetes insipidus	Diabetes insipidus is divided into cranial/central diabetes insipidus and nephrogenic diabetes insipidus. Cranial diabetes insipidus is caused by reduced or inadequate secretion of the ADH/vasopressin hormone while nephrogenic diabetes insipidus is caused by insensitivity response of the collecting duct of the kidney to ADH. Both of these conditions will lead to hypotonic polyuria. Central diabetes insipidus/cranial diabetes insipidus is a rare condition that involves extreme thirst and excessive urination. Symptoms may include increased amount of urine production, excessive thirst and confusion and changes in consciousness due to dehydration. Cranial diabetes insipidus is caused by several factors which include idiopathic causes in more than 50%, trauma such as head injury, neurosurgery, autoimmune hypophysitis or hypophysectomy.
Hemophilia A	Hemophilia A is a hereditary bleeding disorder caused by a lack of blood clotting factor VIII. Without enough factor VIII, the blood cannot clot properly to stop bleeding. Bleeding is the major symptom of this disorder.
Von Willebrand disease	Von Willebrand disease (vWD) is the most common hereditary coagulation abnormality described in humans, although it can also be acquired as a result of other medical conditions. It arises from a qualitative or quantitative deficiency of von Willebrand factor (vWF), a multimeric protein that is required for platelet adhesion. Von Willebrand disease Type I (vWD) is the most common type of the disorder and those that have it are typically asymptomatic or may experience mild symptoms such as nosebleeds although there may be severe symptoms in some cases. There are various factors that affect the presentation and severity of symptoms of vWD such as blood type. It is named after Erik Adolf von Willebrand, a Finnish pediatrician who first described the disease in 1926.

72. PHARMACOKINETICS

The pharmacokinetic property of a drug is normally associated with:

1). Absorption
2). Distribution
3). Metabolism
4). Elimination

1). Absorption: The absorption of the drug generally occurs through the cell membrane via three different mechanisms.

A. Passive transport
B. Active transport
C. Facilitated transport

A. Passive transport: It is an unsaturable, nonselective and energy independent transport. It normally depends on the concentration gradient. Most drugs are absorbed through the cell membrane by the passive transport mechanism.

B. Active transport: It is saturable, selective and energy dependent transport. This type of transport requires carrier molecules to transfer drug molecules from one side of the cell membrane to the other side. The transport normally works against the concentration gradient and therefore energy is consumed. Very few drugs are absorbed through the active transport mechanism.

C. Facilitated transport: It is saturable, nonselective and energy independent transport. It also depends on the concentration gradient. However, unlike passive transport, it is saturable. The major factor that affects the absorption of drugs is the presence of ionic charges on drug particles. Non-ionized drugs are more lipid soluble than ionized drugs, and therefore are more quickly absorbed through the cell membrane.

A similar principal helps in the elimination of drugs. For example, elimination of acidic drugs can be increased in an alkaline pH of urine; this will produce more ionized particles of the drug, which are highly water soluble and easily excreted.

The absorption of drugs through the cell membrane can also be delayed by using vasoconstrictors such as adrenaline. This will help to localize the action of the drug. For example, the addition of adrenaline to a local anesthetic procaine or lidocaine localizes its action.

2). Distribution: Once a drug is absorbed, it is distributed into intestinal, cellular or transcellular fluids. The principal factor that affects the distribution of drugs is protein binding.

Protein binding: It is a very important factor that may lead to severe drug interaction. Normally, a drug is bound to plasma albumin for protein binding.

The influence of protein binding on the distribution of drugs is as follows:

1. Protein binding makes drugs inactive.
2. Protein binding makes drugs impermeable to the cell membrane; this will delay the distribution and elimination of the drug.
3. Protein binding also serves as storage for drugs; the change in protein binding may change the distribution of the drug.

Factors affecting the protein binding of drugs:

1. Renal impairment
2. Hypoalbuminemia
3. Age
4. Pregnancy
5. Uremia

An apparent volume of distribution: It is a hypothetical volume occupied by the drug in the body. It is defined as the ratio of the amount of drug in the body to the plasma concentration of the drug. It is the direct measure of the extent of drug distribution. It can be expressed by the following equation:

$V_d = D_b/C_p$ where,

V_d = volume of distribution
D_b = amount of the drug in the body
C_p = plasma concentration of the drug in the body

Biotransformation (Metabolism of Drugs):

Drugs metabolize or bio transform by two principal pathways:

1. Phase I metabolism
2. Phase II metabolism

Phase I metabolism: It normally involves oxidation, reduction and hydrolysis. It produces more active or toxic substances compared to the parent compound. Phase II metabolism converts the phase I toxic metabolites to water soluble and pharmacologically inactive compounds through the process of conjugation.

1. Oxidation: This normally includes hydroxylation of nitrogen and carbon, N and O dealkylation, and oxidative deamination. These reactions are catalyzed by CP 450 enzymes, e.g. Imipramine.

2. Reduction: They are less common compared to oxidative reactions, e.g. warfarin where its ketone group is converted to a hydroxyl group by reduction.

3. Hydrolysis: Normally, hydrolysis does not require any hepatic microsomal enzymes. It normally occurs in tissues. Both ester and amide are highly susceptible to hydrolysis, e.g. procaine, an ester that rapidly converts to an inactive compound by plasma cholinesterases.

Phase II metabolism: It normally involves conjugation. The conjugates are pharmacologically inactive compounds with high water solubility. The conjugate will help to excrete toxic metabolites from the body through the renal excretion. The groups that are normally involved in conjugated reactions are sulfate, methyl, acetyl, glycyl and glutamyl. The glucuronic acid conjugation is the most common type of conjugate reaction. It involves the enzyme UDP-glucuronyl transferase.

Microsomal enzyme induction and inhibition: A number of drugs have the tendency to increase the activity of various microsomal oxidative enzymes and conjugation reactions; this will increase the metabolism and reduce the pharmacological activity of other drugs. These types of enzyme reactions are defined as enzyme induction reactions. For example, the administration of phenobarbital increases the metabolism and reduces the pharmacological activity of warfarin. Phenobarbital is therefore classified as the enzyme inducer drug.

The opposite is also true. There are a number of drugs that inhibit the activity of enzyme oxidase and prolong the metabolism of various drugs; this will result in increased adverse effects and toxicities of other drugs. This type of reaction is defined as an enzyme inhibition reaction. For example, the administration of Cimetidine may increase the toxicity and adverse effects of theophylline through the enzyme inhibition. Cimetidine is therefore classified as the enzyme inhibitor drug.

List of enzyme inducers	List of enzyme inhibitors
Rifampin	Cimetidine
Carbamazepine	Ciprofloxacin
Phenobarbital	Erythromycin
Phenytoin	Clopidogrel
Nicotine	Ketoconazole
Rifabutin	Fluvoxamine
	Nelfinavir
	Ritonavir

Prodrug: A drug that becomes biologically active after it is metabolized by the liver known as a prodrug. For example, Azathioprine produces its principal pharmacological action after it is metabolized to Mercaptopurine.

Drug excretion: A drug excretes from the body through the kidney, lungs, stool, sweat, bile and tears. Among these, excretion of a drug through the kidneys is very important. Renal excretion of a drug commonly occurs through the following mechanisms:

1. Glomerular filtration
2. Tubular reabsorption
3. Tubular secretion

1. Glomerular filtration: It generally depends on the permeability of capillaries and the difference between hydrostatic and osmotic pressures of plasma. In glomerular filtration, protein cannot be filtered and therefore a drug bound to protein cannot be excreted through this mechanism.

2. Tubular reabsorption: Many times it happens that a drug filtered through glomeruli does not appear in urine; this will normally happen when the drug has high lipid solubility (extensively non-ionized). This type of drug completely reabsorbs through the tubular reabsorption, and may disappear in final urine. The excretion of the drug through this mechanism normally depends on:

1). Extent of ionization of the drug
2). pH of urine

1). Ionization: Drugs that are highly ionized can be easily excreted in urine due to their high water solubility. The opposite is also true; drugs that have weak ionization power may ionize less and possess more lipid solubility. The lipid soluble drug reabsorbs through tubules and may not appear in urine.

2). pH of urine: The term "pH of urine" and ionization of a drug is very interrelated. Ionized drugs are more water soluble and therefore easily excreted via urine. This principal helps the prevention of drug toxicity. For example, an overdose symptom of salicylic acid can be prevented by administrating $NaHCO_3$, which makes a urine pH alkaline. This increases the ionization and water solubility of acidic drugs (such as salicylic acid), and hence increases the excretion of acidic drugs.

3). Tubular secretion: Many drugs are excreted from tubules as a sequence of secretion through an active transport mechanism; these include penicillin, probenecid, p-aminohippuric acid and glucuronic acid. Drugs that are transported through a similar mechanism may compete with each other for tubular secretion. This will delay the absorption of the second drug. For example, the administration of probenecid may prolong the tubular secretion of penicillin and may increase the toxicity and adverse effects of the drug.

Renal clearance: It is defined as the volume of plasma that is completely cleared of a specific compound in the unit time. The normal glomerular filtration rate is 120 ml/minute. It is measured by inulin. The rate at which plasma water is filtered through glomeruli is known as the glomerular filtration rate.

$CrCl = C_u \times V_u / C_p$ where,

CrCl = Creatinine clearance of the drug
C_u = concentration of drug in urine
C_p = concentration of drug in plasma
V_u = total volume of urine in time (t)

73. DRUGS AND THEIR ANTIDOTES

Antidote of Drugs	Drugs
Naloxone (Narcan)	Opioid
Nalmefene (Revex)	Opioid
Naltrexone (ReVia)	Opioid
Digoxin Fab (Digibind)	Digoxin, Digitoxin
Leucovorin Calcium (Wellcovorin)	Methotrexate, Trimethoprim, Pyrimethamine
Mesna (Mesnex)	Cyclophosphamide, Ifosfamide
Vitamin K	Warfarin
Phytonadione (Mephyton)	Warfarin
Protamine sulfate	Heparin
Deferoxamine mesylate (Desferal)	Iron
Dimercaprol (BAL)	Arsenic, Gold
Sodium thiosulfate	Cyanide
Flumazenil (Romazicon)	Benzodiazepines
Physostigmine (Antilirium)	Atropine, anticholinergic agents
Acetylcysteine (Mucomyst)	Acetaminophen
Dexrazoxane (Zinecard)	Doxorubicin
Pralidoxime (Protopam)	Organophosphorus compound
Glucagon	Insulin
Edetate disodium	Digitalis toxicity, hypercalcemia
Edetate calcium disodium	Lead
Atropine	Acetylcholine, cholinergic agents
Hydroxocobalamin	Cyanide