Chapter 26: Local Anesthetics

- **Suppress pain by blocking impulse conduction along axons**
  - **Blockade occurs only in neurons located at or near site of administration**
  - **Advantage**
    - **Pain is suppressed without causing generalized depression of nervous system**
    - **Safer than general anesthesia**
- **Classification**
  - **Ester: Procaine (novocaine) ester link**
  - **Amide: Lidocaine (xylocaine) amide link**

- **Ester *vs* Amide linkages**
  - **Differ in two ways**
    - **Method of inactivation**
    - **Ability to promote allergic responses**
- **Mechanism of Action**
  - **Block sodium channels in axonal membrane**
    - **No depolarization from lack of Na^+ influx**
  - **No selectivity**
    - **Will block action potential in all neurons that are exposed to the anesthetic agent**
    - **Give drug selectively through injection or topical placement in a limited area**
      - **Non-Myelinated neurons blocked more easily than myelinated**

■ Local Anesthetics

- Able to block conduction in both sensory and motor neurons
- After administration onset of effects rapid
  - **Determined by molecular properties of anesthetic**
    - **Molecular size**
    - **Lipid solubility**
    - **Degree of ionization at tissue pH**
  - **Small size, high lipid solubility and low ionization molecule cross neuron membrane most rapidly and have fastest onset of anesthesia**
  - **Termination of action by**
    - **Diffusion out of neurons**
    - **Regional blood flow (faster flow takes away action of anesthetic faster)**

- **Local anesthetics usually used in conjunction with a vasoconstrictor (epinephrine)**
  - **Delays absorption**
  - **Prolongs effects**
  - **Reduces toxicity**
  - **Absorption into blood**
  - **Produces toxicity**
  - **Tachycardia, nervousness, hypertension**
  - **Effects counteracted by use of alpha- and beta- adrenergic antagonists**
- **Metabolism of anesthetics**
  - **Ester-type anesthetics metabolized by esterases in the blood**
  - **Amide-type agents metabolized by enzymes in the liver**

- Adverse Effects
  - CNS: excitation → depression (drowsiness to unconsciousness and death due to respiratory depression
  - Cardiovascular System: cause of bradycardia, heart block, vasodilation (hypotension)
  - Allergic reactions: allergic dermatitis to anaphylaxis (rare, but occur most often by ester-type drugs)
  - Depressed uterine contractions during birth

- **Properties**
  - **Procaine**
    - **Ineffective topically**
    - **Must be administered by injection (usually with epinephrine to delay absorption)**
    - **Plasma esterases degrade it rapidly**
    - **Can cause allergic reactions**
  - **Lidocaine**
    - **Amide-type drug**
    - **Topical or injection**
    - **Rapid and prolonged anesthesia**
    - **Allergic reactions rare**
    - **CNS and cardiovascular toxicity can result**

- **Cocaine**
  - **Ester-type anesthetic**
  - **Produces effects on sympathetic and CNS systems due to ability to block uptake of norepinephrine by adrenergic neurons**
  - **Topical administration of: ear, nose and throat**
  - **Causes intense vasoconstriction (by blocking NE reuptake at nerve terminals) DO NOT GIVE WITH EPINEPHRINE**
  - **Inactivated by plasma esterases and liver enzymes**

■ Clinical Uses of Local Anesthesia

- **Surface anesthesia: topical admin**
  - **Skin to relieve pain, itching, soreness, burns, sunburn, diaper rash, hemorrhoids, etc…)**
- **Infiltration Anesthesia**
  - **Inject directly into immediate area of surgery**
- **Nerve Block Anesthesia**
  - **Inject local anesthetic into nerves that supply surgical field but which are distant from field**
- **Intravenous Regional Anesthesia**
  - **Anesthetize extremities (not entire arm or leg) by 1st removal of blood and then injection into vein**
  - **Do not want anesthetic to go into general circulation**

- **Epidural Anesthesia**
  - **Inject local anesthetic into the epidural space (within spinal cord but outside dura)**
  - **Blocks conduction in nerve roots and in the spinal cord**
  - **Can reach systemic circulation and during delivery there may be depression of of various systems of neonate**

Chapter 27: General Anesthetics

- **Drugs that produce unconsciousness and a lack of responsiveness to all painful stimuli**
- **Two Groups**
  - **Inhalation anesthetics**
  - **Intravenous anesthetics**
    - **Analgesia- loss of sensibility to pain**
    - **Anesthesia- refers not only to loss of pain but to loss of all other sensations**

- **Properties of Ideal Inhalations Anesthetic**
  - **Production of :**
    - **Unconsciousness**
    - **Analgesia**
    - **Muscle relaxation**
    - **Amnesia**
    - **Brief and pleasant effect**
    - **Depth of anesthesia could be raised or lowered with ease**
    - **Adverse effects minimal**
    - **Margin of safety large**
  - **Ideal general anesthetic DOES NOT EXIST**

- **Use of balanced anesthesia**
  - **Combination of drugs to achieve what one drug cannot do alone, to try to make as ideal as possible**
  - **Agents used for balanced anesthesia**
    - **Short-acting barbiturates (induction of anesthesia)**
    - **Neuromuscular blocking agents (for muscle relaxation)**
    - **Opioids and nitrous oxide (for analgesia)**
  - **COMBINATION OF DRUGS CAN LOWER (SAFER) DOSES OF EACH DRUG TO MAKE THE SAME OR GREATER EFFECT ON PATIENT**

■ Stages of Anesthesia (4 Stages)

- I. Stage of Analgesia: begins with onset of anesthetic administration and extends until consciousness is lost
  - Some major surgeries can be performed
- II. Stage of delirium: begins with loss of consciousness and extends to the onset of the stage of surgical anesthesia
  - Characterized by delirious excitement and reflex muscle activity. Irregular respiration. Try to get through this stage quickly

- III. Stage of Surgical Anesthesia: extends from end of stage II to the point where spontaneous respiration ceases
  - Deep unconsciousness
  - Suppression of certain reflexes
  - Large amount of muscle relaxation
- IV. Stage of Medullary Paralysis: begins when all spontaneous respiration is lost
  - Results from anesthetic overdose
  - Death can occur from circulatory collapse

- **Minimum Alveolar Concentration**
  - **Index of inhalation anesthetic potency**
  - **MAC= minimum concentration of drug in the alveolar air that will produce immobility in 50% of patients exposed to a painful stimulus (LOW MAC INDICATES HIGH ANESTHETIC POTENCY)**
- **Pharmacokinetics**
  - **To produce therapeutic effects the anesthetic must reach a high enough concentration in the CNS. Determined by:**
    - **Uptake from Lungs**
    - **Distribution to CNS**

- **Adjuncts to Inhalation Anesthesia**
  - **Adjunct= complement beneficial effects of inhalation anesthetics and counteract adverse effects**
  - **Pre-Anesthetic Medications: given to reduce anxiety, production of pre-operative amnesia, and relief of pre-operative and post-operative pain (suppress excessive salivation, bronchial secretions, coughing, bradycardia and vomiting to certain anesthetics)**
    - **Benzodiazepines- given to reduce anxiety and promote amnesia**
    - **Barbituates- relief of anxiety and induction of sedation**

- Opioids- relieve pre- and post-operative pain
- Clonidine- (Alpha2 Adrenergic Agonist): used for hypertension and pain reduction. Reduces anxiety and causes sedation
- Anticholinergic Drugs- (atropine) decrease the risk of bradycardia during surgery

– **Post-Anesthetic Medications**

- Analgesics- needed to control post-operative pain (severe give opioids, for mild give aspirin)
- Antiemetics- suppression of nausea and vomiting (ondansetron {Zofran}, promethazine and droperidol)
- Muscarinic Agonists- stimulation of muscarinic receptors by bethanechol and relieve abdominal distention and urinary retention in post-operative patients

■ **Classification of Inhalation Anesthetics**

– **Gases: Nitrous Oxide**

- "laughing gas"
- Anesthetic potency very low- never used alone; cannot produce surgical anesthesia (high MAC)
- Analgesic potency very high (20% NO can produce pain relief equal to that of morphine!!)
- Because of analgesic potency, primary anesthetic can be reduced (by 50%)
  - No serious side effects but does induce nausea and vomiting

– **Volatile Liquids: Halothane**

- May cause liver failure
- Low MAC
- Weak analgesic– use of strong analgesic usually required (i.e., opioids)

- **Intravenous Anesthetics**
  - **When used in conjunction with inhalation anesthetics i.v. agents serve two benefits:**
    - **Permit dosage of inhalation agent to be reduced**
    - **Produce effects that cannot be achieved with an inhalation agent alone**
  - **Short Acting Barbiturates**
    - **Thiopental: acts to produce unconsciousness w/i 10-20 seconds**
    - **Highly lipid soluble**
  - **Benzodiazepines (diazepam)**
    - **Unconsciousness in ~ 1 minute**
  - **Ketamine**
    - **Produces state of *dissociative anesthesia***
    - **Sedation, immobility, analgesia and amnesia**

Chapter 28: Opioid (Narcotic) Analgesics, Antagonists and non-opioid centrally acting Analgesics

- **Opioid- any drug that has actions similar to those of morphine**
- **Narcotic- analgesic, CNS depressant, and any drug capable of causing physical dependence**

- **Endogenous Opioid Peptides**
  - **Enkephalins**
  - **Endorphins**
  - **Dynorphins**
- **Opioid Receptors- 3 classes**
  - ***Mu*: most important pharmacologically**
  - ***Kappa***
  - ***Delta***
  - **Endogenous opioid peptides act through all 3 types of receptors while opioid analgesics act primarily through *mu***
    - ***Mu receptors- activation causes analgesia, respiratory depression, euphoria and sedation***

- **Drug can act in one of three ways:**
  - **Agonist- activate *mu* and *kappa* receptors**
  - **Partial agonist- produces low to moderate receptor activation when administered alone, but will block the actions of a full agonist if the two drugs are given together**
  - **Antagonist**
- **Morphine**
  - **Analgesia, sedation euphoria, respiratory depression, cough suppression and suppression of bowel motility; creates sense of well being**
  - **Principle use**
    - **Relief of moderate to severe pain chronic, dull pain rather than sharp pain) without affecting other senses**

- **Morphine- Mechanism of Action**
  - **Bind to *mu* receptors**
  - **Administer by: IM, IV, SC epidural and intrathecal**
  - **In order to relieve pain must cross blood-brain barrier- morphine not very lipid soluble**
  - **Inactivated by hepatic metabolism**
  - **Produces tolerance (*larger dose required to produce same response as initially administered)* and physical dependence *(results from adaptive cellular changes)***

Table 28–2 DRUG ACTIONS AT MU AND KAPPA RECEPTORS

Drugs	Receptor Type	
	Mu	*Kappa*
Pure Opioid Agonists Morphine, codeine, meperidine, and other morphine-like drugs	Agonist	Agonist
Agonist-Antagonist Opioids Pentazocine, nalbuphine, and butorphanol	Antagonist	Agonist
Buprenorphine	Partial agonist	Antagonist
Pure Opioid Antagonists Naloxone, naltrexone, and nalmefene	Antagonist	Antagonist

■ Clinical Uses of Opioids

– Control of Pain management

- **Assessment is hard with pain because of the subjective nature**
- **Patients may claim to have pain when they DO NOT-- they would like to be able to maintain the euphoric effects of the medication**
- **Opioids should be administered on a fixed schedule (every 4 hours) rather than PRN**
- **Give before pain returns**
- **If given for more than 20 days withdrawal effects may occur-- withdraw slowly tapering dosage over 3 days**

Table 28–3 OPIOID ANALGESICS: ABUSE LIABILITY AND MAXIMAL PAIN RELIEF

Drug and Category	DEA* Schedule	Abuse Liability	Maximal Pain Relief
Strong Opioid Agonists			
Alfentanil	II	High	High
Fentanyl	II	High	High
Hydromorphone	II	High	High
Levomethadyl	II	High	NA†
Levorphanol	II	High	High
Meperidine	II	High	High
Methadone	II	High	High
Morphine	II	High	High
Oxymorphone	II	High	High
Remifentanil	II	—	High
Sufentanil	II	High	High
Moderate-to-Strong Opioid Agonists			
Codeine	II	Moderate	Moderate to high
Hydrocodone	III‡	Moderate	Moderate to high
Oxycodone	II	Moderate	Moderate to high
Propoxyphene	IV	Low	Moderate
Agonist-Antagonist Opioids			
Buprenorphine	V	Low	Moderate
Dezocine	NR§	Low	Moderate
Butorphanol	IV	Low	Moderate to high
Nalbuphine	NR§	Low	Moderate to high
Pentazocine	IV	Low	Moderate to high

*DEA = Drug Enforcement Agency.
†NA = not applicable. Levomethadyl is used only for treating opioid addicts. The drug is not used for pain relief.
‡In the United States, hydrocodone is available only in combination with aspirin or acetaminophen. These combination products are classified under Schedule III.
§NR = not regulated under the Controlled Substances Act.

- **Opioid Antagonists**
  - **Naloxone**
    - **Structural analog of morphine that acts as a competitive inhibitor at opioid receptors**
- **Non-Opioid Centrally Acting Analgesics**
  - **Clonidine**
    - **Relief of pain- by continuous epidural infusion**
    - **Hypertension- given by mouth or transdermal patch**
    - **Alpha$_2$ adrenergic agonist**
      - **Relieves pain by binding to pre- and post-synaptic alpha$_2$ receptors in spinal cord**
    - **Can be used with opioid treatment to relieve pain of cancer not relieved by opioid alone**

Table 28–4 INTERACTIONS OF MORPHINE-LIKE DRUGS WITH OTHER DRUGS

Interacting Drugs	Outcome of the Interaction
Adverse Interactions	
CNS depressants Barbiturates Benzodiazepines Alcohol General anesthetics Antihistamines Phenothiazines	Increased respiratory depression and sedation
Agonist-antagonist opioids	Precipitation of a withdrawal reaction
Anticholinergic drugs Atropine-like drugs Antihistamines Phenothiazines Tricyclic antidepressants	Increased constipation and urinary retention
Hypotensive agents	Increased hypotension
Monoamine oxidase inhibitors	Hyperpyrexic coma
Beneficial Interactions	
Amphetamines	Increased analgesia and decreased sedation
Antiemetics	Suppression of nausea and vomiting
Naloxone	Suppression of symptoms of opioid overdose
Dextromethorphan	Increased analgesia; possible reduction in tolerance

Chapter 29: Pain Management in Cancer Patients

- **What is Pain?**
  - **"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"**
    - **Pain is personal and subjective- must listen to patient describe pain experience**
    - **Pain is due to activation due to 3 types of stimuli**
    - **Mechanical (pressure)**
    - **Thermal**
    - **Chemical - bradykinin, serotonin, histamine (prostaglandins and substance P enhance the sensitivity of pain receptors to activation)**

- **Pain**
    - **1st neuron carries impulses from periphery to a synapse in the spinal cord**
    - **Release of either glutamate or substance P as neurotransmitters**
    - **Next neuron carries the impulse up the cord to a synapse in the thalamus**
    - **Next neuron carries impulse from thalamus to the cerebral cortex**
  - **1st neuron carries impulses from periphery to a synapse in spinal cord where it releases either glutamate or Substance P as transmitters**
  - **2nd neuron carries impulse up cord to a synapse in Thalamus & next neuron to cerebral cortex**

– **Brain is able to suppress pain conduction using endogenous opioid compounds**
  - **Enkephalins and beta- endorphin**

- **Nociceptive Pain**
  - **Described as localized and sharp**
  - **respond well to opioid analgesics**
- **Neuropathic Pain**
  - **Described as burning, shooting, numb, dead, and cold**
  - **Respond poorly to opoid analgesics but responds well to adjuvant analgesics (carbamazepine)**

– **Brain is able to suppress pain conduction by releasing opioid-like compounds (*enkephalins and beta-endorphin*)**
– **Two types of pain: respond differently to analgesic drugs: must differentiate to treat effectively**
  - **Nociceptive- results from injury to tissues**
  - **Neuropathic- results from injury to peripheral nerves**

- Sensation of Pain
  - Result of net activity of 2 opposing pathways
    - 1st- carries pain impulses from site of origin to brain and generates sensation
    - 2nd- originates in brain and suppresses impulse conduction along the first pathway and diminishes pain

Assessment of Pain

- Important to assess, without assessment cannot treat pain effectively
  - Patient self report
  - Quality of pain: sharp, stabbing, burning, …
  - Intensity: 1-10 scale of pain ranking
  - Modulating factors: what makes pain worse
  - Previous treatment
  - Impact: how does pain affect ability to function

Drug Therapy for Pain

- Analgesic drugs
  - Nonopioid analgesics (NSAIDs= non-steroidal anti-inflammatory drugs) and acetaminophen
  - Opioid analgesics (codeine and morphine)
  - Adjuvant analgesics (amitriptyline and carbamazepine)
- With nonopioid and adjuvant drugs there is a limit to how much pain relief can be achieved
- With opioids there is no limit to the amount of pain relief
  - Combination of non-opioid with opioid can be more effective than either drug alone

- **NSAIDs- mild to moderate pain**
  - **Aspirin and ibuprofen**
    - **Pain relief**
    - **Suppression of inflammation**
    - **Reduction of fever**
  - **NSAIDs produce effect by inhibiting cyclooxygenase (COX)- COX enzymes produce prostaglandins (promote pain) and if inhibited then pain subsides**
  - **Acetaminophen (Tylenol)**
    - **Analgesic by inhibiting COX in CNS but not in periphery**
    - **Lacks anti-inflammatory activity since it only works in CNS**
    - **Does not affect platelets (clotting OK)**

- **Acetaminophen**
  - **Interacts ADVERSELY with both alcohol and Warfarin (an anticoagulant)**
  - **Acetaminophen with alcohol can cause potentially fatal liver damage (even alcohol in moderate amounts!!)**
  - **Acetaminophen can increase the risk of bleeding in patients taking warfarin (by inhibition of warfarin metabolism so it accumulates to toxic levels)**

- **Opioid analgesics**
  - Relieve pain by mimicking the actions of endogenous opoid peptides (enkephalins, dynorphin and endorphins) at the *mu* receptor
  - Create Tolerance and Physical Dependence
- **Adverse Side Effects of Opioids**
  - Can be reduced by reducing dose of opioid drugs and combining with non-opioid analgesic
    - Respiratory depression- most serious side effect- usually occurs at beginning of treatment (reversed with Naloxone)
    - Constipation- due to decreased peristalsis and reduced fluid secretion into intestinal lumen

- **Treatment in Elderly**
  - Heightened Drug Sensitivity due to decline in organ function (liver and renal)
  - Undertreatment of pain- due to fears about tolerance, addiction and adverse effects
  - Increased interactions with other drugs
- **Treatment in young children**
  - Assessment more difficult
  - Behavior may not indicate how much pain they are in
  - May not report pain because of desire to please, fear of more injections and treatments, lack of awareness that pain can be relieved

Table 29–1 BARRIERS TO CANCER PAIN MANAGEMENT

Barriers related to health care professionals
- Inadequate knowledge of pain management
- Poor assessment of pain
- Concerns stemming from regulations on controlled substances
- Fear of patient addiction
- Concern about side effects of analgesics
- Concern about tolerance to analgesics

Barriers related to patients
- Reluctance to report pain
  - Fear of distracting physicians from treating the cancer
  - Fear that pain means the cancer is worse
  - Concern about not being a "good" patient
- Reluctance to take pain medication
  - Fear of addiction or being thought of as an addict
  - Worries about unmanageable side effects
  - Concern about becoming tolerant to pain medications
- Inability to pay for treatment

Barriers related to the health care system
- Low priority given to cancer pain management
- Inadequate reimbursement: The most appropriate treatment may not be reimbursed
- Restrictive regulation of controlled substances
- Treatment is unavailable or access is limited

Adapted from Jacox A, Carr DB, Payne R, et al. *Management of Cancer Pain* (Clinical Practice Guideline No. 9, AHCPR Publication No. 94-0592). Rockville, MD: Agency for Health Care Policy and Research, 1994.

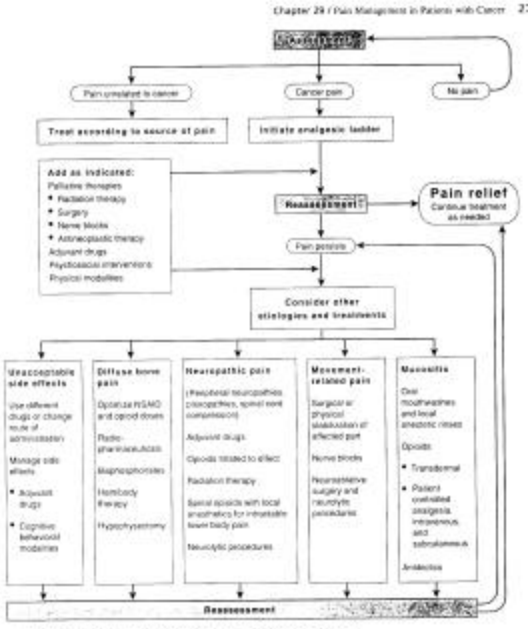

Figure 29–1. Flowchart for pain management in patients with cancer.
– Adapted from Jacox A, Carr DB, Payne R, et al. *Management of Cancer Pain* (Clinical Practice Guideline No. 9, AHCPR Publication No. 94-0592). Rockville, MD: Agency for Health Care Policy and Research, 1994

Table 29–2 DRUGS THAT ARE NOT RECOMMENDED FOR TREATING CANCER PAIN

Class	Drug	Why This Drug Is Not Recommended
Opioids		
Pure agonists	Meperidine	A toxic metabolite accumulates with prolonged use
Agonist-antagonists	Buprenorphine Butorphanol Nalbuphine Pentazocine	Ceiling to analgesic effects; can precipitate withdrawal in opioid-dependent patients; cause psychotomimetic reactions
Opioid Antagonists	Naloxone Naltrexone	Can precipitate withdrawal in opioid-dependent patients; limit use to reversing life-threatening respiratory depression caused by opioid overdose
Benzodiazepines	Diazepam Lorazepam others	Sedation from benzodiazepines limits opioid dosage; no demonstrated analgesic action
Barbiturates	Amobarbital Secobarbital others	Sedation from barbiturates limits opioid dosage; no demonstrated analgesic action
Miscellaneous	Cocaine	No analgesic efficacy, either alone or in combination with an opioid
	Marijuana	Side effects (dysphoria, drowsiness, hypotension, bradycardia) preclude routine use as an analgesic
	Brompton's cocktail	Analgesic efficacy is no better than that of a single opioid

Table 29–3 DOSAGES FOR NONOPIOID ANALGESICS: ACETAMINOPHEN AND SELECTED NSAIDs

Drug	Usual Adult Dosage*	
	Body Weight ≥ 50 kg	*Body Weight < 50 kg*
Acetaminophen	650 mg q 4 h or 975 mg q 6 h	10–15 mg/kg q 4 h or 15–20 mg/kg q 4 h (rectal)
NSAIDs: Salicylates		
Aspirin	650 mg q 4 h or 975 mg q 6 h	10–15 mg/kg q 4 h or 15–20 mg/kg q 4 h (rectal)
Choline salicylate (Arthropan)	870 mg q 3–4 h	—
Magnesium salicylate (Magan)	650 mg q 4 h	—
Sodium salicylate	325–650 mg q 3–4 h	—
NSAIDs: Propionic acid derivatives		
Fenoprofen (Nalfon)	300–600 mg q 6 h	—
Ibuprofen (Motrin, Advil, others)	400–600 mg q 6 h	10 mg/kg q 6–8 h
Ketoprofen (Orudis)	25–60 mg q 6–8 h	—
Naproxen (Naprosyn)	250–275 mg q 6–8 h	5 mg/kg q 8 h
Naproxen sodium (Anaprox, Aleve, Napelan, others)	275 mg q 6–8 h	—
NSAIDs: Others		
Diflunisal (Dolobid)	500 mg q 12 h	—
Etodolac (Lodine)	200–400 mg q 6–8 h	—
Meclofenamate sodium	50–100 mg q 6 h	—
Mefenamic acid (Ponstel)	250 mg q 6 h	—

*All dosages are oral except where indicated.

Table 29–5 ADJUVANT DRUGS FOR CANCER PAIN

Drug	Usual Adult Dosage	Beneficial Actions
Tricyclic Antidepressants		
Amitriptyline [Elavil]	25–150 mg/day PO	Reduce neuropathic pain
Desipramine [Norpramin]	25–150 mg/day PO	
Doxepin [Sinequan]	25–150 mg/day PO	
Imipramine [Tofranil]	20–100 mg/day PO	
Nortriptyline [Aventyl, Pamelor]	25–150 mg/day PO	
Anticonvulsants		
Carbamazepine [Tegretol]	200–1600 mg/day PO	Reduce neuropathic pain
Phenytoin [Dilantin]	300–500 mg/day PO	
Gabapentin [Neurontin]	300–3600 mg/day PO	
Local Anesthetics/Antidysrhythmics		
Lidocaine	5 mg/kg/day IV or SC	Reduce neuropathic pain
Mexiletine [Mexitil]	450–600 mg/day PO	
CNS Stimulants		
Dextroamphetamine [Dexedrine]	5–10 mg/day PO	Enhance analgesia and reduce sedation from opioids
Methylphenidate [Ritalin]	10–15 mg/day PO	
Antihistamine		
Hydroxyzine [Vistaril]	300–450 mg/day IM	Enhances analgesia and reduces anxiety, insomnia, and nausea
Glucocorticoids		
Dexamethasone [Decadron, others]	16–96 mg/day PO or IV	Reduce pain associated with brain metastases and epidural spinal cord compression
Prednisone [Deltasone, Orasone]	40–100 mg/day PO	
Bisphosphonates		
Etidronate [Didronel]	7.5 mg/kg IV for 3 days	Reduce hypercalcemia and possibly bone pain
Pamidronate [Aredia]	60–90 mg IV once	

Chapter 30: Antipsychotic Agents and their use in Schizophrenia

- **Schizophrenia: Characteristics & Etiology**
  - **Disordered thinking and reduced ability to comprehend reality**
  - **Symptoms emerge during adolescence or early adulthood**
  - **Positive and negative symptoms:**
    - **Positive- exaggeration or distortion of normal function (hallucinations, delusions, agitation, tension and paranoia)**
    - **Negative- loss or lessening of normal function (lack of motivation, poor self care, social withdrawal)**

- Etiology:
  - Biological basis (????)
    - Genetic
    - Neuroanatomic
    - Neurodevelopmental
  - Defects
    - Excessive activation of CNS receptors for dopamine
    - Insufficient activation of CNS receptors for glutamate

- **Group I Agents:**
  - Low potency (chlorpromazine– thorazine)
  - Medium potency
  - High potency (Haloperidol– Haldol)
  - – Potency refers to size of dose needed to elicit a given response, NOT the ability to relieve symptoms of psychosis (dose required to relieve symptoms of psychosis for haldol is smaller than dose required for throazine)
    - Low, medium and high potency drugs while having the same ability to relieve symptoms, have different SIDE EFFECTS

- **6 chemical categories (Table 30-4)**
- **Mechanism of Action**
  - – Block receptors within and outside the CNS: blockage of these receptors is responsible to the adverse effects observed
    - Dopamine- bolckage of D_2 receptors in the mesolimbic and mesocortical areas of brain exert positive effects of psychosis
    - Acetylcholine
    - Histamine
    - Norepinephrine

- **Therapeutic uses**
  - Schizophrenia
  - Bi-polar disorder
  - Tourette's Syndrome
- **Extrapyramidal Symptoms**
  - Movement disorders resulting from effects of antipsychotic drugs on EP motor response: due to blockade of D_2 receptors??? Low potency drugs exert less side effects
    - Acute dystonia (early in treatment)- upward deviation of eyes and spasm of back muscles)
    - Parkinsonism (early in treatment) – bradykinesia, drooling, tremor, rigidity, stooped posture)
    - Akathisia (early in treatment) – pacing (need to be in motion
    - Tardive dyskinesia (late in treatment– no satisfactory treatment)- involuntary twisting of tongue and face

- **Nursing Implications:**
  - **Therapeutic Goal**
    - Suppression of acute episodes, prevention of acute exacerbations and maintenance of the highest possible level of functioning
  - **Baseline Data**
    - Mental examination- gait, pacing, restlessness, volatile outbursts, emotional state (depression, agitation, mania), intellectual function (stream of thought, coherence, hallucinations, delusions, and responsiveness to environment
    - Family history and social history
    - Complete blood work up, electrolytes, hepatic and renal functions
  - **ID high risk patients**

Chapter 31: Antidepressants

- **Depression**
  - **Most common of psychiatric illnesses**
    - **Depressed mood**
    - **Loss of pleasure or interest in nearly all of one's usual activities and pastimes**
      - **Insomnia**
      - **Anorexia and weight loss (sometimes hyperphagia and weight gain)**
      - **Loss of concentration**
      - **Feelings of guilt, worthlessness, helplessness**
      - **Thoughts of death and suicide**

- **Must distinguish between major depression and normal grief or sadness**
- **Can be triggered by stress**

- **Monoamine hypothesis of depression**
  - **Depression is caused by a functional insufficiency of monoamine neurotransmitters (norepinephrine, serotonin or both)**
- **Treatment**
  - **Drugs- tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and lithium**
  - **Electroconvulsive shock therapy (ECT)- fast response- for patients who are severely depressed, suicidal, elderly at risk of starving to death, patients who fail to respond to antidepressant drugs**
  - **Psychotherapy- supportive**

- **TCA**
  - **Block monoamine reuptake (NE and serotonin)**
    - **Intensify effects due to continued exposure to neurotransmitters**
    - **TCAs have long, but variable ½ lives (must individualize with each patient)**
- **Monoamine Oxidase Inhibitors**
  - **Accumulation of NE in adrenergic neurons by blocking NE inactivation**
- **Selective serotonin reuptake inhibitors (SSRIs)**
  - **As effective as TCAs without causing hypotension, sedation, or cardiotoxicity**

- MAOIs
  - More dangerous than TCAs abd SSRIs
  - Cannot tolerate foods with tyramine (pepperoni, sausage, some cheeses, …)
  - Interaction may cause severe hypertension
- Nursing implications
  - Observe and record patients behavior (thought content, interest in environment, appetite, sleep patterns, appearance)
  - Reduce risk of suicide
  - Promote compliance

Chapter 32: Drugs for Bipolar Disorder

- **Bipolar Disorder**
  - **Cyclic disorder characterized by recurrent fluctuation in mood**
  - **Alternating episodes of mania and depression separated by "normal" moods**
    - **Overactivity at work and reduced need for sleep**
    - **Extreme self confidence, delusions of importance, excessive talkativeness**

  - **Chronic disorder that requires supportive therapy and education for patient and family**
  - **Should be treated with combination of drugs and psychotherapy**
  - **Certain stresses can precipitate mood change**
- **Drug Therapy**
  - **Lithium**
    - **Control of both manic phase and depressed phase**
      - **Can be taken prophylactically**
    - **Lithium usually combined with benzodiazepine or haloperidol (these suppress symptoms until Lithium takes effect)**

- **Lithium**
  - **Inorganic ion with single positive charge**
  - **Well absorbed following oral ingestion**
  - **Short ½ life due to renal excretion (should not be used in patients with kidney disease)**
    - **Has high toxicity– use in small multiple doses, not one large dose**
    - **Do not use with diuretic usage**
    - **Dehydration will increase lithium retention**
    - **Sodium depletion will decrease renal excretion**
    - **Must measure plasma lithium levels (at or below 1.5 mEq/L (check blood in morning, 12 hours after nighttime dose)**

- **Therapeutic uses**
  - **Bipolar disorder**
    - **Reduces euphoria, hyperactivity but does not cause sedation**
    - **Antimanic effects begin 5-7 days after initial administration**
    - **Lithium may not reduced episodes of depression, and if this is the case there must be adjunctive therapy with antidepressant**
  - **Anticonvulsants**
    - **Carbamazepine- superior to lithium if patients have severe mania and for those who cycle rapidly between moods**
    - **When given to patients where lithium has failed, carbamazepine has 60% success**

- Valproic Acid
  - Only anti-seizure medication that has received FDA approval for bipolar disorder
  - Is as effective as Lithium in controlling symptoms

- Nursing Implications
  - Therapeutic Assessment
    - Goal- control of acute manic episodes in patients with bipolar disorder
    - Baseline data-
      - Cardiac status (EKG, BP, counts)
      - Serum electrolytes
      - Renal function
      - Thyroid function

Chapter 33: Benzodiazepines and Drugs for Anxiety and Insomnia

- Anti-anxiety agents (anxiolytics = tranquilizers)

- Hypnotics- drugs that promote sleep
  - Anti-anxiety agents and hypnotic agents may act the same if given at high enough doses

- **Benzodiazepines**
  - **Anxiety, insomnia, general anesthesia and seizure disorders**
    - **Also muscle spasm, panic disorder and withdrawal from alcohol**
    - **Safer than the general CNS depressant (barbiturates) and do not have as high a potential for abuse or for building up tolerance**
    - **Valium**
  - **All work within the CNS– depending upon dosage work to induce sedation, hypnosis to stupor**
    - **Reduce anxiety thorough effect on Limbic System (area associated with emotionality)**
    - **Promote sleep through effects on cortical areas**

- **Mechanism of Action**
  - **Potentiate actions of GABA (inhibitory neurotransmitter)**
    - **Enhance actions of GABA by binding to specific GABA receptor– chloride channel complex (do not act as direct agonists**)
    - **Cause CNS depression by enhancing effects of endogeous GABA and do not cause toxicity because there is a finite amount of GABA (cannot over dose like agonist actions can)**
  - **Well absorbed following oral administration**
  - **Have high lipid solubility and cross blood brain barrier readily**
  - **Have a lot of metabolic metabolites made and these are active, thus responses last long after parent compound is degraded**

- All benzodiazepines have equivalent actions, and selection of which to use may depend upon differences in time course of effects
  - If needed as medication for speeding up falling asleep, a benzodiazepine with a faster onset (triazolam) would be indicated; is one needs a drug to prevent waking during the night a benzodiazepine with a slower onset (estazolam) is indicated::
  - for anxiety, need a drug with intermediate duration::
  - for older people, lorazepam is indicated which is less likely to accumulate with repeated dosing
- Table 33-2 for applications of drugs

- **Barbiturates**
  - Non-specific depression of CNS
    - Used for daytime sedation
    - Induction of sleep
    - Suppression of seizures
    - General anesthesia
  - Cause tolerance and physical dependence and high potential for abuse
  - Strong respiratory depressants
- **Mechanism of Action**
  - Bind to GABA receptor-chloride channel complex to…
    - Enhance inhibitory action of GABA
    - Directly mimic actions of GABA
    - Since they can act as agonists there is no end to how much they can suppress CNS (can cause death)

■ Management of Anxiety

- – Six classes of anxiety
  - Generalized anxiety disorder (GAD)
  - Panic disorder
  - Phobic disorders
  - Obsessive-compulsive disorders
  - Post-traumatic stress disorder
  - Acute stress disorder
- – GAD most common
  - Must discriminate between situational anxiety and GAD- situational is short term and due to normal stress event versus GAD which is unrealistic anxiety about several events that last > 6 months

■ Treatment of Insomnia

- – Inability to sleep
- – Two divisions of sleep
  - Rapid-eye-movement (REM)
    - – Dream state of sleep (30% of sleep time)
    - – Except for benzodiazepines, the drugs used to remedy sleep disorders often reduce total REM time
    - – Deprivation of REM can cause psychotic disorders
  - Non-rapid-eye-movement

Chapter 34: CNS Stimulants and use in ADHD

- **CNS stimulants**
  - **Increase activity of CNS neurons**
    - **Use for ADHD and narcolepsy**
    - **Obesity**
    - **(antidepressants act by selectively altering mood, but do not effect other CNS functions, so CNS stimulants are NOT the same as antidepressants)**

- **Amphetamines- refer to 50:50 mixture of dextroamphetamine and levamphetamine (optical isomers of each other (mirror images))**
  - **Amphetamine**
  - **Dextroamphetamine**
  - **Methamphetamine**
  - **Mechanism of action**
    - **Promote release of biogenic amines from neurons**
      - **NE, dopamine, serotonin**
      - **Release takes place in both CNS and periphery**
    - **Promote wakefulness, alertness, reduce fatigue, elevate mood, augment self-confidence and increase motor activity**

- Amphetamines promote tolerance, physical dependence and abuse potential

■ **Methylphenidate (Ritalin)**

- Structure not similar to amphetamines, but effects of drugs are identical
  - Use in ADHA and narcolepsy

■ **Methylxanthines (caffeine)**

- Medical uses rare
- Action by reversible blockade of adenosine receptors and by enhancement of calcium permeability in the sarcoplasmic reticulum, and inhibition of cyclic nucleotide phosphodiesterase (accumulation of cAMP)

■ **Attention-Deficit/Hyperactivity Disorder**

- Characterized by inattention, hyperactivity and impulsivity
  - 1 ADHD child/classroom
  - 4-8 times incidence in boys over girls
- Symptoms managed by Ritalin
  - Use of stimulant to depress hyperactivity
    - Improves ability to maintain attention and focus
    - Does not create positive behavior, but reduces negative behavior
  - Adverse effects: growth suppression & insomnia
    - Growth suppression- take after meals and use "drug holidays on weekends and summers to allow growth to catch up
    - Rebound effect on growth after stopping drug
    - Do not use continuously for more than 1 year

- **ADHD in Adults: maybe as high as 70%**
  - **Poor concentration**
  - **Stress intolerance**
  - **Antisocial behavior**
  - **Outbursts of anger**
  - **Inability to maintain a routine**
  - **– Trials with non-stimulants being used**
    - **Wellbutrin (bupropion) and Inderal (propranolol)**

Chapter 35: Other Psychologic Disorders- Panic Disorder, OCD, and Alzheimer's Disease

- **Panic Disorder**
  - **– Defined by DSM (Diagnostic and Statistical Manual)**
    - **Sudden onset, reach peak intensity within 10 minutes, and have 4 or more of the following symptoms**
      - **– Palpitations, chest pain or discomfort, sensation of shortness of breath, feeling of chocking, dizziness, nausea, derealization or depersonalization, fear of losing control, fear of dying, tingling of hands, flushes of chills**

- Symptoms usually disappear within 30 minutes after onset
- Incidence in women 2-3 times more frequent than in men
- Usually occurs in late teens or early 20's
- Dysregulation of noradrenergic and serotonergic systems is thought to be involved in symptoms
  - Agoraphobia- condition characterized by anxiety about being in places or situations from which escape might be difficult or embarrassing– leads to avoidance of certain places or situations (elevators, tunnels, being outside home, being in crowd, being on bus or train,…)

- Treatment
  - Drug therapy and cognitive-behavioral therapy
    - Avoid caffeine and sympathomimetics and avoid sleep deprivation, and do regular aerobic exercises
  - Drug therapy
    - Antidepressants and benzodiazepines
      - Antidepressants: SSRIs, TCA's, MAOI's: take 6-12 weeks to take effect
      - Benzodiazepines- Xanax: rapid relief of symptoms of panic attack
        - » Tolerance and physical dependence occur

- **Obsessive-Compulsive Disorder**
  - **Persistent obsessions that consume at least one hour/day and cause distress**
    - **Comes involuntarily to mind despite attempts to ignore or suppress it**
    - **Common Fears**
      - **Acquiring disease**
      - **Need for orderliness**
      - **Repeated doubts (did I unplug iron?)**
    - **If compulsion is delayed or suppressed, there is intense anxiety that interferes with normal life style**
  - **Treatment**
    - **Drugs and Behavioral therapy**
    - **5 drugs approved: clomipramine, fluoxetine, fluvoxamine, sertraline and paroxetine**

- **Clomipramine (Anafranil)**
  - **Only TCA effective in treatment of OCD**
  - **Takes 4-12 weeks to see maximal improvements**
  - **Clomipramine is a TCA drug that has SSRI properties:**
    - **Blocks uptake of norepinephrene in addition to serotonin**
    - **Like other TCA's, blocks adrenergic, cholinergic and histaminergic receptors (antagonist action)**
    - **SSRI drugs for treatment of OCD**
      - **Prozac, Luvox, Zoloft,**

- **Alzheimer's Disease**
  - **Characterized by:**
    - **Progressive memory loss, impaired thinking, personality changes, inability to perform daily tasks**
    - **Affects ~4 million Americans and kills ~100,000 people/year**
    - **Pathologic findings: degeneration of cholinergic neurons and presence of neuritic plaques and neurofibrillary tangles**
    - **Cause is unknown**
  - **Early in AD neuronal degeneration begins in hippocampus and moves into cerebral cortex**

- **Hippocampus serves important role in memory**
- **Cerebral cortex in important to speech, perception, reasoning, and other higher functions**
- **With advanced AD the ACh levels are 90% below normal**
  - **Important neurotransmitter in hippocampus and cerebral cortex**
  - **Critical to forming memories**
- **Neuritic Plaques**
  - **Form outside neurons- spherical bodies that are composed of beta-amyloid (may help to destroy neurons)and remnants of axons and dendrites**

- **Beta Amyloid**
  - Kills hippocampal cells grown in culture
  - Can release free radicals
  - Can disrupt potassium and calcium channels in cell membranes
  - Cause vasoconstriction, blood vessel injury and leads to "starvation" of neurons and neuron cell death
  - Injection of beta-amyloid into brains of monkeys leads to symptoms and characteristics of AD (ole monkeys only, young monkeys not affected)

- **Neurofibrillary Tangles**
  - Tangles form inside neurons in cerebral cortex (orderly arrangement of microtubules becomes disrupted)
    - Cause is production of abnormal form of *tau*, a protein that forms cross-bridges between microtubules and keeps them in stable configuaration
- **Apolipoprotein E4 (ApoE)**
  - Role in cholesterol transport
  - E4 associated with AD but E2 is protective
  - ApoE4 binds to beta-amyloid to make it insoluble
  - E4 neither necessary nor sufficient to cause AD

- **Risk factors for AD**
  - **Age:**
    - **Onset of AD in 90% of patients occurs in people over 65**
    - **After 65 years, chance of getting AD doubles every 10 years**
    - **Family history**
    - **Women have higher incidence of AD (because they live longer???)**
    - **Head injury**
    - **Low educational level**
    - **Production of ApoE4**
  - **No specific test for AD**

- **Drug therapy for AD**
  - **Tacrine (Cognex) & Donepezil**
    - **Reversible inhibitor of acetylcholinesterase (AChE) {increases ACh at cholinergic synapses}**
    - **Does not stop progression of AD, but does alleviate symptoms for short times**
    - **Only about 30% improve with treatment**
    - **Causes hepatotoxicity**
    - **Bioavailability is low because of 1st Pass Metabolism**
  - **Experimental drug treatments**
    - **Estrogens, non-steroidal anti-inflammatory drugs (NSAIDs), vitamin E, selegiline, and *Ginko biloba***