

## CNS PHARMACOLOGY

The CNS [brain and spinal cord (SC)] can be divided into its anatomical areas or its physiological functions, both of which our knowledge base of the entire system is not complete. The study of the drugs that can affect the brain and their varied mechanisms of action (MOA) compounds the complexity of this system.

### I. MACROANATOMY

The brain can be subdivided into its regions: cerebrum and its hemispheres, midbrain, pons, medulla, thalamus, hypothalamus, cerebellum, and basal ganglia. As well, there are systems such as the limbic system and the reticular activating system.

**A. CEREBRUM**-Is the largest and main portion of the brain with the outer layer, which covers the hemispheres, being the cerebral cortex which is made up of several layers of gray cells. The cortex receives information from the senses and directs the conscious movements of the body and therefore is perceived to be the thinking and reasoning part of the brain. Regions of the cortex can be classified according to: 1) the modality of information processed (i.e. sensory, motor, auditory, olfactory, etc.) 2) the anatomical area (frontal, temporal, parietal, occipital) 3) by the geometrical relationship between cell types which serve to interconnect the systems via pathways in order to modulate information (i.e. between the cortical and subcortical systems).

**B. BRAIN STEM**- Is the rostral stemlike portion of brain connecting the cerebral hemispheres with the SC and is comprised of the midbrain, pons, and medulla oblongata. The MIDBRAIN is just below the thalamus and contains a center for visual reflexes such as moving the head and eyes. The PONS is inferior to the midbrain and connects the cerebellum to the motor output from cortex and has a respiratory center. The MEDULLA oblongata is the caudal part of the brainstem and contains centers that regulate the heart, vasculature, and respiratory system. It is also a point for central integration for coordination of reflexive actions such as swallowing and vomiting. It is also where the motor and sensory nerves cross over. The brainstem contains most of nuclei of the cranial nerves as well as the reticular activating system.

**C. DIENCEPHALON-THALAMUS & HYPOTHALAMUS**- Forms central core of brain and surrounds the 3<sup>rd</sup> ventricle. The THALAMUS lies deep within the center of the brain beneath the basal ganglia and above the hypothalamus. It functions as a relay station between the incoming sensory pathways and integrates these sensations on the way to the cortex. It also acts as a pathway between the basal ganglia and associative regions of the cortex. There is also a pathway to the hypothalamus. The HYPOTHALAMUS lies below the thalamus at the base of the cerebrum. It is the principal integrating center for the entire autonomic nervous system. As well, it is important in vital functions such as regulation of body temperature, water balance, blood glucose levels, metabolism, and emotion. It directs many of the body's daily rhythms such as sleep & activity, appetite & digestion, sexual functions, and menstrual & reproductive cycles.

**D. CEREBELLUM**-It arises from the posterior pons and behind the cerebral hemispheres. It has projections to the motor cortex via the thalamus and to brainstem nuclei concerned with vestibular function. The three primary functions of the cerebellum include: 1) aid in controlling axial muscles in posture and therefore balance and equilibrium, as well as coordinating hand and eye movements; 2) regulation of muscle tone and movement; 3) modulation of output of the motor cortex (esp. rapid skeletal muscle activities such as typing, playing an instrument, & running). It functions to coordinate the motion of various muscles involved in voluntary movement-it operates below the level of our consciousness and assists

in the optimal coordination and performance of movements. It also plays a role in learning and memory.

Lesions to the cerebellum result in ataxia, reduced muscle tone, delayed initiation of movements, nystagmus, dysarthria, and oscillation at end movements.

**E. BASAL GANGLIA**-Are deep nuclei of the cerebrum and include the striatum (caudate nucleus & putamen) and globus pallidus. Brainstem nuclei closely associated with the basal ganglia are the substantia nigra and subthalamic nucleus. Many of the impulses from the basal ganglia are inhibitory with the inhibitory neurotransmitters being dopamine and gamma-aminobutyric acid (GABA). It is part of the extrapyramidal system (EPS) which complements the pyramidal system (voluntary). Diseases of the basal ganglia result in disorders of movement as well as posture dependent upon the area and specific neurotransmitters involved. For example, damage to the striatum where GABA is secreted results in random and continuous uncontrolled movements termed chorea. Destruction to the substantia nigra results in a loss of dopamine creating an predominance of acetylcholine (Ach) and results in movement disturbances such as tremors, bradykinesia, and dystonia.

**F. LIMBIC SYSTEM**-Is the term for an combination of brain regions (hippocampus, amygdaloid complex, olfactory nuclei, basal ganglia, selected nuclei of the diencephalon) which lie beneath the cerebral cortex and where a variety of complex emotional and motivational functions have been attributed. It seems to integrate one's emotional state with motor and visceral activities.

**D. RETICULAR ACTIVATING SYSTEM**- It determines one's overall CNS activity level: thus it is essential for regulation of sleep, wakefulness, level of arousal, and coordination of eye movements. The neurons of the RAS are both excitatory and inhibitory with the primary neurotransmitter being Ach.

## II.

### MICROANATOMY OF THE BRAIN

The specific connections between neurons within or across the anatomical or functional divisions of the brain are essential to the brain's functions. Cells in the CNS are classified as either neurons or nonneuronal cells.

**A. NEURONS**-Can be classified according to either function (sensory, motor, interneuron), location, or by the identity of the transmitter released.

**B. NONNEURONAL CELLS:** 1) Macroglia-is the most abundant supportive cell and includes astrocytes (plays a variety of metabolic supportive roles) and oligodendroglia (myelin-producing cells insulating the axon). 2) Microglia-related to macrophages & monocytes process. 3) cells of the cerebral vasculature and the CSF forming cells of the choroids plexus. 4) Meninges

**C. BLOOD-BRAIN BARRIER**-Permeability barrier between the CNS and PNS limiting the diffusion of substances into various regions of the CNS. It is as a result of the tight junction between the vascular endothelial cells of brain capillaries and secondarily to the neighboring glial cells which further decrease permeability. The exception is in the areas around the posterior pituitary and the CRTZ where it does not exist

### III. CENTRAL NEUROTRANSMITTERS

**A. Neurotransmitters** are chemical mediators which are released from nerve endings into the synaptic cleft once an action potential has been reached eliciting an influx of Ca<sup>++</sup> ions (a voltage dependent action). The neurotransmitter then reaches its target postsynaptic receptor site with the result being either direct excitation or inhibition or enhancing excitation or inhibition.

#### 1. Biogenic amines:

a. dopamine-precursor of norepinephrine. Approximately 1/2 of CNS content of catecholamines is dopamine with large amounts in the basal ganglia (esp. caudate nucleus), olfactory tubercle, central nucleus of the amygdala, limbic system, and certain areas of the frontal cortex. There are 5 dopamine receptor subtypes: D1 (and D5) activate adenylyl cyclase, D2 (and D3 & D4) inhibit adenylyl cyclase. Some D2 receptors may also suppress Ca<sup>++</sup> currents and activate K<sup>+</sup> currents.

b. norepinephrine-relatively large amounts are located in hypothalamus and in certain zones of the limbic system (parts of amygdala & hippocampus) but is present in most brain regions (cerebral cortex, brain stem, cerebellum, and spinal cord) but in lower amounts. It is primarily an excitatory neurotransmitter but in selected areas in the CNS & PNS it has inhibitory effects.

c. epinephrine-epi containing neurons are found in medullary reticular formation with some connections to the pontine region, diencephalic nuclei, and paraventricular nucleus of the dorsal thalamus. Also found in periaqueductal gray area and spinal cord.

d. serotonin (5-hydroxytryptamine or 5-HT)-is primarily an inhibitory neurotransmitter. Is found in hypothalamus, limbic system, cerebellum, piriform cortex, cerebral cortex, choroids plexus, and retina. It is found in the highest concentration in platelets and the GI tract. There are 14 receptor subtypes each of which is composed of a further set of subtypes.

e. histamine-most of histamine receptors are found in ventral posterior hypothalamus and extends to ascending and descending tracts in the brain. The histamine system is thought to function in regulating arousal, body temperature, vascular dynamics, the reticular activating system. There are 3 histamine receptor subtypes.

**2. acetylcholine**-seems to be an excitatory transmitter in the CNS vs. its inhibitory effects in the PNS.

**3. amino acids**-most common inhibitory and excitatory neurotransmitters in CNS.

a. gamma-aminobutyric acid (GABA)-is major inhibitory mediator in brain with cells containing GABA are some neurons in basal ganglia, cerebellar Purkinje, cerebral cortex, and certain interneurons in spinal cord. There are two subtypes of GABA: GABA-A (a ligand-gated Cl<sup>-</sup> channel) and GABA-B (a G-protein coupled receptor).

b. glycine-inhibitory transmitter released by brainstem and interneurons in spinal cord.

c. glutamate-major excitatory neurotransmitter found in cerebral cortex and brainstem.

d. aspartate-an excitatory neurotransmitter found in the visual cortex.

**4. neuropeptides** (polypeptides)

a. substance P

b. vasopressin

c. oxytocin

d. somatostatin

e. glucagons

f. angiotensin II

g. atrial natriuretic peptide

h. enkephalins

i. endorphins

**5. purine nucleotides**

a. adenosine

b. ATP

## IV.

### ACTIONS OF DRUGS IN THE CNS

A. The structural and functional properties of neurons and their specific receptors provides a means to modify CNS function, either specifically or generally, by administering drugs that can act at defined receptor sites, either causing inhibition or excitation at the receptor. Drugs that act within the CNS include anticonvulsants, antiparkinsonian agents, opioid & nonopioid analgesics, antiemetics, antipyretics, antidepressants, antipsychotic & antimanic agents, and sedatives & hypnotics.

The drugs that selectively modify CNS function act either specifically or nonspecifically according to its effect or response. For example, the effect of the drug is specific when it binds to a target cell's receptors and affects an identifiable intracellular mechanism and imparts a specific therapeutic action. (These include all the drug categories listed above.) A drug is considered nonspecific if it produces effects on many different target cells and results in diverse molecular mechanisms. The nonspecific drugs are classified according to whether they produce behavioral depression or stimulation. Examples of nonspecific CNS depressants include the anesthetic gases, ethanol, and some hypnotics-sedatives. Example of nonspecific CNS stimulants are caffeine and amphetamines.

The specific drugs affecting the CNS include the psychotropic drugs which are utilized to correct the "pathological" aspects of the CNS. The four primary categories include the antidepressants, antipsychotics (neuroleptic), antimanic drugs, and anti-anxiety drugs.

It was previously recommended to discontinue certain classes of these drugs, i.e. TCAs and MAOIs, approximately two weeks before surgery; however it is now recommended to continue these medications as the discontinuation of these medications before surgery could possibly increase the risk of the patient developing suicidal ideation or psychotic disturbances. As well, it has been determined that the patient can safely undergo anesthesia and surgery while currently taking these medications.

### V. ANTIDEPRESSANTS (MOOD ELEVATORS)

Major depression is a mood disorder characterized by significant changes in behavior, physical functioning, cognition, and leads to an alteration in the individual's perception of their immediate and more global environment, all of which inhibits the ability to function. This depression of mood and impairment of functioning is characterized by intense feelings of sadness & despair, mental slowing, loss of concentration, pessimistic worrying, self-depreciation, inability to feel pleasure, and agitation. In addition, there are physical S/S: insomnia, hypersomnia, altered eating patterns, weight loss or gain, decreased energy, decreased libido, and disruptions of circadian rhythms such as body temperature and endocrine functions.

Depression has various causes which basically include a complex interplay of genetic, social, environmental, and biochemical factors, thus is really not one single factor directly resulting in depression. As well, though family history is a variable, the genetic contribution seems to be less a contribution as compared to having a history of schizophrenia in one's family.

Most current theories of major depression focus on neurochemical processes, specifically with regard to that there may be either an abnormal amount of neurotransmitter released or that there may be decreased postsynaptic sensitivity. The theories tend to focus on the neurotransmitters serotonin and norepinephrine with some suggesting dopamine.

The antidepressants create a therapeutic effect by increasing the amount of neurotransmitter available at the synaptic cleft either by decreasing the rate at which it taken

back up into the presynaptic neuron or by inhibiting its metabolic degradation. All antidepressants work by affecting one or more of the neurotransmitters thought to be responsible for depression. The classes of antidepressants include tricyclic antidepressants (TCAs), selective serotonin-reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants.

Antidepressants also have a growing role in attention-deficit disorder, hyperactive disorders, and severe anxiety disorders including generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder (OCD). As well, they are used for chronic pain disorders, peripheral neuropathic syndromes, fibromyalgia, irritable bowel syndrome, chronic fatigue, migraines, and sleep apnea.

## **A. TRICYCLIC ANTIDEPRESSANTS**

- amitriptyline (Elavil)
- clomipramine (Anafranil)
- desipramine (Norpramin)
- doxepin (Sinequan)
- imipramine (Tofranil)
- nortriptyline (Pamelor)
- protriptyline (Vivactil)

**1. TCAs** were previously the most commonly prescribed antidepressants until the advent of the SSRIs. The MOA is to potentiate the action of biogenic amines, particularly the noradrenergic norepinephrine as well as serotonin, by preventing the uptake of these amines (thereby increasing neurotransmitter concentration at the synaptic cleft). TCAs do not block dopamine transport. Approximate time frame for a therapeutic effect is 2-3 weeks. In general, TCAs are very lipid soluble, highly bound to plasma proteins, resulting in a large volume of distribution and consequently a long elimination half-time (about 24 hrs.). They are metabolized by microsomal enzymes in the liver with subsequent conjugation with glucuronic acid. The elimination process occurs over several days with most being completely eliminated in 7-10 days.

The structure is similar to the phenothiazines. TCAs have anti-cholinergic (muscarinic) effects, anti-alpha1 adrenergic effects, and antihistamine (H1) effects. In addition, the TCAs exhibit Na<sup>+</sup> channel blockade. As a consequence, TCAs have many adverse effects which have resulted in their now being used for severe depression if the patient is refractory to the treatment with SSRIs. (They are also used in chronic neuropathic pain patients.)

The side effects include 1) antihistamine effects (sedation, weakness, fatigue), 2) anticholinergic effects (dry mouth, constipation, dizziness, tachycardia, blurred vision, urinary retention, confusion, delirium), 3) alpha1 antagonistic effects (orthostatic hypotension), 4) sodium channel blockade (prolongation of cardiac conduction times, such as prolonged PR interval, widened QRS, flat or inverted T waves, arrhythmias) 5) decreased seizure threshold 6) weight gain 7) rashes, jaundice, leukopenia.

### **2. Anesthetic implications**

a. Avoid indirect-acting sympathomimetics as the increase in circulating catecholamines at the synaptic site may result in an exaggerated vasoconstrictive and pressor response.

b. Use direct-acting sympathomimetics such as phenylephrine but consider titrating and using a smaller than normal dose, especially in patients recently started on a TCA.

c. Be aware of the added cardiac and vasoactive responses with the use of epinephrine in the local anesthetics.

d. Ethrane and ketamine may interact and increase the chance of seizures secondary to the increased CNS stimulation..

e. Consider avoiding halothane, ketamine, and pancuronium due to an increased incidence of dysrhythmias.

f. Avoid centrally-acting anticholinergics due to the increased likelihood of the development of post-op delirium and confusion secondary to the additive effect.

g. TCAs can potentiate the sedative effects of benzodiazepines, barbituates, opiates, and anticholinergics so use cautiously and consider using decreased doses and assessing the effect.

h. TCAs have also been noted to augment the analgesic and ventilatory properties of opioids; therefore use smaller amounts and titrate.

i. Use caution with the antihypertensives secondary to the alpha1 antagonistic effect of the TCAs.

## **B. SELECTIVE SEROTONIN REUPTAKE INHIBITORS**

citalopram-Celexa

fluoxetine-Prozac

fluvoxamine-Luvox

paroxetine-Paxil

sertraline-Zoloft

**1. The SSRIs** are considered to be second generation antidepressants and are now first line therapy and the most commonly prescribed class of antidepressants for major depression. They are also utilized to manage panic disorders and can be effective for obsessive-compulsive disorders. The use of SSRIs over TCAs and MOAIs is due to their having fewer adverse effects. For ex., SSRIs lack anticholinergic effects, have virtually no cardiac effects, no effect of postural hypotension, and little effect on the seizure threshold.

SSRIs are also very lipophilic and protein bound. They are also metabolized by isoenzymes of the hepatic microsomal cytochrome P450 system. As a consequence, they can inhibit the metabolism of other drugs that are oxidized by the same enzymes. These drugs include benzodiazepines, clozapine, theophylline, warfarin, TCAs and some class IC antiarrhythmics.

SSRIs inhibit the reuptake of serotonin (and this is apparently indefinitely) in the synaptic cleft. The effect on depression is apparent in approximately 3-4 weeks.

The side effects of SSRIs include restlessness, insomnia, agitation, anxiety, headache, nausea, vomiting, diarrhea, and sexual dysfunction. Another adverse effect of the use of SSRIs is serotonin syndrome which occurs as a result of excessive serotonin typically as a result of the interaction with MAOIs and l-tryptophan. However, it can also occur with concurrent use of lithium, sumatriptan, dextromethorphan, and dihydroergotamine. The syndrome is characterized by mental status changes, restlessness, fever, diaphoresis, tachycardia, ataxia, myoclonus, hyperreflexia, hypertension, and can progress to heat stroke and vascular collapse. With discontinuation of the drug and supportive measures, symptoms usually resolve with hours or possibly weeks.

### **2. Anesthetic implications**

a. It is recommended to avoid using indirect-acting sympathomimetic agents but instead use direct-acting agents but in smaller doses, titrating to effect.

b. For the above drug, be aware of the implications of the epinephrine in the local anesthetics. As well, avoid the use of halothane, pancuronium, and ketamine.

c. As SSRIs have a milder but possible effect on increasing a patient's seizure potential, particularly on patients with a pre-existing history of seizures, avoid the use of ethrane and ketamine.

d. Avoid meperidine as it is believed to increase serotonin in the CNS by competing with serotonin for binding sites and can cause an exaggerated hypertensive and/or hyperpyretic reaction. To note, morphine does not inhibit the uptake of serotonin.

e. Be aware that the coadministration of ketoralac and fluoxetine should be avoided secondary to the development of hallucinations in some patients.

### **C. MONOAMINE OXIDASE INHIBITORS**

phenelzine-Nardil

tranylcypromine-Parnate

selegiline-Eldepryl

isocarboxazid-Marplan

**1. MAOIs** form an irreversable complex with the MAO enzyme therefore increasing the amounts the amounts of dopamine, NE, and serotonin at the synapse by decreasing the degradation at the synapse in the CNS and PNS. MAO is found principally in the outer mitochondrial membranes and cause the oxidative deamination of the amines. It is also found in some organs. MAO regulates metabolic degradation of the catecholamines and serotonin in the CNS and periphery as well as monoamines absorbed from food (such as tyramine). There are two subtypes of the MAO enzyme: MAO-A and MAO-B. MAO-A (60% of the MAO enzyme) is preferential for NE, epi, dopamine, and serotonin. MAO-B is preferential for dietary tyramine and phenylethylamine. MAO-A and MAO-B are found in the liver and intestines. MAO-B is found in platelets. Phenelzine and tranylcypromine are nonspecific inhibitors of MAO and selegiline is MAO-B specific but loses its specificity in higher doses. Selegiline is approved for treatment of early Parkinson's disease but may have antidepressant effects, especially at doses > 20 mg.

The use of MAOIs is limited to patients refractory to other forms of treatment, such as those with major depression who do not respond to TCAs. MAOIs are also used to treat panic disorder. MAOIs should not be used concurrently with TCAs and SSRIs.

The side effects include orthostatic hypotension, impotence, weight gain, parasthesias, restlessness, agitation, GI effects, and impotence. MAOIs are not noted to have anticholinergic effects nor cardiac effects such as dysrhythmias. A severe adverse effect of MAOIs is a hypertensive crisis, particularly a risk if the patient consumes tyramine containing foods. This can lead to stroke and death. The MAO enzyme is found in the liver, intestines, kidneys, lungs, platelets, and the mitochondrial membranes in nerve terminals. In addition the metabolic oxidation of the biogenic amines, MAO-A is the enzyme found in the intestines & liver and prevents monoamines such as tyramine and phenylethylamine from being absorbed from certain foods. The combination of tyramine and MAOIs can result in a hypertensive crisis with the symptoms of severe hypertension, hyperpyrexia, and stroke. As a consequence, patients taking the nonselective MAOIs need to follow a tyramine free diet, which prohibits foods including cheese, liver, fava beans, avocado, and chianti wine. To note, selegiline selectively inhibits MAO-B and patients do not need to follow a tyramine free diet; however, at higher doses (>25-30 mg/day) it becomes nonselective. If the patient develops a hypertensive crisis, treatment is best managed with specific and direct agents such as direct vasodilators such as nitroprusside or nitroglycerine and direct beta1 antagonists such as esmolol.

### **2. Anesthetic implications**

- a. Use direct acting sympathomimetics in lieu of indirect acting due to the possible exaggerated vasopressor response (and use a smaller dose).
- b. Avoid topical cocaine and the use of epinephrine in local and regional anesthesia.
- c. Avoid meperidine as it seems to increase serotonin in the CNS and can cause an exaggerated hypertensive reaction.
- d. Avoid halothane due to its dysrhythmogenic properties. Also, consider avoiding ketamine and pancuronium as well secondary to the additive effect with the increased circulating catecholamines.
- e. The side effects of morphine and other opioids may be potentiated by MAOIs with the result of increased respiratory depression.
- f. Ensure the patient is not currently taking any other prohibited drugs such as TCAs, fluoxetine, cold/allergy meds, and nasal decongestants.

#### **D. ATYPICAL ANTIDEPRESSANTS**

bupropion-Wellbutrin—affects dopamine, NE, and serotonin uptake. In addition to treatment of major depression, it is utilized to treat sexual dysfunction and aid in smoking cessation. Rarely causes orthostatic hypotension and anticholinergic effects. Side effects include GI effects, an increased incidence of seizures compared with other antidepressants (with exception of TCAs), anorexia, and lightheadedness.

mirtazapine-Remeron—affects both NE and serotonin. Also may exhibit some alpha<sub>2</sub> antagonistic effects and histamine antagonistic effects. Side effects include sedation, increased appetite, weight gain, nausea, and sexual dysfunction.

nefazodone-Serzone—inhibits serotonin uptake with some possible antagonistic effect at serotonin receptors. It has fewer side effects than trazadone and has no anticholinergic and antihistamine effects. Side effects include sedation and GI effects and some sexual effect such as impotence.

trazadone-Desyrel—is a weak serotonin receptor antagonist that also blocks serotonin reuptake but to a lesser degree than the others. It is also used to treat insomnia associated with the SSRIs and also used for anxiolysis. Side effects include sedation, GI effects, weight gain, and sexual effects such as priapism.

venlafaxine-Effexor—inhibits the reuptake of NE and serotonin. Side effects include agitation, GI effects, and sexual effects.

## **VI.**

### **ANTIPSYCHOTIC (NEUROLEPTIC) DRUGS**

Psychosis is defined as a state in which a person's mental capacity to recognize reality, communicate, and relate to others is impaired, thus interfering with the capacity to deal with life's normal everyday demands. The most common mental disorder in which psychotic sx may be present is schizophrenia. Schizophrenia is a general term for a mental disorder characterized by disturbances of multiple psychological processes including delusions, loosening of associations, poverty of speech content, auditory hallucinations, inappropriate affect, disturbed sense of self, and withdrawal from the external world. The onset is usually in early adulthood previous to which the patient had a normal level of functioning. There are various theories regarding the cause of schizophrenia with the most common theory being that there is dopamine hyperactivity or a hypersensitivity of central dopaminergic receptors (in that there is overactive neuronal activity with dopamine being the primary neurotransmitter involved). More recent theories on causes of schizophrenia seem to focus on anatomical abnormalities in the brain, including temporal lobe dysfunction, prefrontal lobe dysfunction, speech region abnormalities, and the tendency for these patients

to have enlarged ventricles and smaller cerebral size. The thought process is that there may not be specific problems in these regions of the brain but there may be circuitry abnormalities. There does seem to be a genetic predisposition coupled with psychosocial environmental factors. There definitely seems to be a genetic vulnerability for schizophrenia in that there is an increased number of abnormal genes and gene segments that have been identified. Additional types of psychotic disorders include alcoholic, depressive, postpartum, senile, and toxic psychoses.

The drugs included in this category are diverse groups that are used in the treatment of schizophrenia, the manic phase of the bipolar illness, depression with psychotic features, and certain organic and idiopathic psychotic disorders marked by severe agitation & impaired reasoning. The target sx for which antipsychotic agents seem to be especially effective agitation, combativeness, hostility, hallucinations, insomnia, anorexia, poor self-care, negativism, acute delusions, and sometimes withdrawal & seclusion.

This is no one particular antipsychotic or combination thereof that has selective effect on a specific symptom or complex of symptoms. As there is no reliable means to determine which drug will reliably and consistently create an anticipated therapeutic effect, the determination of which agent to use is often a matter of trial and error with regard to a favorable response and side effects. To note, there is no evidence that a combination of these agents can offer further advantages.

Antipsychotic drugs have additional uses such as for the treatment of nausea and vomiting, alcoholic hallucinations, pruritis, intractable hiccups, and neurological diseases with movement disorders (i.e. Tourette's syndrome, Huntington's chorea).

The classes of antipsychotic agents that exhibit clinical effectiveness include the following:

**PHENOTHIAZINES**  
chlorpromazine (Thorazine), fluphenazine (Prolixin), perphenazine (Trilafon), thioridazine (Mellaril), and trifluoperazine (Stellazine)

**THIOXANTHINES**  
chlorprothixene (Taractan), thiothixene (Navane)

**BUTYROPHENONES**  
droperidol (Inapsine), haloperidol (Haldol)

**DIBENZEPINES**  
clozapine (Clozaril), loxapine (Loxatane)

**BENZISOXAZOLE**  
resperidone (Risperdal)

**OTHER ATYPICAL ANTIPSYCHOTICS**  
molindine (Molan), olanzapine (Zyprexa), pimozide (Orap), quetiapine fumarate (Seraquel)

The primary effectiveness and MOA of the above drugs seems to be secondary to dopamine receptor blockade (esp. D2), particularly in the basal ganglia and limbic portions of the brain. These drugs have varying effects on D4 and D5 receptors, serotonin receptors, and alpha adrenergic receptors. In general, the antipsychotics share many similar pharmacological therapeutic effects and side effects. As well, in general, these drugs are highly lipid soluble and protein bound and are metabolized by hepatic oxidative mechanisms with subsequent conjugation. The average elimination half-time is 12-24 hours (particularly the phenothiazines and thioxanthines). The maximum efficacy occurs over several weeks with clinical improvement in about 3 weeks.

**A. The side effects** are dependent upon the receptor site affected. In addition to dopamine antagonistic activity, they exhibit cholinergic and alpha 1 antagonistic actions. The side effects of clozapine, loxapine, risperidone, and the other atypical antidepressants seem to be fewer the first three listed categories, especially with regard to having fewer extrapyramidal side effects and anticholinergic side effects but still cause sedation, hypotension, tachycardia, and a decreased seizure threshold. The following side effects are those consistent for phenothiazines, thioxanthenes, and butyrophenones with varying degrees of these side effects dependent upon the particular drug:

**1. dopaminergic blockade side effects:**

- a. akathisia-motor restlessness-probable related to dopamine antagonism but exact MOA is unknown
- b. acute dystonic reactions-acute skeletal muscle spasms or rigidity, often of the tongue, face, neck, and back and includes oculogyric crises and torticollis. Often occurs within the first 72 hrs. of treatment. The treatment for a dystonic reaction includes benzodiazepines, diphenhydramine, benztropine, and amantadine or bromocriptine.
- c. pseudoparkinsonism-characterized bradykinesia, tremors, rigidity, mask-like face, shuffling gait and pill-rolling.
- d. perioral tremors-a late sign noted after months or years of treatment
- e. tardive dyskinesia-this is also a late sign (often irreversible) noted after months or years which consists of oral-facial dyskinesia, dystonia, or choreoathetosis.
- f. neuroleptic malignant syndrome (NMS)-the exact MOA is unknown with theories including excess dopamine blockade in the hypothalamus or basal ganglia, disruption of the central thermoregulatory process, or excess heat production due to skeletal muscle contractions. Risk factors are dehydration and concurrent illness. The signs and symptoms are temperature > 38C, altered LOC (stupor, catatonia), unstable BP & tachycardia, diaphoresis, and hypertonicity (leading to myoglobinemia & renal failure). The differential diagnosis with malignant hyperthermia is that patients with NMS maintain normocapnia and NDMR produce flaccid paralysis whereas patients with MH develop hypercapnia and NDMRs do not produce paralysis. Treatment includes bromocriptine, dantrolene, amantadine, and NDMRs (in severe cases).

**2. alpha receptor antagonism-nonselective blockade**

- a. decrease in BP secondary to alpha 1 blockade
- b. central depression of vasomotor reflexes

**3. cardiovascular effects**-noted particularly with chlorpromazine and other phenothiazines

- a. direct relaxant effect on vascular smooth muscle
- b. direct cardiac depression-inotropic effect
- c. quinidine-like antiarrhythmic effect which could result in prolonged QT progressing to Torsades de pointes.

**4. lowered seizure threshold**

**5. increased prolactin levels** resulting in galactorrhea, amenorrhea, and gynecomastia

**6. sedation**

**7. depression**

**8. antimuscarinic effects**

**9. antihistamine effects**

**10. mild leukocytosis and leukopenia**

**11. increased appetite & weight gain**

**12. decreased thermoregulation**

**13. urticaria, dermatitis**

**14. impaired glucose tolerance and insulin clearance**

**B. Anesthetic implications:**

1. BP considerations: Carefully titrate the inhalational agents, narcotics, and any antihypertensives used secondary to antipsychotics promoting postural hypotension. Caution with the IV induction agents as well and consider a narcotic/IV agent combination. Ensure an adequate intravascular volume.

2. Use direct acting vasopressor agents in order to overcome the alpha1 blockade-is more effectively titrated.

3. Due to alpha1 blockade, epinephrine could enhance the beta2 effect resulting in vasodilation and hypotension.

4. Avoid the use of ethrane and ketamine due to the patient having a decreased seizure threshold.

5. As the antipsychotics antagonize dopamine receptors, they can inhibit the action of dopamine agonists resulting in a decreased response to the drugs.

6. Potentiation of sedatives and analgesics resulting in greater sedation and respiratory depression.

7. Enhancement of any antimuscarinic effects (in CNS or PNS) which could result in increased tachycardia, confusion, and delirium.

8. Maintain awareness of quinidine-like cardiac depression effects.

9. The effect of exogenous dopamine may be blunted (i.e. the vasopressor effect).

10. Decreased thermoregulation may be potentiated by the inhalation agents.

**VII. BIPOLAR DRUGS**

Bipolar disorder, also referred to as manic-depressive disorder, is a mood disorder marked by alternating periods of depression and mania. Mania is characterized by high energy levels: patients may be talkative and continuously active, as well as euphoric or even irritable. These patients may exhibit risk-seeking behavior such as reckless driving, shopping sprees, or sexual indiscretions. Additional criteria for the diagnosis are that the duration is greater than a week and the condition can not be secondary to another variable such as alcohol or schizophrenia. Theories on the cause of a bipolar disorder are that it is due to electrolyte imbalances, deficiencies in neurotransmitter such as DA, NE, serotonin, or GABA, a change in receptor sensitization, or an abnormality in membrane transport and secondary messenger system.

The treatment is aimed at the management of acute mania and the prevention of reoccurrences of mania. Lithium is the drug of choice and remains the most well-established drug utilized to prevent reoccurrences and is used often as the long-term agent. The anticonvulsants, particularly carbamazepine and valproic acid, are increasingly utilized especially with acute mania in order to more rapidly bring about antimanic effects as lithium has a slow onset of action and it can be difficult to determine the correct therapeutic dose in the acute manic phase. (Lithium, however, can be administered adjunctly and can be effective in acute mania.) The mechanism of action is unknown but they seem to reduce the sensitization of the brain to repeated mood swings. Another and newer mode of pharmacological treatment is the use of lamotrigine (Lamictal), also an anticonvulsant agent, that has shown efficacy in the prevention of mood episodes in bipolar patients. The mechanism of this particular agent may be related to the inhibition of Na<sup>+</sup> & Ca<sup>++</sup> channels in presynaptic neurons resulting in stabilization of the membrane. The exception with lamotrigine as compared to the other

anticonvulsants is that it has not demonstrated efficacy in acute mania but has been shown to be an effective maintenance therapy for bipolar patients. Side effects of lamotrigine include nausea, headache, insomnia, diarrhea, tremors, and rash.

The use of carbamazepine and valproic acid anticonvulsants for long-term use is limited as the effectiveness is inconclusive. Also, potent benzodiazepines (lorazepam, clonazepam) and antipsychotics (resperidone, olanzapine) are commonly administered in the acute phase.

### **A. Lithium**

Lithium is a very complex drug and the precise mechanism of mood stabilization for these patients is unknown; however the following is just a partial list of its various cellular actions:

1. Lithium ( $\text{Li}^+$ ) itself has a small gradient of distribution across biological membranes.  $\text{Li}^+$  is the lightest of all alkali metals.
2. Lithium can replace  $\text{Na}^+$  in the nerve cells and can support a single action potential but cannot maintain membrane potential as it is not a full adequate substrate for  $\text{Na}^+$  (chemically,  $\text{Li}^+$  shares some characteristics of  $\text{Na}^+$  and  $\text{K}^+$ ).
3. It can inhibit the depolarization provoked and  $\text{Ca}^{++}$  dependent release of NE and dopamine from nerve terminals, but not serotonin.
4. It may enhance serotonin release, especially in the limbic system.
5. It has some effect on adenylyl cyclase activity with respect to catecholamine release and limited effect on the binding of ligands to monoamine receptors in the brain. It can also modify some hormonal responses mediated by adenylyl cyclase.
5. It inhibits inositol monophosphatase therefore interfering with the phosphatidylinositol pathway.
6.  $\text{Li}^+$  also leads to decreases in the functioning of protein kinases in the brain, including protein kinase C. It may also cause decreased functioning of phospholipase C.
7. It can interact with nuclear regulatory factors thus affecting gene transcription.

Lithium is almost completely absorbed from the GI tract with peak plasma concentrations occurring within 2-4 hours; however there are slow release preparations. It is much less lipophilic than other psychotropic agents. It does not significantly bind to plasma proteins. Passage thru the blood-brain barrier is slow. A single dose is 95% eliminated in the urine but with steady state 80% of the filtered Lithium is reabsorbed from the proximal tubules. The elimination half-life is 20-24 hours. Lithium has a very narrow therapeutic range of 1.0-1.2 meq/L. A serum concentration of 0.4-0.9 is often sought and little gain in alleviating sx seems to be appreciated in levels  $> 0.75$  meq/L. It takes approximately 1-2 weeks to observe any effects.

In general, the side effects are related to the serum concentration of Lithium and its rate of rise in the serum following ingestion. The milder side effects include N&V, diarrhea, abdominal pain, sedation, fine tremor, weight gain, acne, polyuria, and polydipsia. More serious side effects are mental confusion, hyperreflexia, coarse tremor, ataxia, dysarthria, seizures, coma, death, hypotension, cardiac dysrhythmias, and albuminuria. The more serious side effects are noted especially for serum levels  $> 2.0$  meq/L with deleterious effects for levels  $> 2.5$ . It is important to note that thiazide, loop diuretics, and possibly ACEIs can decrease  $\text{Na}^+$  concentrations thus leading to  $\text{Li}^+$  toxicity and increased side effects at lower levels.

### **Anesthetic considerations**

1. Lithium can decrease the MAC of inhaled anesthetics.
2. It does cause sedation so use caution in your administration with barbiturates, benzos, and opioids.
3. It does decrease the seizure threshold so avoid the use of enflurane and ketamine.

4. Check electrolyte and Li<sup>+</sup> levels preoperatively.
5. Do a preoperative EKG.
6. It can prolong neuromuscular blockade for both depolarizing and nondepolarizing muscle relaxants.

### **VIII. ANTIANXIETY MEDICATIONS**

Anxiety disorders include generalized anxiety disorder (GAD), panic disorder, and OCD. Specifically GAD is characterized by at least 6 months of excessive and persistent worry. Panic disorder is characterized by specific periods during which there is usually a sudden onset of intense anxiety, fear, terror, and/or sense of impending doom with the patient feeling as if he may be having an MI secondary to sx of CP, SOB, & palpitations. OCD is characterized by obsessions which caused significant anxiety/ distress and compulsions which serve to neutralize the anxiety. NE, GABA, and serotonin are the major transmitters studied with respect to the pharmacological treatment of anxiety disorders. The classes of drugs utilized are benzodiazepines, hydroxyzines, as well as buspirone, and meprobamate.

**1. Benzodiazepines (BZDs)**-bind to GABA-A receptors to increase the duration of Cl<sup>-</sup> influx in order to hyperpolarize the cell resulting in inhibitory effect on cell firing. BZDs are used to treat GAD and panic disorder. In general, they are highly lipid soluble, highly bound to proteins (70-90%) with the duration of action relative to the lipid solubility and the degree of hepatic transformation to active metabolites. BZDs differ little in their pharmacological properties but can differ significantly in the potency, half-lives, and ability to cross the blood-brain barrier.

The side effects include drowsiness, ataxia, mild & transitory cognitive memory impairment, confusion, headache, GI disturbances, changes in libido, urticaria, and increased depression.

- a. diazepam (Valium)
- b. alprazolam (Xanax)
- c. clonazepam (Klonopin)
- d. oxazepam (Serax)
- e. chlordiazepoxide (Librium)

**2. hydroxyzines (Atarax, Vistiril)**-antihistamines, primarily H<sub>1</sub>. These are used as an adjunct in the relief of anxiety & tension and in organic disease states causing anxiety. Side effects include drowsiness and sedation.

**3. buspirone (Buspar)**- is in class of azapirones. It inhibits the uptake of dopamine, NE, & serotonin and seems to be an agonist at serotonin receptors. It has no direct effect at GABA receptors. It is effective in the treatment of GAD. It does not produce dependence and has minimal abuse potential. Also, it lacks the sedative, anticonvulsant, and skeletal muscle relaxant effects of BZDs. It has no hypnotic effect. It also lacks the propensity for interactions with alcohol and CNS depressants. Side effects include nausea, headache, dizziness, and nervousness.

**4. meprobamate (Equinal, Miltown)**-Is utilized as short-term relief in anxiety disorders. Side effects include drowsiness and ataxia. It has a higher potential for abuse than any of the other anti-anxiety agents.