Psychiatric Pharmacotherapy

A Review

Prof. (Mrs) Malathi R. Baichwal Visiting Fellowship Lecture

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Introduction

- Currently there is no cure for mental illness.
- Globally the estimated prevalence of Schizophrenia (about 1.5%), Depression (about 16%), and Bipolar (about 1.5%).
- Pharmacological treatment, in addition to being prohibitively expensive, is often complicated by serious side effects, drug-drug interactions, and drug-induced co-morbidities.
- Compliance is the single primary factor in successfully controlling the symptoms

Major Manifestations of Mental Disorder

- Schizophrenia
- Depression
- Bi-polar
- Anxiety Disorders

Global attitudes toward Mental Illness

Most of us are familiar with either a member of our family, or a neighbor who used to talk to themselves, or behave oddly in different ways; they were usually left alone and looked after as long as they are not a threat to themselves or others. Of course, the other aspect of this is mental illness is considered a stigma on the family, and most families try to hide it. Unfortunately that means the patient goes untreated, and eventually things would only get worse.

For about 30 years, Americans have been exporting their ideas of mental illness; their definitions and treatments have become the international standards.

The Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association provides a common language and standard criteria for the classification of mental disorders.

In 1994, DSM-IV was published**,** listing 297 specific mental disorders in 886 pages. DSM – V is scheduled for publication in May 2013.

DSM IV Multi-axial system

The DSM-IV organizes each psychiatric diagnosis into five dimensions (axes) relating to different aspects of disorder or disability. For example,

Axis I – Major Mental Disorders	Axis II – Major Personality Disorders
Schizophrenia	Paranoid personality
Depression	Schizoid personality
Bipolar	Borderline personality
Anxiety	Antisocial personality
ADHD	Narcissistic personality
Autism	Histrionic personality
Anorexia	Avoidant personality
	Dependent personality
	Obsessive-compulsive personality

Axis III: Medical / Neurological such as brain damage, HIV etc.

Axis IV: Psychosocial stressors (death in the family, unemployment, etc.)

Axis V: Current highest level of functioning.

The Nature of Mental Illness

Neurotransmission

The nervous system is composed of billions of specialized cells called neurons. Efficient communication between these cells is crucial to the normal functioning of the central and peripheral nervous systems. Neurons allow the brain to communicate with the rest of the body through the propagation of waves of depolarization, known as action potentials.

The transmission of information is accomplished in two ways:

Electrically: the neuron is directly adjacent to other neurons. As the action potential reaches the end of the axon, the depolarization continues across the membrane to the postsynaptic neuron directly.

Chemically: there is a space (the synaptic cleft) between the axon terminus and the adjacent neuron. As the action potential reaches the end of the axon, a chemical is released that travels across the synaptic cleft to the next neuron to alter its electric potential.

With very few exceptions, mammalian organisms use chemical means to transmit information.

Conduction

To begin conduction, an action potential (an electrical signal in which ions, which are electrically charged particles, move across the neuronal membrane) is generated near the cell body portion of the axon.

An action potential ends at the axon terminals. Axon terminals are where neurotransmission begins.

At electrical synapses, the OUTPUT will be the electrical signal itself. At chemical synapses**,** the OUTPUT will be neurotransmitter.

Neurotransmission

Neurotransmission (or synaptic transmission) is communication between neurons, accomplished by the movement of chemicals across a synapse.

A resting neuron has a negative charge. That is, there are more negative ions inside the axon than outside the axon. (Ions are molecules with an electric charge.) In contrast, the fluid outside the

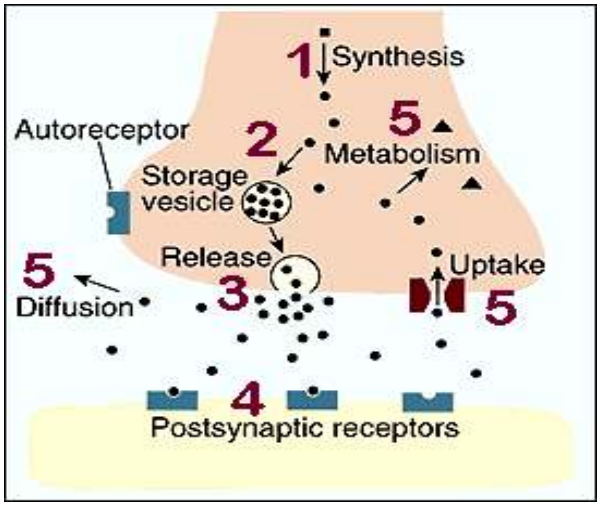
axon has a positive charge. Because the outside and inside of the axon have different charges, the axon is said to be polarized.

When a neuron is excited or fires, several events take place to create an electrical impulse. Sodium ions, which have a positive charge, enter the axon. This depolarizes the axon-that is, changes the electrical charge inside the axon from negative to positive. This change starts at one end of the axon and continues all the way to the other end. In response to this electrical impulse (called an action potential), the vesicles swarm to the very edge of the axon and release neurotransmitters into the synapse.

After the neurotransmitters are released, potassium ions flow out of the axon. Potassium ions have a positive charge, so their absence restores the negative charge inside the axon. The neuron is again polarized and at rest, waiting to fire another impulse.

In chemical neurotransmission, the pre-synaptic neuron and the post-synaptic neuron are separated by a small gap — the synaptic cleft. The synaptic cleft is filled with extracellular fluid (the fluid bathing all the cells in the brain). Although very small, typically on the order of a few nanometers (a billionth of a meter), the synaptic cleft creates a physical barrier for the electrical signal carried by one neuron to be transferred to another neuron. In electrical terms, the synaptic cleft would be considered a "short" in an electrical circuit. The function of neurotransmitter is to overcome this electrical short. It does so by acting like a chemical messenger, thereby linking the action potential of one neuron with a synaptic potential in another.

Chemical neurotransmission



Steps involved in chemical neurotransmission

Step 1: Neurotransmitter Biosynthesis

Step 2: Neurotransmitter storage

Step 3: Neurotransmitter release into synaptic/junctional cleft

Step 4: Interaction with neurotransmitter receptors

Step 5: Termination of neurotransmitter action (uptake, metabolism)

Synaptic vesicles contain Neurotransmitters (chemical substances which ultimately cause postsynaptic changes in the receiving neuron). Common neurotransmitters include:

- Acetylcholine
- Dopamine
- Nor-epinephrine (a.k.a., nor-adrenaline)
- Serotonin (5-HT)

Whether due to genetics, drug use, aging process, or other various causes, Biological dysfunction at any of the four steps of synaptic transmission often leads to imbalances and is the ultimately source of conditions such as schizophrenia, Parkinson's disease, and Alzheimer's disease.

Schizophrenia

Schizophrenia is a heterogeneous, psychotic thought disorder characterized by a mix of symptoms including delusions, hallucinations, disorganized speech or disorganized / catatonic behavior.

It is characterized by Positive Symptoms and Negative Symptom.

Positive Symptoms (symptoms that are present, but should not be)**:**

- Suspiciousness
- Hyperactivity
- Delusions (fixed, false beliefs, beliefs without a basis in reality)

- Hallucinations (hearing, feeling, tasting, or smelling things that are not there; and very commonly, hearing voices
- Conceptual disorganization (difficulty in speaking or organizing thoughts and paying attention

Negative Symptoms (symptoms that are absent, but should not be):

- Alogia: **(**poverty of speech, inability to speak because of mental deficiency, mental confusion
- Avolition**:** (literally meaning "poverty of will or motivation", characterized by general lack of drive, or motivation and may sit still for long periods of time)
- Anhedonia**:** (inability to take pleasure in usually pleasurable activities. Nothing is fun — not eating, playing, socializing or having sex)
- Flat Affect**:** unable to express emotions.

Epidemiology

The prevalence of schizophrenia among adults globally is about 1% - 3%.

Etiology

Contributing factors are:

- Genetics: First degree biol. relative - 10X higher risk.
- Environmental stresses**:** Low socioeconomic class, living in an urban area, stress, being born in winter (!).
- Neuro-developmental: Neurotransmitter imbalance**,** Upper respiratory tract infections in the second trimester of pregnancy, neonatal hypoxia, low birth-weight, intrauterine trauma.
- AT scans and MRI studies have shown brain asymmetry, and an overall decrease in brain size, and an increase in the ventricle size.

Treatment Options

Non-Pharmacological (Psychosocial rehabilitation): Oriented toward improving the patient's adaptive functioning, and includes:

- Case management

- Disease-education
- Cognitive behavioral therapy
- Social skills training
- Basic education
- Work programs
- Supported housing and financial support (very difficult)

Although well directed non-pharmacological efforts contribute significantly (up to 50%) to the overall treatment goals, unfortunately, it is almost impossible to implement these without concurrent antipsychotic medication regimen.

Pharmacological

Antipsychotics are generally classified as: Typical (1st generation) and Atypical (2nd generation) These are distinguished by unique receptor binding profiles with Dopamine and Serotonin (5-HT) receptors.

Side Effects (Adverse Drug Reactions, ADRs)

Since the treatment with antipsychotics tend to be long term, the serious side effects of both the first and second generation medications present challenges in their management as well as in life style changes.

For all antipsychotics FDA requires the following black-box warning:

"Increased Mortality in Elderly patients with Dementia-Related Psychosis

When used in adjunctive therapy for depression (MDD), the risk of suicidality increases in children, adolescents, and young adults."

- CNS effects: Sedation, Seizures, Weight gain
- Autonomic: Anticholinergic (dry mouth, constipation, urinary hesitancy, blurred vision.)
- Anti-adrenergic: Cardiovascular effects (Orthostatic hypotension, QTc prolongation)
- Endocrine effects: Hyperprolactinaemia / Galactorrhea / amenorrhea / Hyperlipidemia
- Extra Pyramidal Syndrome (EPS) Symptoms:

  Dystonia (muscle spasms of head, neck, limbs or trunk)

Akathisia (restlessness, inability to stay still / calm)

Parkinsonism or Pseudo-parkinsonism (decreased motor activity, mask-like face, resting tremor, rigidity, pill rolling, and drooling (Sialorrhea)**)**

- Tardive dyskinesia (Involuntary movements of face (tics, blinking, grimacing), tongue,chewing, protrusion), lips (smacking, puckering, pursing), toe tapping). This could be a long-term side effect; however, it is not seen much today due to the newer anti-psychotic medications.
- Neuroleptic Malignant Syndrome (NMS): (Rare but serious)

  Hyperpyrexia

  Muscle rigidity

  Altered mental status

  Irregular pulse or BP

  ECG Changes, tachycardia

  Cardiac dysrhythmia

  Diaphoresis (sweating)
- Urinary effects: Hesitation, retention, incontinence
- Sexual dysfunction **:** Erectile dysfunction and Anorgasmia
- Weight gain
- Ophthalmic effects: Cataracts. (And rarely narrow angle glaucoma, opaque deposits in cornea and lens, pigmentary retinopathy with Thioridazine))
- Hematologic effects: Transient leucopenia, Agranulocytosis
- Dermatologic effects: Photosensitivity, Rashes

First Generation Antipsychotics (FGAs)

- Efficacy is primarily related to their binding to Dopamine D2 receptors.
- High potency agents have the highest affinity for D2 receptors, and are effective at relatively lower doses (more EPS related side effects).
- Low potency agents have lower D2 affinity and require larger doses (less EPS related side effects).
- More effective on positive symptoms.

First Generation (Typical) Antipsychotics (FGAs)

Low Potency:

- Chlorpromazine (Thorazine)
- Mesoridazine (Serentil)
- Thioridazine (Mellaril)

Mid Potency:

- Loxapine (Loxitane)
- Molindone (Moban)
- Perphenazine (Trilafon)

High Potency:

- Fluphenazine (Prolixin)
- Haloperidol (Haldol)
- Pimozide (Orap)
- Thiothixine (Navane)
- Trifluoperazine (Stelazine)

Drug	Sedation	EPS	Anticholinergic	Prolactin	Orthostasis	Seizures	Wt. gain
FIRST GENERATION (TYPICAL) ANTIPSYCHOTICS							
Chlorpromazine (Thorazine)	++++	+++	+++	+++	++++	+++	++
Thioridazine (Mellaril)	++++	+++	++++	+++	++++	++	+
Loxapine (Loxitane)	++	+++	++	++	++	++	++
Molindone (Moban)	+	+++	++	+++	++	++	+
Perphenazine (Trilafon)	++	+++	++	++++	+	++	+
Fluphenazine (Prolixin)	+	+++	++	++++	++	++	+

Haloperidol (Haldol)	+	+++++	+	++++	+	++	++
Thiothixine (Navane)	+	++++	++	++++	++	++	++
Trifluoperazine (Stelazine)	+	+++	++	+++	++	+++	++

Notes:

- Inexpensive
- Low potency agents have higher sedation, orthostasis, anticholinergic effects and lower EPS
- May be as effective as some atypicals for positive symptoms
- Thioridazine has the FDA mandated Black Box Warning regarding QT prolongation
- Concomitant anti-cholinergics could be used to reduce EPS

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2nd Generation (Atypical) Antipsychotics (SGAs or Atypicals)

The characteristics that define "atypicality" are not all agreed upon, but in general they all share at least three characteristics:

- Lower risk of EPS than with typical antipsychotics at usual clinical doses
- The risk of tardive dyskinesia is reduced
- The ability to block 5-HT2 receptors, which improves activity for the negative symptoms

Atypical Antipsychotics (SGAs)

- Aripiprazole (Abilify)
- Asenapine (Saphris)
- Clozapine (Clozaril, Fazaclo)
- Lurasidone (Latuda)
- Olanzapine (Zyprexa)
- Quetiapine (Seroquel)
- Risperidone (Risperdal)
- Iloperidone (Fanapt)

- Paliperidone (Invega)
- Ziprasidone (Geodon)

Drug	Sedation	EPS	Anticholinergic	Prolactin	Orthostasis	Seizures	Wt. gain
SECOND GENERATION (ATYPICAL) ANTIPSYCHOTICS							
Aripiprazole (Abilify)	+	+	+	+	+	++	+
Asenapine (Saphris)	+	++	+ / -	+	++	++	+
Clozapine (Clozaril)	++++	+	++++	+	++++	++++	+++ +
Lurasidone (Latuda)	++	+	++	+	+	++	++
Olanzapine (Zyprexa)	++	++	+++	+	++	++	+++ +
Quetiapine (Seroquel)	+++	+	++	+	++	++	++
Risperidone (Risperdal)	+	++	++	++++	++	++	++
Iloperidone (Fanapt)	+	+ / -	+++	+	++	++	++
Paliperidone (Invega)	+	++	++	++++	++	++	+++
Ziprasidone (Geodon)	++	++	++	+	++	++	+

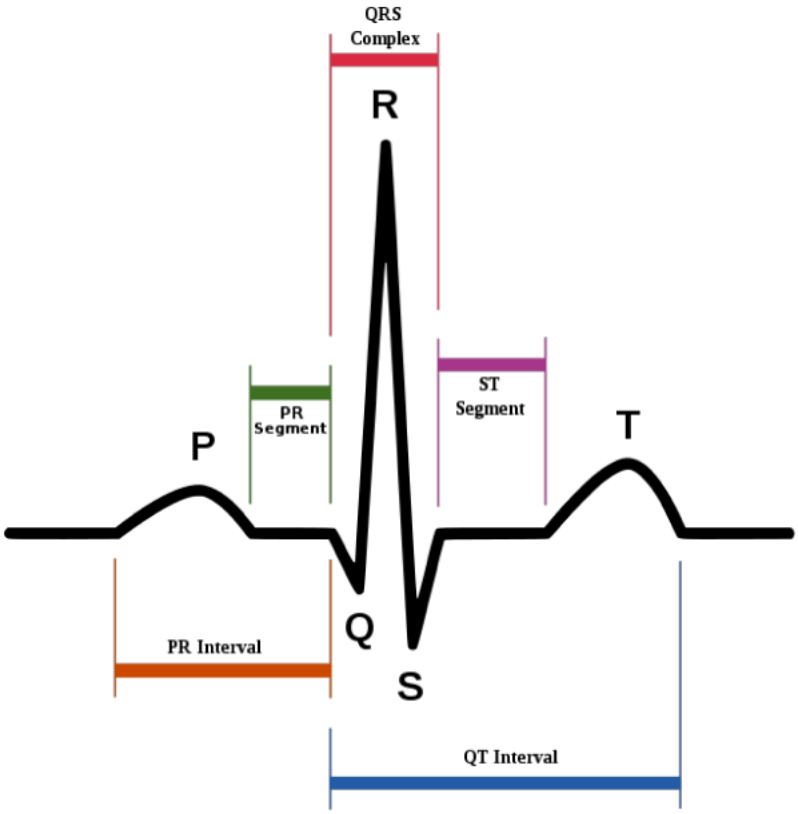
Special Problems:

- Orally Disintegrating Tablets for Cheeking, Acute conditions (Asenapine), Dyspahagia (Asenapine)
- Long acting (Depot) injections for Cheeking & better compliance: Haloperidol decanoate, Fluphenazine decanoate, Risperdal Consta.
- For acute agitated behavior: Ziprasidone (Geodon) I

- Other injectables: Invega sustenna, Zyprexa relprev

QT Interval

Since 2005, the FDA has required that nearly all new molecular entities are evaluated in a Thorough QT (TQT) study to determine a drug's effect on the QT interval. The TQT study serves to assess the potential arrhythmia liability of a drug.



Schematic ECG Trace

In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, and represents electrical depolarization and re-polarization of the left and right ventricles.

A lengthened QT interval ("normal" QTc ≤440 msc, where the “c” is a constant, to adjust for heart rate) is a biomarker for ventricular tachy-arrhythmias like torsades de pointes (a lethal form of ventricular tachycardia) and a risk factor for sudden death.

Prolongation of the QT interval may be due to an adverse drug reaction. Many drugs, such as Haloperidol, Thioridazine, Ziprasidone, Asenapine, Lurasidone, and Iloperidone, can prolong the QT interval.

Clozapine

It is considered the "last resort SGA" for 20% - 30% of patients who are RESISTANT TO TREATMENT.

(Treatment Failure is defined as failure to respond to two or more antipsychotics (one of which should be an atypical) when given at an adequate dose of 6-8 Wks.)

- Clozapine is the only antipsychotic that can effectively reduce both the positive and negative symptoms. It also reduces suicidality.
- Causes agranulocytosis, sedation, seizures, myocarditis, Orthostasis, Hyperlipidemia; however, decreased risk of EPS / TD.
- The patient, the physician, and the pharmacy must use a Clozaril registry.
- MUST BE MONITORED WEEKLY. For Clozapine: weekly WBC for 1st 6-months, then biweekly for 7 through 12 months. To Start: WBC > 3500 nm3 and ANC > 2000 nm3;
- DC Clozapine if WBC < 2000 nm3 or ANC < 1000 nm3.

Pharmacokinetics of Antipsychotics

Pharmacokinetics: How the body acts on drugs, to absorb, distribute, metabolize, and then excrete them.

Pharmacodynamics: How drugs act upon the body, especially the brain

Pharmacokinetics/Drug – Drug Interactions (DDIs)

Pharmacokinetic actions are mediated predominantly through hepatic drug-metabolizing system known commonly as Cytochrome P450 enzyme system. There are several known cytochrome P450 systems. Five of these are most important for psychotropic drug metabolism. These are: 1A2, 2D6, 2C9, 2C19, and 3A4.

Drugs that inhibit these enzymes increase the levels of the antipsychotics in the blood.

- 1A2 inhibited by SSRI (Fluoxamine) - Raises the levels of Clozapine and Olanzapine
- IA2 also inhibited by grapefruit juice, Ciprofloxacin, Smoking
- 2D6 is inhibited by SSRI (antidepressants like Paroxetine, Fluoxetine, and Sertraline) --- Raises the levels of Risperidone, Clozapine, Olanzapine.
- 3A4 inhibitors would raise the levels of Clozapine, Quetiapine, and Ziprasidone, which could cause QTc interval prolongation, which in turn could result in cardiac arrhythmias.

Depression

Depression (Major Depressive Disorder, MDD) is a serious, yet often overlooked or under-recognized psychiatric disorder, often described as a disturbance of mood associated with changes in behavior, with a life-time prevalence of about 16%.

Many with this illness do not seek treatment or are unaware of the presence of this potentially debilitating condition. If left untreated, the effects of Clinical Depression, MDD, can range from loss of productivity and motivation to thoughts and attempts at suicide.

Epidemiology

- Depression, along with Bipolar Disorder, is classified as a Mood Disorder.
- Depressive disorders are common during adolescence and are frequently associated with substance abuse, suicide attempts, and poor academic performance.
- Episodes of MDD are often precipitated by a severe psychological stressor (divorce, death in the family, loss of livelihood, etc.)

Etiology

Includes several factors:

- Genetic predisposition
- Psychological stressors, acute and chronic.
- Patho-physiological factors
- Decreased levels of 5-HT, NE, and DA
- Dysregulation of neurotransmitters

These theories have been supported by the mechanism in which the current antidepressants work – they increase synaptic monoamine (5-HT, DA, NE) concentrations.

Non-pharmacological Therapy

1. Psychotherapy, cognitive therapy, behavioral therapy, interpersonal psychotherapy are all equally effective, supplemental to antidepressant therapy.
2. Electroconvulsive Therapy (ECT): Safe and effective option for patients requiring a rapid response, and patients with a history of poor response to antidepressants. Administered 2 to 3 times weekly for 6 to 12 weeks. Results seen in 10 to 14 d. Must be supplemental to antidepressant therapy.
3. Bright light therapy: Patient gazes into a 10,000-lux intensity light, daily. Effective for treating Seasonal Effective Disorder (SAD). Well tolerated. Frequent eye exams recommended (seen mostly in people living in northern and southern latitudes, like Scandinavia or Southern Argentina)

Pharmacological Therapy

In October 2004, the FDA directed manufacturers of all antidepressants to include a boxed warning detailing the risk of suicide in children and young adults (18 to 24 years of age) with MDD and othe depressive disorder.

Main types of antidepressants:

1. Non-selective antidepressants (Tricyclics)
2. Selective Reuptake Inhibitors
    - Selective Serotonin Reuptake Inhibitors (SSRIs)
    - Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)
    - Selective Noradrenaline Reuptake Inhibitors (NARIs)
    - Norepinephrine and Dopamine Reuptake Inhibitors (NDRIs)
3. Receptor blockers
    - Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs)
    - Serotonin Receptor Blockade with Serotonin Reuptake Inhibition (SARIs)

In general, the older antidepressants (Tricyclics) are just as effective as the newer ones (SSRIs) but, have more side effects and can be lethal in OD, and are not so dangerous if someone takes an overdose.

Mode of Action

For reasons that are not completely understood, depressives often have low levels of certain neurotransmitters.

Antidepressants work by increasing the amount of neurotransmitters and making them flow normally in the brain. Neurotransmitters cannot be taken orally or intravenously because they cannot pass blood-brain barrier.

Tricyclic antidepressants and SSRIs stop the nerve cells from reabsorbing neurotransmitters

NOTE: About 25% of the patients experience a hyper-stimulatory response to antidepressants, especially when therapy first starts, which can be confused with a worsening of the anxiety symptoms; especially with Prozac & Venlafaxine.

Antidepressants – Side Effects

Agent	Nausea GI	Agitation Insomnia	Sexual Dysfunction	Weight Gain	Notes
SSRIs					
Citalopram (Celexa)	++	+	++	---	QTc issues
Escitalopram (Lexapro)	++	++	++	---	
Fluoxetine (Prozac)	++	++	+++	---	Least risk of
Fluvoxamine (Luvox)	++	+	+++	++	
Paroxetine (Paxil)	+++	+++	+++	+	EPS, Sedation
Sertraline (Zoloft)	++	++	++	---	Diarrhea
SNRIs					
Duloxetine (Cymbalta)	++	++	+	---	Also for Fibromyalgia
Venlafaxine (Effexor)	++	++	++	---	HBP, Needs Dose titration
SARIs					
Trazodone (Desyrel)	+	---	++	+	Priapism,

Antidepressants – Side Effects (Cont.)

Agent	Anticholinergic	Sedation	Orthostatic Hypotension	Wt. Gain	Notes
NDRIs					
Bupropion (Wellbutrin)	+	---	---	---	Also for smoking cessation
TRICYCLICS					
Amitriptyline (Elavil)	++++	+++	+++	+++	Lowers seizure
Clomipramine	++++	+	++	++	Lowers seizure
Desipramine	++	---	+	+	Insomnia
Doxepin (Sinequan)	+++	++++	+++	++	
Imipramine (Tofranil)	+++	+	++	++	Lowers seizure
Nortriptyline	++	+	+	+-	Lowers seizure
TeCAs / NaSSAs					
Mirtazapine	+	+++	++	++	

Bipolar Disorder

- Bipolar disorder is a cyclic, mood disorder characterized by recurrent fluctuations in mood, energy, and behavior ranging from major depression to mania.
- Bipolar disorder differs from recurrent major depression in that a manic, hypomanic, or mixed episodes occur during the course of the illness.
- Patients with Bipolar disorder have a high risk of suicide.
- Lifetime prevalence rates of psychiatric comorbidity co-existing with bipolar disorder are 42% to 50%.

There are 3 types of bipolar disorder:

Bipolar I patients have full-blown manic and/or mixed episodes often followed by a full depressive episode.

Bipolar II patients are characterized by at least one hypomanic episode and one full depressive disorder.

Cyclothymic disorder is characterized by mood swings less severe than full mania and full depression, but still waxing and waning above and below the boundaries of normal mood (rarely suicidal but usually treatment resistant).

Etiology

It is thought to be a complex genetic disease that is environmentally influenced and caused by a wide range of neurobiologic abnormalities.

Pathophysiology: Neurotransmitter / neuroendocrine abnormality, such as : dysregulation between excitatory (NE, DA, glutamate and aspartate,) and inhibitory (5-HT and GABA) neurotransmitter systems (excess of catecholamines (NE & DA) cause mania.)
Several classes of drugs can induce mania (Anticonvulsants, Antidepressants, Antimicrobials, Anti-Parkinson's Drugs, Anxiolytics/ hypnotics, AAPs, CNS stimulants, Drugs of Abuse, Sympathomimetics, Herbals, etc.

Non-pharmacological treatments

- Adequate nutrition, Sleep, exercise and stress reduction
- Mood charting to help detect early signs and symptoms of mania and depression
- Psycho-educational programs
- Supportive counseling
- Family therapy
- Crisis intervention plan
- Cognitive behavioral therapy
- Electroconvulsive therapy is the application of prescribed electrical impulses to the brain (inducing controlled seizures) for the treatment of severe depression, mixed states, psychotic depression, and treatment-refractory mania. May be used in pregnant women who cannot take carbamazepine, lithium or divalproex.

Pharmacological Treatment

Pharmacotherapy is the cornerstone of acute and maintenance treatment of Bipolar Disorder. Mood stabilizing drugs are the usual first choice of treatment.

FDA-Approved Medications for Bipolar Disorder				
Drug	Mania	Mixed	Depression	Maintenance
Carbamazepine (ER	X	X		
Lamotrigine				X
Lithium	X			X
Divalproex Sodium	X	X		
Aripiprazole	X	X		X
Olanzapine	X	X		X
Quetiapine	X		X	
Risperidone	X	X		
Ziprasidone	X	X		

Lithium (Gold standard for mood stabilization)

- The first-choice drug for the classic presentation of bipolar disorder.
- Effective for both the manic and depressive components of bipolar and reduction in suicides.
- Only lithium is FDA-approved in children /adolescents as young as 12.
- It is a unique agent (an element that behaves like an electrolyte) which has almost no psychotropic effect in normal individuals; it is not a Sedative, depressant or euphoriant.
- It takes about 2 weeks to see the full effects of Lithium; hence interim use AAP and/or benzodiazepines is recommended.
- Lithium toxicity which can occur at serum concentrations over 2mEq/L, can be severe and life-threatening requiring ICU admission and a push of IV fluids and possible renal dialysis.

Lithium - DDIs

- Common and Significant drug interactions involve drugs that increase lithium levels, and very commonly prescribed drugs such as thiazide diuretics, NSAIDs (non-steroidal anti-inflammatory agents), and ACE inhibitors.
- If a diuretic must be used, a loop diuretic such as furosemide is less likely to increase lithium retention (but must be given with lot fluids and potassium to avoid dehydration and replace potassium)

- ACE inhibitors should be avoided at any cost since they can abruptly increase serum lithium with the potential for acute and fatal toxicity.
- Drugs that reduce lithium levels include Caffeine and theophylline.
- Drugs that increase CNS toxicity include Carbamazepine, phenytoin, and neuroleptics.

Lithium Side Effects - ADRs

- GI upset: Dose related. Nausea, dyspepsia, and diarrhea
- Tremors
- Kidney function: Causes increases in frequency and Volume of urine, and increase in thirst. (Diabetes insipidus, inhibits kidney's ability to concentrate urine).
- Thyroid function: Lithium induced hypothyroidism
- Cardiac effects (EKG changes & Cardiac arrest, due to inhibition of Potassium reuptake at cellular level resulting in intracellular hypokalemia & extracellular hyperkalemia)
- Dermatological effects such as rashes & psoriasis
- Weight gain
- Metallic taste
- Reduced libido and sexual dysfunction

Alternatives and Adjuncts to Lithium

- Antipsychosis

Aripiprazole, Olanzapine, Quetiapine, Risperidone, Ziprasidone are all approved for Bipolar Mania, Quetiapine is approved also for Bipolar Depression, and Aripiprazole and Olanzapine for maintenance therapy.

- Benzodiazepines

High potency agents such as Clonazepam and Lorazepam are helpful acutely for agitation, insomnia, and hyperactivity

- Valproate (Depakote)

Primarily an anticonvulsant, but also for mood stabilization, especially good for rapid cyclers. FDA approved for the treatment of manic episodes or bipolar disorder (great for use if the patient is not able to tolerate or respond to Lithium.)

- Lamotrigine (Lamictal)

DDI: Carbamazepine / Phenytoin / Phenobarb / Valproate

- Carbamazepine (Tegretol) for both acute and prophylactic management.
- Oxcarbazepine (Trileptal) Effective substitute for carbamazepine. Much better tolerated, less monitoring required.(No CBC, WBC, platelets, LFTs, and eye exams).

Anxiety Disorders

Generalized anxiety disorder: 6 months or more of excessive worry or anxiety, generally with an unidentified cause.

Panic disorder: discrete periods of sudden, intense fear or terror and feelings of impending doom lasting about 10 min.

Obsessive-compulsive disorder: Obsessive or intrusive thoughts that cannot be controlled, and involve repetitive ritualistic behavior, such as washing hands, combing hair, cleaning house, etc.

Post-traumatic stress disorder: follows a traumatic event

Social anxiety disorder

Pharmacotherapeutic options

Benzodiazepines

These drugs have anxiolytic properties, and some have preventive efficacy for panic attacks.

Pharmacologically all these agents share, to various degrees, five properties:

a) anxiolytic, b) hypnotic, c) muscle relaxation, d) anticonvulsant, and e) amnesic

AGENT	HALF-LIFE	DOSE (mg)
Alprazolam (Xanax)	6-12	1
Chlordiazepoxide (Librium)	5-30	25
Clonazepam	20-50	0.5
Diazepam (Valium)	20-100	10
Lorazepam (Ativan)	10-18	1

Short half-life / high potency: Rapid acting, tolerance prone, withdrawal problems. For acute management

Long half-life / low potency: Long lasting, less pronounced withdrawal symptoms. They can accumulate in elderly patients.

The primary issue associated with Benzos is tolerance and dependence.

Generalized Anxiety Disorder: Antidepressants (SSRIs), Benzodiazepines, Buspirone

Panic Disorder: Antidepressants (SSRIs), Benzodiazepines.

Obsessive Compulsive Disorder: Serotogenic agents such as SSRIs, especially in combination with Atypical antipsychotics.

Post-traumatic Stress Disorder: Sertraline and Paroxetine. Valproic acid has been used effectively to control and reduce aggression and anger.(Benzos are not effective and should be avoided).

Role of Pharmacy and Pharmacists in Psychiatric Treatment

Pharmacy and Pharmacists become critical players in treatment because Pharmacological treatment:

- Is prohibitively expensive (help with generic substitution)
- Needs Medication Reconciliation (such as drug-drug interactions, adjustments in the dose or how to take the medication, etc., becomes necessary due to number of medications taken by the patient, medications to treat the main condition, medications to treat the side effects, and other over-the-counter medications
- Is often complicated by (help by consultation):
    - ✓ Long term, often lifelong treatment
    - ✓ Need to modify changes in life style
    - ✓ Serious side effects
    - ✓ Drug-drug interactions,
    - ✓ Drug-induced co-morbidities.
    - ✓ Denial
    - ✓ Non-compliance

The Following Sources are gratefully acknowledged:

- Psychiatry Textbooks and Handbooks
- Articles from Psychiatry Journals
- Manufacturers' Drug Information Brochures / Drug Seminars
- Practical Knowledge from the practice of psychiatric pharmacy and
- The collective practical knowledge of the Psychiatric Pharmacy Staff.