Everything You Always Wanted to Know About Psychopharmacology (*But were Afraid to Ask – A Refresher)

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CEO, Geriatric Pharmacotherapy Institute

The Continuum Hypothesis

- Genetic
- Structural neuroimaging
- Neurophysiological
- Pharmacology
  - Psychosis
  - Mood disorder
    - Bipolar
    - Major Depressive disorder

The Genetic Spectrum of Schizophrenia and Related Disorders

- Anxiety
- Schizophrenia
- Schizotypal
  - Schizotypal Paranoid Personality Disorder
  - Atypical
  - Psychosis
  - Psychotic Depression
  - Depression
- Bipolar Disorder

Olanzapine: a clinical review
Module I: Schizophrenia
Opening Remarks

Linkage Studies

Bipolar Disorder

18q22
21q21
4p16
12q24

Schizophrenia

18p11
13q32
10p14
22q11-13

6p22
6q21
8p22


Four dopamine pathways in the brain

• (a) nigrostriatal dopamine pathway
• (b) mesolimbic dopamine
• (c) mesocortical dopamine pathway
• (d) tuberoinfundibular dopamine pathway

NMDA Receptor Function: A Pharmacological Model of Schizophrenia

- NMDA receptor antagonists (e.g., PCP, ketamine)\(^1\),\(^2\)
  - Induce psychosis in normal human volunteers
  - Discontinue psychotic symptoms in patients with schizophrenia
  - Induce limbic dysfunction (hypertocormotion) in rodents

- Marked alteration in regional prefrontal cortex brain metabolism by NMDA receptor antagonists may reflect activation of glutamatergic neurotransmission\(^3\)

- Reduction of a presumed hyperglutamatergic state in schizophrenia may result in the improvement of psychosis\(^4\)

NMDA=N-methyl-D-aspartate, PCP=Phencyclidine


Olanzapine: a clinical review
Module I: Schizophrenia
Opening Remarks

NMDA Receptor Function: A Pharmacological Model of Schizophrenia

Genetic factors
- Neurogenin
- Dysregulin
- DAGO/C72
- Isolated variants

Environmental factors
- Postperinatal insult
- Developmental neurotoxicity
- Activity/motoric status
- Metabolic variation

NMDA Dysfunction
- Sensory deficits
- Generalized cognitive deficits
- Impaired learning & memory
- Negative symptoms
- Thought disorder
- Positive symptoms
- Gating deficits
- Executive dysfunction

Dopamine dysregulation

Glutamate is the Primary Excitatory Neurotransmitter in the CNS

CNS Conditions Hypothesized to Involve Inappropriate Glutamatergic Neuronal Transmission
- Epilepsy
- Neurodegeneration
- Ischemia/reperfusion
- Alzheimer’s disease
- Neurogenic pain
- Parkinson’s disease
- Schizophrenia
- Mood disorders
- Substance abuse
- Drug withdrawal
- Cognition

Serotonin

- Psychological functions in which the serotonergic system is involved
  - Mood
  - Anxiety
  - Arousal
  - Vigilance
  - Impulsivity
  - Aggression
  - Suicidality
  - Cognition
  - Control of intrusive thinking

Olanzapine: a clinical review
Module I: Schizophrenia

Opening Remarks

Pharmacology: Psychotic Disorders

Features of Schizophrenia

Positive Symptoms
- Delusions
- Hallucinations
- Disorganized speech
- Catatonia

Negative Symptoms
- Affective flattening
- Alogia
- Avolation
- Anhedonia
- Social withdrawal

Social/occupational Dysfunction
- Work
- Interpersonal relationships
- Self-care

Cognitive Deficits
- Attention
- Memory
- Executive functions (e.g., abstraction)

Comorbid Substance Abuse

Mood Symptoms
- Depression
- Anxiety
- Hopelessness
- Demoralization
- Stigmatization
- Suicidality

Developments in Medical Treatments for Psychotic Disorders

ECT
- Chlorpromazine

First-generation antipsychotics
- Haloperidol
- Fluphenazine
- Thioridazine
- Loxapine
- Perphenazine

Second-generation antipsychotics
- Clozapine
- Risperidone
- Olanzapine
- Quetiapine
- Ziprasidone
- Aripiprazole

ECT = electroconvulsive therapy.
Mechanism of Action of Psychoactive Medications

- Psychoactive medications seem to have an immediate or acute action in hours or days and then a latent action which may occur weeks later and continue for sometime even after stopping medication.
- The initial response is generally mediated by some direct or indirect effect on some neurotransmitter (i.e., 5HT reuptake, dopamine blockade, GABA release)
- After chronic treatment the latent action suggests alterations at the genomic level which would explain the time to full effect and the continued effect even after the medication is stopped.

Classes of Antipsychotics

- Dopamine antagonists
- Dopamine/Serotonin antagonist
- Partial Dopamine antagonists

Broad Spectrum Receptor Binding Profile of Olanzapine and Clozapine as Compared to Other Antipsychotic Drugs

Module I: Schizophrenia
Opening Remarks

Pharmacological Profile for: Haloperidol

Haloperidol

Pharmacological Profile for: Risperidone

Risperidone

Pharmacological Profile for: Olanzapine

Olanzapine

Indirect NMDA

NE transporter inhibitor

5-HT

M1

D2

M3

D4

5-HT2a

5-HT3a

5-HT6

α1

D1

D3

Olanzapine: a clinical review
Pharmacological Profile for: Aripiprazole

Aripiprazole
Antagonist

\( \alpha_2c \)

Aripiprazole

D2

Partial Agonists

Antipsychotics

• Side Effects
  • Extrapyramidal side effects
    • tremor, akathisia, dystonic reactions
  • secondary negative symptoms
  • Neuroleptic malignant syndrome
    • significant mortality rate
  • Neuroendocrine
    • amenorrhea
    • galactorrhea
  • Tardive syndromes
    • Tardive dyskinesia
    • Tardive dystonia

Neuroleptic Malignant Syndrome

• Triad
  • Muscle rigidity
  • Decreased level of consciousness
  • Autonomic instability (hyperthermia, labile BP, tachycardia, diaphoresis)
• Incidence: 1/300. Mortality rate as high as 30%
• Most common with high potency antipsychotics
Tardive Dyskinesia

- Involuntary, repetitive, hyperkinetic movements
- Prevalence varies with age and chronicity, ranging from 0.5% to 70%
- Incidence 5% per year of antipsychotic exposure
- 10% of cases are severe and interfere with eating, speech, breathing or mobility
- Often permanent, no consistently effective treatment

Hyperprolactinemia

- Incidence: 15% - 50%
- Short term effects
  - Galactorrhea
  - Amenorrhea/irregular menses
  - Sexual dysfunction
- Long term effects
  - Diminished fertility
  - Osteoporosis
  - Immune disorders
  - Breast cancer

Other Side Effects

- Sedation
- Orthostatic hypotension
- Dry mouth
- Blurry vision
- Constipation
- Weight gain
Atypical Antipsychotics: Common Features

- High ratio of serotonin to dopamine antagonism
- Fewer side effects
  - Extrapyramidal side effects
  - Tardive syndromes
  - Neuroendocrine
- Superior efficacy
  - In drug refractory patients
  - In negative symptoms
  - In preventing relapse

Advancements in Pharmacotherapy: Long Acting Injectables (LAIs)

- Zyprexa Relprevv
  - T ½ 28 days
  - Dosing q 2 weeks 300mg
  - Dosing q 4 weeks 405mg
  - Range 405 to 600mg every 4 weeks
  - REMS

Advancements in Pharmacotherapy

Risperdal Consta

- T ½ q 14 days
- Dosing q 2 weeks
- Refrigerated
- Dosage: 12.5mg, 25mg, 37.5mg, 50mg
- Range: 25mg to 100mg q 2 week
Advancements in Pharmacotherapy

Invega Sustenna
- T ½ q 28 days
- Dosing q 4 weeks
- Refrigerated: NO
- Dosage: 39 mg, 78 mg, 117 mg, 156 mg, 256 mg
- Range: 117 mg to 256 mg

Advancements in Pharmacotherapy

Aripiprazole Long-acting injectable (Abilify Maintena, Aristada)
- T ½ q 28 days
- Dosing q 4 weeks
- Refrigerated (maybe)
- Dosage: 300mg to 400mg q 4 weeks

Advancements in Pharmacotherapy: Second Generation

Iloperidone (Fanapt)
- T ½ q 10-12 hours
- Dosing: BID
- Pharmacology: D2, 5HT1A antagonist, affinity for other receptors. Possible QTc prolongation
- Nausea, somnolence, akathisia, common side effects
- Dosage: 1mg BID titrate to 6-24 mg per day in divided doses
Advancements in Pharmacotherapy

Asenapine (Saphris) sublingual
- T ½ q 10-12 hours
- Dosing: BID
- Pharmacology: D2, 5HT1A antagonist, affinity for other receptors. Possible QTc prolongation
- Nausea, somnolence, akathisia common side effects
- Dosage: 5mg BID titrate to 10 mg BID

Advancements in Pharmacotherapy

Lurasidone (Latuda)
- T ½ q 20 – 24 hours
- Dosing: once daily
- Pharmacology: D2, 5HT1A antagonist, no affinity for other receptors.
- Nausea and somnolence common side effects
- Dosage: 20mg, 40mg, 80mg, 120mg
- Should be administered with food due to bioavailability

Advancements in Pharmacotherapy: Third generation partial dopamine agonists

Brexpiprazole (Rexulti)
- T ½ q 91 hours
- Dosing: once daily
- Pharmacology: D2, 5HT1A partial agonist, 5HT2A and Noradrenergic Alpha 1B, Alpha2C.
- Akathisia (4-14%) Weight gain (2-11%) Head ache (4-9%) common side effects
- Dosage: Titration to 4mg/day for schizophrenia and 3mg/day for Augmentation for MDD
- Can be given with or without
Advancements in Pharmacotherapy: Third generation partial dopamine agonists

Cariprazine (Vraylar)
- T 1/2 2–4 days
- Dosing: once daily
- Pharmacology: D2, 5HT1A partial agonist, 5HT2A
- Akathisia (9–20%), Vomiting (4–10%), EPS (15–26%), Somnolence (5–8%), Restlessness (4–7%)
- Dosage: Titration to 6mg/day for schizophrenia and bipolar disorder 3mg
- Can be given with or without

The Ultimate Goal: Reintegration

- Reintegration
  - Different for every patient
  - Resuming personal care habits
  - Leaving long-term care facility
  - Returning to work, school, or family
  - Enhanced functionality and independence

Pharmacology: Mood Disorders
Pharmacology of Bipolar Disorder

Mood Disorders Can Be Depressive or Bipolar

<table>
<thead>
<tr>
<th>Depressive Disorders</th>
<th>Bipolar Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Major Depressive Disorder</td>
<td></td>
</tr>
<tr>
<td>• Single / Chronic / Recurrent</td>
<td></td>
</tr>
<tr>
<td>• Atypical</td>
<td></td>
</tr>
<tr>
<td>• Melancholic</td>
<td></td>
</tr>
<tr>
<td>• Catatonic</td>
<td></td>
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<tr>
<td>• Psychotic</td>
<td></td>
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<tr>
<td>• Postpartum onset</td>
<td></td>
</tr>
<tr>
<td>• Seasonal</td>
<td></td>
</tr>
<tr>
<td>• Dysthymic Disorder</td>
<td></td>
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<tr>
<td>• Depressive Disorder NOS</td>
<td></td>
</tr>
<tr>
<td>• Bipolar I Disorder</td>
<td></td>
</tr>
<tr>
<td>• Manic / Mixed episodes</td>
<td></td>
</tr>
<tr>
<td>• Bipolar II Disorder</td>
<td></td>
</tr>
<tr>
<td>• Hypomanic + Major Depression</td>
<td></td>
</tr>
<tr>
<td>• Cyclothymic Disorder</td>
<td></td>
</tr>
<tr>
<td>• Hypomanic + Depressive</td>
<td></td>
</tr>
<tr>
<td>• Bipolar Disorder NOS</td>
<td></td>
</tr>
</tbody>
</table>


Proposed Mechanism of Mood Stabilization of Atypical Antipsychotics: Multireceptorial Normalization of Neurotransmission

For antidepressant effect—olanzapine increases extracellular levels of dopamine and norepinephrine and blocks 5HT2A

Parallel glutamatergic segregated circuits mediate and integrate diverse inputs (in white)

Alexander DR et al Biol Psychiatry 1996;21(11)
Li XM et al Psychopharmacology (Berl) 1998;136(2)
Mood Stabilizing/Antimanic Mechanism

- Topiramate – anticonvulsant
- Gabapentin – anticonvulsant
- Lamotrigine – anticonvulsant
- Carbamazepine - anticonvulsant
- Oxcarbazepine – anticonvulsant
- Haloperidol – dopamine antagonist
- Risperidone – dopamine antagonist
- Quetiapine – dopamine antagonist
- Ziprasidone – dopamine antagonist
- Aripiprazole – partial dopamine antagonist/agonist

Expert Consensus
Treatment of Acute Bipolar Mania

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Preferred Initial Strategy</th>
<th>Alternate Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euphoric (classic) mania*</td>
<td>TMS alone</td>
<td>Antipsychotic alone</td>
</tr>
<tr>
<td></td>
<td>TMS + antipsychotic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Add BZD to other agent(s)</td>
<td></td>
</tr>
<tr>
<td>Dysphoric mania† or true mixed mania‡</td>
<td>TMS + antipsychotic</td>
<td>Add BZD to other agent(s)</td>
</tr>
<tr>
<td></td>
<td>TMS alone</td>
<td>Combination of 2 TMSs</td>
</tr>
<tr>
<td>Mania with history of rapid cycling</td>
<td>TMS + antipsychotic</td>
<td>Add BZD to other agent(s)</td>
</tr>
<tr>
<td></td>
<td>TMS alone</td>
<td>Antipsychotic alone</td>
</tr>
<tr>
<td>Mania with psychosis</td>
<td>TMS + antipsychotic</td>
<td>Add BZD to other agent(s)</td>
</tr>
<tr>
<td></td>
<td>AP alone</td>
<td>Antipsychotic alone</td>
</tr>
<tr>
<td>Hypomania without history of rapid</td>
<td>TMS alone</td>
<td></td>
</tr>
<tr>
<td>cycling</td>
<td>Psychotherapy + medication§</td>
<td></td>
</tr>
<tr>
<td>Hypomania with history of rapid</td>
<td>TMS alone</td>
<td></td>
</tr>
<tr>
<td>cycling</td>
<td>Psychotherapy + medication § Carbamazepine</td>
<td></td>
</tr>
</tbody>
</table>

*Euphoric mania: manic episode without depressive features
†Dysphoric mania: manic episode with some depressive features
‡True mixed mania: meeting criteria for both a manic episode and a major depressive episode for 1 week

Tolerability of Approved Treatments for Bipolar Disorder

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>CNS</th>
<th>EPS</th>
<th>Derm</th>
<th>GI</th>
<th>PRL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>++</td>
<td>+++</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Divalproex</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>+/-</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>+/-</td>
<td>+</td>
<td>0</td>
<td>+++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
</tbody>
</table>
Patients With Major Depressive Disorder (MDD) May Present with Emotional and Physical Symptoms

<table>
<thead>
<tr>
<th>Emotionally Significant Symptoms</th>
<th>Physical Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sadness (S)</td>
<td>Energy (E)</td>
</tr>
<tr>
<td>Lack of Interest (I)</td>
<td>Concentration (C)</td>
</tr>
<tr>
<td>Guilt (G)</td>
<td>Appetite (A)</td>
</tr>
<tr>
<td>Psychomotor (P)</td>
<td>Sleep (S)</td>
</tr>
<tr>
<td>Suicide (S)</td>
<td></td>
</tr>
</tbody>
</table>

Symptoms must be present for at least 2 weeks:

- Sad (S)
- Interest (I)
- Guilt (G)
- Energy (E)
- Concentration (C)
- Appetite (A)
- Psychomotor (P)
- Sleep (S)
- Suicide (S)

One symptom must be depressed mood or loss of interest.

In addition to depressed mood and/or loss of interest, additional symptoms must be present for a total of at least 5 of the 9 symptoms listed.


DSM-IV-TR Diagnostic Criteria for a Major Depressive Episode (MDE)

A. An MDE is defined as having at least 5 of the following symptoms for at least 2 weeks:

1. Loss of interest or pleasure in nearly all activities
2. Significant change in weight or appetite
3. Insomnia or hypersomnia
4. Psychomotor retardation or agitation
5. Fatigue or loss of energy
6. Feelings of worthlessness or inappropriate guilt
7. Diminished ability to concentrate
8. Depressed mood
9. Suicidal ideation

One symptom must be depressed mood or loss of interest.

In addition to depressed mood and/or loss of interest, additional symptoms must be present for a total of at least 5 of the 9 symptoms listed.

A. Symptoms do not meet criteria for a mixed episode (no manic or hypomanic symptoms)
B. Symptoms must cause significant distress or impairment in social, occupational or other important areas of functioning
C. Symptoms cannot be due to the direct physiological effects of a substance (medication or drug abuse) or general medical condition
D. Symptoms cannot be better accounted for by bereavement

Module I: Schizophrenia

Opening Remarks

Associated Symptoms of A Major Depressive Episode (MDE)

- Tearfulness
- Irritability
- Brooding or obsessive rumination
- Anxiety or phobias
- Excessive worry over physical health
- Complaints of Pain
  - Headaches,
  - Joint pain,
  - Abdominal pain,
  - Other pains


Proposed Roles for 3 Key Monoamine Systems

Dopamine
- Euphoria
- Pleasure
- Motivation
- Energy
- Appetite
- Sex
- Aggression

Norepinephrine
- Vigilance
- Mood
- Emotion
- Cognition
- Anxiety
- Irritability

Serotonin
- Impulse

Healy & McMonagle, J Psychopharm, 1997

Developments in Medical Treatments for Major Depressive Disorder

ECT
ECT = electroconvulsive therapy.

Olanzapine: a clinical review
Treatment Options for Major Depression Include Pharmacological and Non-Pharmacological Therapies

**Pharmacological Therapy**
- Selective Serotonin Reuptake Inhibitors (SSRI)
- Selective Serotonin and Noradrenaline Reuptake Inhibitors (SNRI)
- Mixed Reuptake Inhibitors (bupropion)
- Mixed Selective Serotonin Reuptake Inhibitors and Receptor Blockers (mirtazapine, nefazodone, trazodone)
- Tricyclic Antidepressants (TCA)
- Monoamine Oxidase Inhibitors (MAOI)

**Non-Pharmacological Therapy**
- Psychotherapy
  - Cognitive Behavioral Therapy (CBT)
  - Interpersonal Therapy (IPT)

Characteristics of the Ideal Antidepressant

- Efficacy and Tolerability for Children and Elderly
- Low Drug-Drug Interactions
- Safety in Overdose
- Rapid Onset of Action
- Simpler to Administer
- High Rate of Efficacy
- Functional and Symptomatic Improvements
- Cost-Effective
- Efficacy for Spectrum of Psychiatric Illnesses
- Minimal Side Effects

Tricyclic Antidepressants

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Usual daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipramine</td>
<td>Tofranil</td>
<td>100-300 mg/day</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Norpramin</td>
<td>150-300 mg/day</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Pamelor</td>
<td>100-200 mg/day</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>Vivactil</td>
<td>30-60 mg/day</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Elavil</td>
<td>150-300 mg/day</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Anafranil</td>
<td>100-250 mg/day</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>Surmontil</td>
<td>150-225 mg/day</td>
</tr>
<tr>
<td>Mapiroline</td>
<td>Ludronil</td>
<td>150-300 mg/day</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>Asendin</td>
<td>300-600 mg/day</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Anafranil</td>
<td>100-250 mg/day</td>
</tr>
</tbody>
</table>

SSRIs

- Developed out of the need for an antidepressant with both improved efficacy and decreased adverse events.
- Nonselectively increase serotonin levels by inhibiting its uptake
- Anti-obsessive compulsive disorder, anti-panic, anti-social phobia and anti-bulimia properties

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Dosage range</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Prozac</td>
<td>20-80 mg</td>
<td>2-3 days</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft</td>
<td>50-200 mg</td>
<td>1 day</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paxil</td>
<td>20-60 mg</td>
<td>21 hours</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Celexa</td>
<td>20-40 mg</td>
<td>1-2 days</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Lexapro</td>
<td>10-20mg</td>
<td>1-2 days</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Luvox</td>
<td>50-300 mg</td>
<td>12-15 hours</td>
</tr>
</tbody>
</table>

SSRI adverse events

- 5-HT\textsubscript{2} receptor mediated
  - agitation
  - akathisia
  - anxiety
  - panic attacks
  - sexual dysfunction
  - insomnia
- 5-HT\textsubscript{3} receptor mediated
  - nausea
  - diarrhea
  - GI distress
  - headache
Advancements in Pharmacotherapy

Vortioxetine (Trintellix)
- T ½ q 66 hours
- Dosing once daily titrate to (10-20mg/day)
- Pharmacology: Selective serotonin and antagonizes 5HT3, 5HT1D and 5HT7, agonizes 5HT1A and 5HT1B partial and has no significant affinity for adrenergic, dopaminergic, cholinergic, opioid, glutamate or histaminergic
- Nausea (21-32%), Vomiting (3-6%) common side effects
- Dosage: 10mg, 20mg, titrate to 20mg/day
- Take without regard to meals

Advancements in Pharmacotherapy

Vilazodone (Viibryd)
- T ½ q 25 hours
- Dosing once daily titrate to maximum of 40mg/day
- Pharmacology: Selective serotonin reuptake inhibitor and a partial agonist of 5HT1A and has no significant affinity for adrenergic, dopaminergic, cholinergic, opioid, glutamate or histaminergic
- Diarrhea (26-29%), Nausea (22-24%), Vomiting (4-5%), Insomnia (6-7%) common side effects
- Dosage: Initial 10mg and titrate to 40mg/day
- Give with food

SNRIs
- Venlafaxine
- Duloxetine
- Levomilnacipran
Venlafaxine (Effexor)

- At low doses, inhibits reuptake of 5-HT
- At medium doses, inhibits reuptake of 5-HT and NE
- At high doses, inhibits reuptake of 5-HT, NE and DA.
- Usual daily dose is 75-225 mg


Venlafaxine adverse events

- At low doses
  - nausea, agitation, sexual dysfunction, insomnia
- At medium to high doses
  - hypertension, severe insomnia, severe agitation, headache


Duloxetine

Duloxetine (Cymbalta)

- T ½ q 8 – 17 hours
- Dosing once daily
- Pharmacology: Selective serotonin and norepinephrine reuptake inhibitor and has no significant affinity for adrenergic, dopaminergic, cholinergic, opioid, glutamate or histaminergic
- Nausea (18-23%), Xerostomia (11-14%), Dizziness (8-9%), Headache (13-18%) and somnolence common side effects
- Dosage: 20mg, 60mg. (range 20-120mg/day)
- Should be swallowed whole, do not chew, or open. Patients who have difficulty swallowing, who may open capsules and mix with 30ml of applesauce or apple juice.
Advancements in Pharmacotherapy

Levomilnacipran (Fetzima)
- T ½ q 12 hours
- Dosing once daily
- Pharmacology: Selective serotonin and norepinephrine reuptake inhibitor, no affinity for other receptors.
- Increased heart rate (6%), Palpitations (5%), Tachycardia, Diaphoresis (9%), Nausea (17%), Vomiting (5%), Erectile dysfunction (6%), Disorder of ejaculation (5%) are common side effects
- Dosage: 20-120mg/day with titration
- Give at approximately same time each day with or without food. Capsule should not be opened, chewed, or

Trazodone (Desyrel)
- A 5-HT₂ antagonist as well as a 5-HT reuptake inhibitor
- Usual dose is 150-600 mg/day
- Adverse events include
  - sedation
  - cognitive slowing
  - dizziness
  - priapism
  - orthostatic hypotension

Bupropion (wellbutrin, wellbutrin SR, zyban)
- Inhibits reuptake of both norepinephrine and dopamine.
- Usual dosage range is 300-450 mg/day.
- Contraindicated in patients with seizure disorders or prior diagnosis of bulimia or anorexia nervosa.
- When added to SSRIs, can reverse sexual dysfunction
- Also used in smoking cessation.
Bupropion adverse events
- stimulating
- agitation
- nausea
- insomnia
- seizures
- dizziness
- tremor
- dry mouth

Mirtazapine (remeron)
- Inhibits presynaptic alpha-2 adrenergic receptors which results in increase central concentration of NE and 5-HT.
- Strong affinity for 5-HT1, avoids 5-HT2 and 5-HT3.
- Usual dosage range is 15-45 mg/day.
- Contraindicated in patients who have used a MAOI within 14 days
- Adding to a SSRI or venlafaxine can reduce insomnia or nausea


Mirtazapine adverse events
- Sedation – due to H1 blockade
- Somnolence
- Weight gain
- Dry mouth
- Constipation
- Dizziness
- Agranulocytosis (rare)
- LFT elevation (rare)
Monoamine Oxidase Inhibitors

- Phenelzine sulfate (Nardil)- usual dose 15-90 mg/day
- Tranylcypromine sulfate (Parnate)- usual dose 20-60 mg/day
- Isocarboxazid (Marplan)- usual dose 20-40 mg/day
- Act by increasing the concentration of NE, 5-HT and DA in the neuronal synapse by inhibition of MAO.
- Selegeline Transdermal Patch

MAOIs

- Second line therapy that may be beneficial in patients with mood reactivity, irritability, hypersomnia, hyperphagia or psychomotor agitation.
- Contraindicated for use within 5 weeks of discontinuation of fluoxetine and 2 weeks of sertraline or paroxetine discontinuation.
- Adverse events include orthostatic hypotension, insomnia, sexual dysfunction, dry mouth, constipation, weight gain, dietary restrictions

Serotonin Syndrome

- A potentially life-threatening drug-related condition characterized by a number of mental, autonomic and neuromuscular changes.
- Can occur with MAOIs, SSRIs and TCAs.
- Usually develops after the addition or increase in dose of an agent that increases serotonin

Diagnosis of serotonin syndrome

Presence of 3 or more of the following after the recent addition or increase in dose of an agent that increases 5-HT activity

- mental status changes
- myoclonus
- fever
- diaphoresis
- diarrhea


Diagnosis of serotonin syndrome

- agitation
- hyperreflexia
- shivering
- ataxia
- tremor

• Other etiologies must be ruled out
• No neuroleptic agents have been started or increased in dosage prior to the onset of symptoms.


Drugs involved in serotonin syndrome

<table>
<thead>
<tr>
<th>Action on serotonin</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase 5-HT synthesis</td>
<td>L-tryptophan</td>
</tr>
<tr>
<td>Decrease 5-HT metabolism</td>
<td>Isocarboxazid, Phenelzine, Selegiline, Tranylcypromine</td>
</tr>
<tr>
<td>Increase 5-HT release</td>
<td>Amphetamines, Cocaine, Reserpine</td>
</tr>
</tbody>
</table>

Drugs involved in serotonin syndrome

<table>
<thead>
<tr>
<th>Inhibit 5-HT uptake</th>
<th>TCAs, SSRI's, nefazodone, trazodone, amphetamines, cocaine, dextromethorphan, meperidine, venlafaxine, St. John’s Wort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct 5-HT receptor agonists</td>
<td>Buspirone, LSD, sumatriptan, Lithium</td>
</tr>
<tr>
<td>DA agonists</td>
<td>Amantadine, bromocriptine, bupropion, levodopa</td>
</tr>
</tbody>
</table>

Management of serotonin syndrome

- Supportive care
- Discontinuation of all serotonergic drugs
- Consider use of a 5-HT antagonist
  - ciproheptadine: 4-8 mg po then 4 mg every 2-4 hours up to a maximum of 0.5 mg/kg/day
  - methysergide: 2-6 mg po; mdd=6mg

Length of Treatment of Depression

- First episodes can be treated up to 1 year
- Treatment length for a second episode can last from 4-5 years. If complicating factors exist treatment can go on indefinitely.
- If a third episode occurs, treatment should last indefinitely.
Remission of Major Depressive Disorder is the Goal of Treatment

• Remission is:
  • Minimal to no residual symptoms
  • Low scores on scales used to track depression severity in research settings
    • 17-item HAMD ≤ 7
    • MADRS ≤ 10
  • Function restored