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

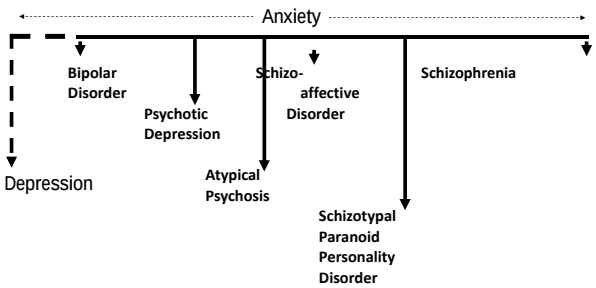
Terrance J Bellnier, RPh, MPA, FASCP
Assistant Professor, SUNY University at Buffalo
CEO, Geriatric Pharmacotherapy Institute

University at Buffalo The State University of New York
School of Pharmacy and Pharmaceutical Sciences

The Continuum Hypothesis

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

The Genetic Spectrum of Schizophrenia and Related Disorders



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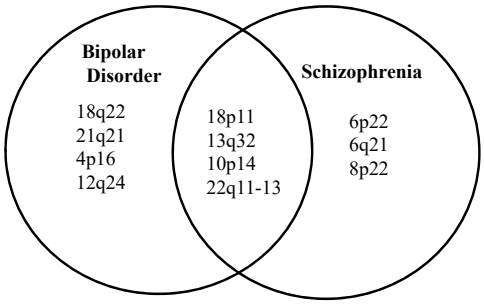
Linkage Studies



Barrettini Biol Psychiatry 47:245-251, 2000.

Four dopamine pathways in the brain

- (a) nigrostrial dopamine pathway
- (b) mesolimbic dopamine
- (c) mesocortical dopamine pathway
- (d) tuberoinfundibular dopamine pathway

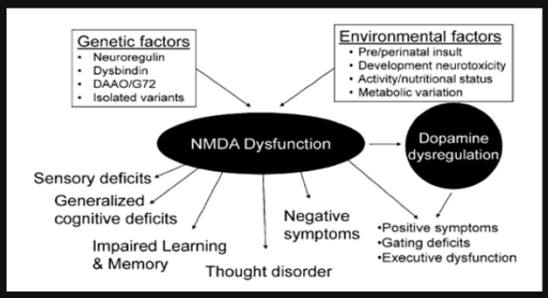
NMDA Receptor Function: A Pharmacological Model of Schizophrenia

- NMDA receptor antagonists (e.g., PCP, ketamine) [1,2,3]
  - Induce psychosis in normal human volunteers
  - Exacerbate psychotic symptoms in patients with schizophrenia
  - Induce limbic dysfunction (hyperlocomotion) in rodents
- Marked alteration in regional prefrontal cortex brain metabolism by NMDA receptor antagonists may reflect activation of glutamatergic neurotransmission[2]
- Reduction of a presumed hyperglutamatergic state in schizophrenia may result in the improvement of psychosis[4]

NMDA=*N*-methyl D-aspartate; PCP=Phencyclidine

1. Rorick-Kehn LM, et al. J Pharmacol Exp Ther 2006;316(2):905-13.
2. Kargieman L, et al. Neurotox Res 2008;14(2-3):129-40.
3. Duncan GE, et al. Brain Res 1998;787(2):181-90.
4. Moghaddam B, et al. Science 1998;281(5381):1349-52.

NMDA Receptor Function: A Pharmacological Model of Schizophrenia

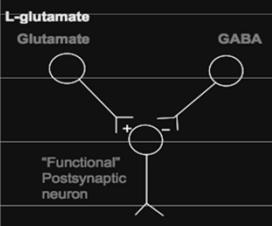


Kantrowitz, JT, Javitt DC. Brain Res Bull (2010) doi.1016/j.brainresbull.2010.04.006.

Glutamate is the Primary Excitatory Neurotransmitter in the CNS

CNS Conditions Hypothesized to Involve Inappropriate Glutamatergic Neuronal Transmission

- Epilepsy
- Neurodegeneration
  - Ischemia/trauma
  - Alzheimer's disease
- Neuropathic pain
- Parkinson's disease
- Schizophrenia
- Mood disorders
- Substance abuse
- Drug withdrawal
- Cognition



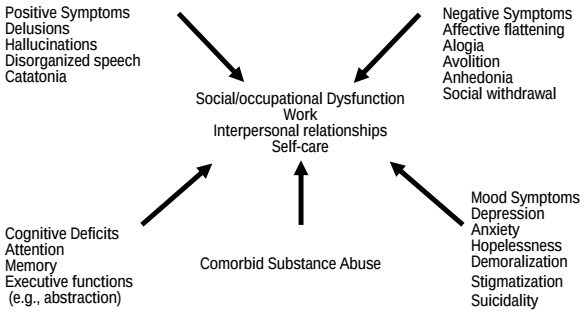
1. Monn et al. *J Med Chem.* 1997;40:528-37.
2. Goudet et al. *Brain Res Rev.* 2009 ;60(1):43-56.
3. Rorick-Kehn et al. *J Pharmacol Exp Ther* 2006;316(2):905-13.

Serotonin

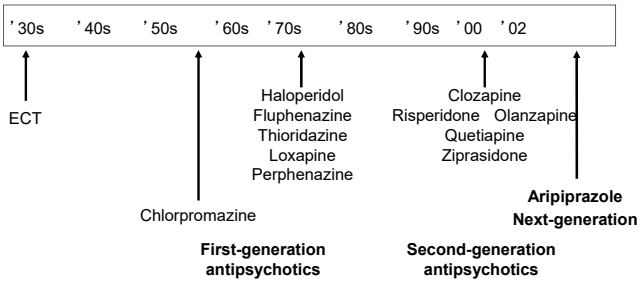
- Psychological functions in which the serotonergic system is involved
  - Mood
  - Anxiety
  - Arousal
  - Vigilance
  - Impulsivity
  - Aggression
  - Suicidality
  - Cognition
  - Control of intrusive thinking

Pharmacology: Psychotic Disorders

Features of Schizophrenia



Developments in Medical Treatments for Psychotic Disorders



ECT = electroconvulsive therapy.

Kapur and Remington. *Ann Rev Med.* 2001;52:503.
Worrel et al. *Am J Health Syst Pharm.* 2000;57:238.

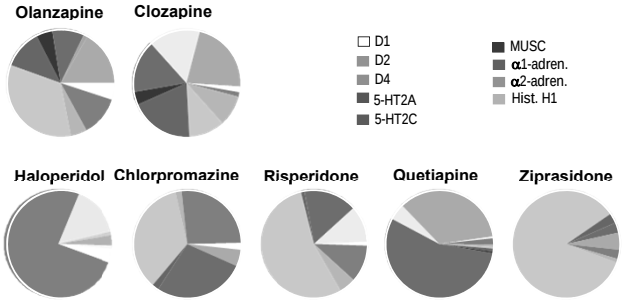
Mechanism of Action of Psychoactive Medications

- Psychoactive medications seem to have a immediate or acute action in hours or days and than 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 suggest 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

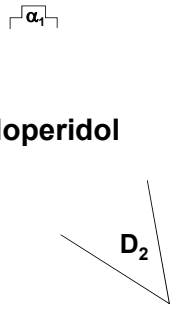
- Dopamine antagonists
- Dopamine/Serotonin antagonist
- Partial Dopamine antagonists

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

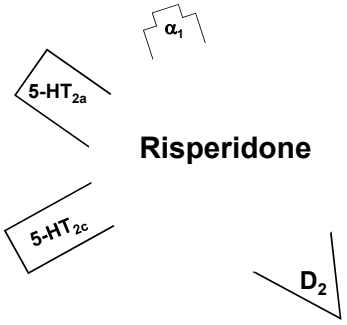


Data from: Bymaster FP, et al. Unpublished observations. 1996.
Schotte A, et al. *Psychopharmacology (Berl.).* 1996;124(1-2):57-73.

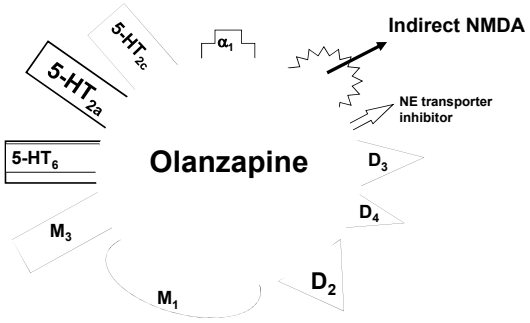
Pharmacological Profile for: Haloperidol



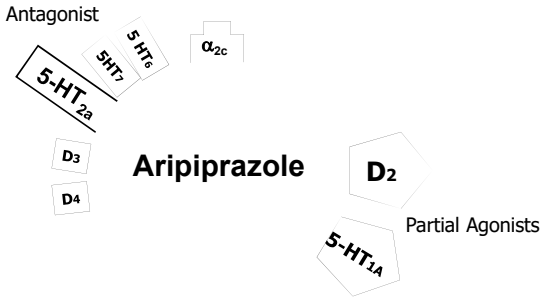
Pharmacological Profile for: Risperidone



Pharmacological Profile for: Olanzapine



Pharmacological Profile for: Aripiprazole



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, 25 mg, 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 , 78mg, 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) sublinqual

- 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 ½ 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

Depressive Disorders

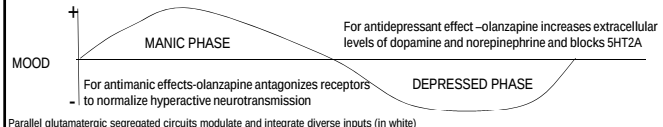
- Major Depressive Disorder
  - Single / Chronic / Recurrent
    - Atypical
    - Melancholic
    - Catatonic
    - Psychotic
    - Postpartum onset
    - Seasonal
- Dysthymic Disorder
- Depressive Disorder NOS

Bipolar Disorders

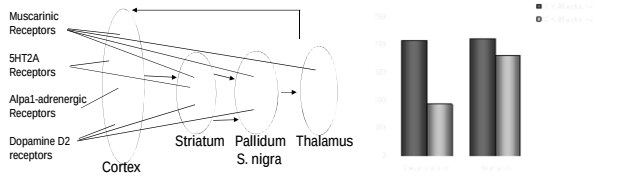
- Bipolar I Disorder
  - Manic / Mixed episodes
- Bipolar II Disorder
  - Hypomanic + Major Depression
- Cyclothymic Disorder
  - Hypomanic + Depressive
- Bipolar Disorder NOS

Adapted from: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association; 2000:345-428.

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



Parallel glutamatergic segregated circuits modulate 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
- Quetiapine – dopamine antagonist
- Ziprasidone – dopamine antagonist
- Aripiprazole – partial dopamine antagonist/agonist

Expert Consensus

Treatment of Acute Bipolar Mania

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

TMS = traditional mood stabilizer, defined as highest-rated mood stabilizing agents in 2000 survey: carbamazepine, divalproex, and lithium; BZD = benzodiazepine.
*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
§Very high second line (rated first line by more than two thirds of the experts)

Keck, PE, Jr., Perlis RH, Otto MW, et al. The Expert Consensus Guideline Series: Treatment of Bipolar Disorder 2004. Postgrad Med Special Report. 2004(December):1-120.

Tolerability of Approved Treatments for Bipolar Disorder

Drug	Weight Gain	CNS	EPS	Derm	GI	PRL
Lithium	++	+++	0	++	++	0
Divalproex	++	++	0	+	++	0
Carbamazepine	+/-	+++	0	+++	+	0
Lamotrigine	+/-	+	0	+++	+	0
Olanzapine	+++	++	+	+	+	+
Risperidone	++	+	++	+	+	+++
Ziprasidone	+/-	+	+	+	+	0
Quetiapine	++	++	0	+	+	0
Aripiprazole	+/-	+	+	+	++	0

Modified from Strakowski SM, DelBello MP, Adler CM. CNS Drugs. 2001;15(9):701-718; Strakowski SM, DelBello MP, Adler CM, Keck PE. Exp Op Pharmacother. 2003;4(5):751-760 (Review).

Pharmacology of Major Depressive Disorder

Patients With Major Depressive Disorder (MDD) May Present with Emotional and Physical Symptoms

Symptoms must be present for at least 2 weeks:

S	**Sad (↑)**	**Emotional**
I	**Interest (↓)**	**Emotional**
G	**Guilt (↑)**	**Emotional**
E	**Energy (↓)**	**Physical**
C	**Concentration (↓)**	**Physical**
A	**Appetite (↑ or ↓)**	**Physical**
P	**Psychomotor (↑ or ↓)**	**Physical**
S	**Sleep (↑ or ↓)**	**Physical**
S	**Suicidal (↑)**	**Emotional**

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association; 2000:356.

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 area 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

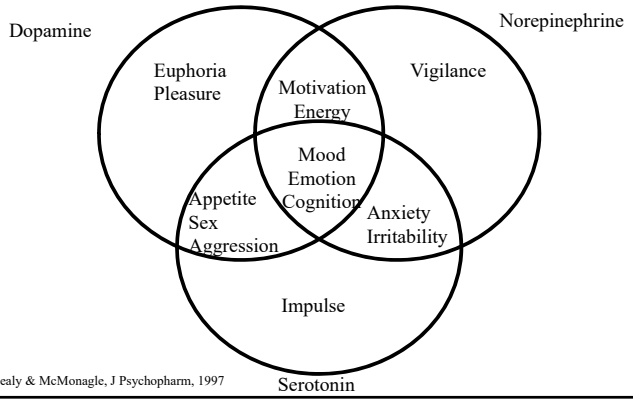
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association; 2000:356.

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**

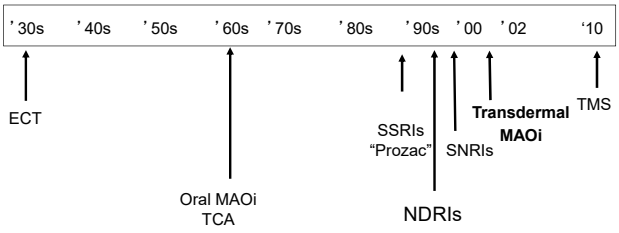
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).* Washington, DC: American Psychiatric Association; 2000:352.

Proposed Roles for 3 Key Monoamine Systems



Healy & McMonagle, J Psychopharm, 1997

Developments in Medical Treatments for Major Depressive Disorder



ECT = electroconvulsive therapy.

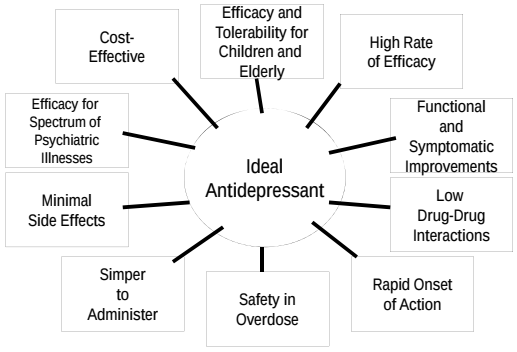
Kapur and Remington. *Ann Rev Med.* 2001;52:503.
Worrel et al. *Am J Health Syst Pharm.* 2000;57:238.

Treatment Options for Major Depression Include Pharmacological and Non-Pharmacological Therapies

- **Pharmacological Therapy**
  - Selective Serotonin Reuptake Inhibitors (SSRI)
  - Selective Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)
  - Mixed Reuptake Inhibitors (bupropion)
  - Mixed Selective Serotonin Reuptake Inhibitors and Receptor Blockers (mirtazepine, nefazodone, trazadone)
  - Tricyclic Antidepressants (TCA)
  - Monoamine Oxidase Inhibitors (MAOI)
- **Non-Pharmacological Therapy**
  - Psychotherapy
    - Cognitive Behavioral Therapy (CBT)
    - Interpersonal Therapy (IPT)

Hales RE, Yudofsky SC, eds. *Textbook of Clinical Psychiatry, 4th ed.* Arlington, VA: American Psychiatric Publishing, Inc; 2003:491-503.

Characteristics of the Ideal Antidepressant



Tricyclic Antidepressants

Generic Name	Brand Name	Usual daily dose
Imipramine	Tofranil	100-300 mg/day
Desipramine	Norpramin	150-300 mg/day
Nortriptyline	Pamelor	100-200 mg/day
Protriptyline	Vivactil	30-60 mg/day
Amitriptyline	Elavil	150-300 mg/day
Doxepin	Sinequan	150-300 mg/day
Trimipramine	Surmontil	150-300 mg/day
Maprotiline	Ludiomil	150-225 mg/day
Amoxapine	Ascendin	300-600 mg/day
Clomipramine	Anafranil	100-250 mg/day

14. Anderson PO, Knoben JE, Troutman WG. Handbook of Clinical Drug Data. 10th edition. McGraw-Hill. 2002;456-459.

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

SSRIs

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

SSRI adverse events

- 5-HT_2 receptor mediated
  - agitation
  - anxiety
  - sexual dysfunction
  - akathisia
  - panic attacks
  - insomnia
- 5-HT_3 receptor mediated
  - nausea
  - GI distress
  - diarrhea
  - 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

15. Harvey AT, Rudolph RL, Preskorn SH. Evidence of the dual mechanisms of action of venlafaxine. Archives of General Psychiatry. 2000;57:503-509.

Venlafaxine adverse events

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

16. Kent JM. SNaRIs, NaSSAs, and NaRIs: New agents for the treatment of depression. Lancet. 2000;355:911-918.

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-HT_2 antagonist as well as a 5-HT reuptake inhibitor
- Usual dose is 150-600 mg/day
- Adverse events include
  - · sedation
  - · dizziness
  - · orthostatic hypotension
  - · cognitive slowing
  - · priapism

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 SSRI therapy, 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-HT_1, avoids 5-HT_2 and 5-HT_3.
- 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

19. Puzantian T. Mirtazapine, an antidepressant. American Journal of Health-System Pharmacy. 1998;55:44-49.

Mirtazapine adverse events

- Sedation – due to H_1 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

22. Martin TG. Serotonin Syndrome. Ann Emerg Med. 1996;28:520-526.

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

23. Brown TM, Skop BP, Mareth TR. Pathophysiology and Management of the Serotonin Syndrome. Ann Pharmacother. 1996;30:527-533.

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

Action on serotonin	Medications
Increase 5-HT synthesis	L-tryptophan
Decrease 5-HT metabolism	Isocarboxazid Phenelzine Selegiline Tranylcypromine
Increase 5-HT release	Amphetamines Cocaine reserpine

24. Mills KC. Serotonin Syndrome. American Family Physician. 1995;52:1475-1482.

Drugs involved in serotonin syndrome

Inhibit 5-HT uptake	TCAs, SSRIs, nefazodone, trazodone, amphetamines, cocaine, dextromethorphan, meperidine, venlafaxine, St. John's Wort
Direct 5-HT receptor agonists	Buspirone, LSD, sumatriptan, Lithium
DA agonists	Amantadine, bromocriptine, bupropion, levodopa

Management of serotonin syndrome

- Supportive care
- Discontinuation of all serotonergic drugs
- Consider use of a 5-HT antagonist
  - cyproheptadine: 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

25. Mills KC. Serotonin Syndrome. American Family Physician. 1995;52:1475-1482.

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.

21. Institute for Clinical Systems Improvement. Major Depression in Adults for Medical Health Care Providers. Bloomington (MN). 2002;p.43. Available at www.guideline.gov.

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

Depression Guideline Panel. *Depression in Primary Care: Vol 2. Treatment of Major Depression: Clinical Practice Guideline Number 5.* Rockville, MD: AHCPR, US Department of Health and Human Services; 1993:23.