Dr. Jack's MedQuik Guide

A Psychotropic Medication Guide for Board Exam Preparation

By

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Part 1: FDA Approvals and New Indications for Medications of Interest to Psychiatrists 2012-2015

Abilify Maintena (aripiprazole): once monthly extended-release injectable suspension for the treatment of **schizophrenia** (February 2013)

Belsomra (suvorexant)**:** Merck; For the treatment of **insomnia** (Approved August 2014)

Belviq (lorcaserin): for the treatment of **obesity** (Approved June 2012)

Brintellix (vortioxetine): for the treatment of **major depressive disorder** (Approved Oct 2013)

Contrave (naltrexone HCl and bupropion HCl): Takeda Pharmaceuticals U.S.A.; For **chronic weight management** (Approved September 2014)

Fetzima (levomilnacipran): for the treatment of **major depressive disorder** (Approved July 2013)

Hetlioz (tasimelteon)**:** Vanda Pharmaceuticals; For the treatment of **non-24-hour sleep-wake disorder in the totally blind** (January 2014)

Horizant (gabapentin enacarbil): for the treatment of **restless legs syndrome** (Approved April 2011) and for **postherpetic neuralgia** (Approved July 2012)

Namzaric (memantine extended-release + donepezil hydrochloride): Forest Laboratories; For the treatment of **moderate to severe dementia of the Alzheimer's type** (Approved December 2014)

Neupro (Rotigotine Transdermal System): for the treatment of **restless legs syndrome** (Approved April 2012)

Osphenia: (ospemifene): for the treatment of **dyspareunia** (Approved Febraury 2013)

Qsymia (phentermine + topiramate extended-release): for the treatment of **chronic weight management** (Approved July 2012)

Stendra (avanafil): for the treatment of **erectile dysfunction** (Approved April 2012)

Viibryd (vilazodone): for the treatment of **major depressive disorder**. (Approved January 2011)

Vyvanse (lisdexamfetamine dimesylate): new indication for **adult ADHD** (February 2012)

Part 2: List of Psychiatric Disorders With Their FDA Approved Medications

Disorders with a Childhood Onset

ADHD:

Atomoxetine (Strattera) for children, adolescents, & adults;

Amphetamine Formulations:
Dextroamphetamine (Dexedrine, Dextrostat,)
Mixed Amphetamine Salts (Adderall)
Mixed Amphetamine Salts Extended Release (Adderall XR)
Methamphetamine (Desoxyn)
Lisdexamfetamine (Vivanse)

Methylphenidate Formulations:
Methylphenidate (Ritalin)
Methylphenidate extended or continuous release (Ritalin SR, Ritalin LA, Concerta ER, Metadate CD)
Methylphenidate Transdermal Patch ((Daytrana)
Dexmethylphenidate (Focalin)
Dexmethylphenidate extended release (Focalin XR)

Alpha 2 Agonist:
Guanfacine extended release (Intuniv)

Note: Pemoline – removed from US market due to its association with life-threatening hepatic failure

Note: Dexmethylphenidate: d-*threo*-enantiomer of racemic methylphenidate, the more pharmacologically active enantiomer of methylphenidate

Tourette's Disorder: Haloperidol for control of tics and vocal utterances; Pimozide (Orap) for patients who have failed to respond to other medications

Childhood Enuresis: Imipramine (Tofranil)

Irritability Associated with Autistic Disorder: Risperidone for children & adolescents 5-16 years of age; Aripiprazole for children & adolescents 6-17 years of age.

Cognitive Disorders

Dementia of Alzheimer's Type

Mild to Moderate Dementia of Alzheimer's Type: Donepezil (Aricept); Rivastigmine (Exelon, Exelon Patch); Galantamine (Razadyne, Razadyne ER); Caprylic Triglyceride Medical Food (Axona)

Moderate to Severe Dementia of Alzheimer's Type: Donepezil; Memantine (Namenda); Memantine extended-release + Donepezil (Namzaric)

Dementia Associated with Parkinson's Disease: Rivastigmine

Substance Use Disorders

Smoking Cessation: Bupropion (Zyban); Transdermal Nicotine Patch, Varenicline (Chantix)

Alcohol Withdrawal: Diazepam (Valium); Chlordiazepoxide (Librium); Oxazepam (Serax)

Alcohol Dependence: Acamprosate (Campral); Disulfiram (Antabuse); Naltrexone (Vivatrol); Ondansetron (Zofran) is used but not FDA indicated

Opioid Dependence: Methadone, Buprenorphine; Naltrexone-Buprenorphine

Benzodiazepine Sedation Reversal: Flumazenil (Romazicon)

Psychotic Disorders

Schizophrenia:

First Generation Antipsychotics: Chlorpromazine (Thorazine); Thioridazine; Loxapine (Loxitane); Perphenazine (Trilafon); Molindone (Moban); Thiothixene (Navane); Trifluroperazine (Stelazine); Fluphenazine (Prolixin); Haloperidol (Haldol)

Second Generation Antipsychotics (for adults unless specified): Clozapine (Clozaril); Risperidone (Risperdal) for adolescents & adults; Risperidone Depot (Risperdal Consta); Olanzapine (Zyprexa); Quetiapine (Seroquel); Ziprasidone (Geodon); Aripiprazole (Abilify) for adolescents & adults; Paliperidone (Invega); Paliperidone Depot (Invega Sustenna); Iloperidone (Fanapt); Asenipine (Saphris); Lurasidone (Latuda)

Schizoaffective Disorder: Paliperidone (Invega)

Agitation Associated with Schizophrenia and Mania: Olanzapine IM

Mood Disorders

Major Depressive Disorder:

TCA: Amoxapine; Amitriptyline, Nortriptyline (Pamelor); Imipramine (Tofranil); Desipramine (Norpramin); Doxepin (Sinequan)

MAOI: Isocarboxazid (Marplan); Phenelzine (Nardil); Tranylcypromine (Parnate) for MDD without Melancholia, Selegiline Transdermal (Emsam)

SSRI: Fluoxetine (Prozac) for children, adolescents & adults; Sertraline (Zoloft), Paroxetine (Paxil & Paxil CR); Citalopram (Celexa); Escitalopram (Lexapro) for adolescents (12-17 year olds) and adults

SSRI+: Vilazodone (Viibryd), Vortioxetine (Brintellix)

SNRI: Venlafaxine (Effexor & Effexor XR); Desvenlafaxine (Pristiq); Duloxetine (Cymbalta); Levomilnacipran(Fetzima)

Other: Maprotiline; Trazodone (Desyrel); Bupropion (Wellbutrin); Mirtazapine (Remeron)

Aripiprazole: Adjunctive Treatment

Depression without Melancholic Features: Tranylcypromine (Parnate)

Depression with Anxiety: Limbitrol (Amitriptyline and Chlordiazepoxide); Doxepin (Sinequan); Lorazepam (Ativan) for anxiety associated with depressive symptoms

Bipolar Disorder:

Bipolar Manic or Mixed Episodes, Acute Treatment: Lithium for mania only (Eskalith, Lithobid); Divalproex Sodium (Depakote); Risperidone for children 10-17 years of age & adults; Olanzapine (Zyprexa, ZYDIS); Quetiapine; Ziprasidone; Aripiprazole, Carbamazepine ER (Equetro)

Bipolar Depression, Acute Treatment: Olanzapine-Fluoxetine combo (Symbyax); Quetiapine

Bipolar Maintenance: Lithium; Olanzapine; Risperidone Long-Lasting Injectable (Risperdal Consta) as monotherapy or as adjunct therapy to Lithium or Valproate; Aripiprazole for maintenance of manic and mixed episodes; Lamotrigine (Lamictal) to delay onset of a mood episode; Quetiapine as adjunct therapy to lithium or divalproex

Premenstrual Dysphoric Disorder: Fluoxetine (Serafim only), Sertraline, Paroxetine CR (Paxil CR)

Anxiety Disorders

Anxiety Disorders Or Anxiety Symptoms: Chlordiazepoxide (Librium); Chlorazepate (Tranxene); Hydroxyzine (Vistoril); Meprobamate (Miltown); Lorazepam (Ativan); Oxazepam (Serax); Buspirone (Buspar)

Panic Disorder: Alprazolam (Xanax); Clonazepam (Klonopin); Fluoxetine in children, adolescents & adults; Paroxetine; Sertraline; Venlafaxine (Effexor XR only)

GAD: Alprazolam, Paroxetine; Duloxetine, Escitalopram, Venlafaxine (Effexor XR only)

OCD: Clomipramine (Anafranil) in children, adolescents, and adults; Fluvoxamine for children, adolescents, & adults; Fluoxetine for children, adolescents & adults; Sertraline for children, adolescents, & adults; Paroxetine

Social Anxiety Disorder: Paroxetine; Sertraline; Venlafaxine (Effexor XR only)

PTSD: Paroxetine; Sertraline

Eating Disorder Medications

Bulimia Nervosa: Fluoxetine

Sleep Disorders

Insomnia

Benzodiazepines: Flurazepam (Dalmane); Quazepam (Doral); Estazolam (Prosom); Temazepam (Restoril); Triazolam (Halcion)

Non-Benzodiazepine Hypnotics: Zolpidem (Ambien & Ambien CR); Zaleplon (Sonata); Eszopiclone (Lunesta)

Melatonin Agonist: Ramelteon (Rozerem)

Antihistamine: Doxepin (Silenor)

Note: These medications are for Sleep Initiation only: Triazolam; Zolpidem; Zaleplon; Ramelteon

Note: These medications are for Sleep Initiation and Sleep Maintenance: Flurazepam, Quazepam, Estazolam, Temazepam, Ambien CR, and Eszopiclone

Narcolepsy:

To Improve Daytime Wakefulness: Dextroamphetamine (Dexedrine); Methylphenidate (Ritalin); Modafinil (Provigil)

Hypnotic Agent: Sodium Oxybate (Xyrem)

Obstructive Sleep Apnea: Modafinil

Shift Work Sleep Disorder: Modafinil

Sexual Disorders

Dyspareunia: Estradiol Vaginal Ring (Estring)

Erectile Dysfunction: Tadalafil (Cialis); Vardenafil (Levitra); Sildenafil (Viagra); Alprostadil injection (Edex Injection, Caverject Impulse Injection)

Diagnosis of Erectile Dysfunction: Alprostadil (Caverject Impulse Injection)

Pain Disorders

Migraine Headaches:

Prophylaxis: Divalproex Sodium; Topiramate (Topamax); propranolol (Inderal LA); timolol (Blocarden)

Acute Treatment: Almotriptan (Axert); Naratriptan (Amerge); Rizatriptan (Maxalt); Sumatriptan (Imitrex)

Diabetic Peripheral Neuropathic Pain: Duloxetine (Cymbalta)

Dyspareunia: Ospemifene (Osphena) is an estrogen agonist/antagonist indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause

Pruritis Due to Allergies: Hydroxyzine (Vistaril)

Part 3: Review of Individual Psychotropic Medications

ADHD Medications

Amphetamine

- **Formulations**
  - Dextroamphetamine (Dexedrine, Dextrostat,)
  - Mixed Amphetamine Salts (Adderall)
  - Mixed Amphetamine Salts Extended Release (Adderall XR)
  - Methamphetamine (Desoxyn)
  - Lisdexamfetamine (Vivanse)
- **Indications**
  - ADHD
- **Mechanisms of Action**
  - Norepinephrine and Dopamine synaptic release
  - Norepinephrine and Dopamine reuptake inhibitor
- **Black Box Warnings**
  - Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods may lead to dependence.
  - Misuse of amphetamines may cause sudden death and serious cardiovascular events.
- **Alerts & Warnings**
  - Severe Liver Injury (W)
  - Serious Cardiovascular Events, including Sudden Death (W)
  - Emergence of New Psychotic or Manic Symptoms
- **Dosing**
  - Mixed Amphetamine Salts (Adderall)
    - Age 3-5: start at 2.5 mg qd; increase by 2.5mg q week until response
    - Age 6-12: start at 5mg qd; increase by 5mg q week until response
    - Age 12 and older: start 5mg bid; increase by 10mg q week until response
  - Mixed Amphetamine Salts ER (Adderall XR)
    - Age 6-12: start at 10mg qd; increase by 5-10mg q week until response
    - Age 13-17: start at 10mg qd; increase to 20mg qd if inadequate response
    - Adults: start 20mg qd;
    - Doses over 30mg not recommended
  - Lisdexamfetamine (Vivanse)
    - Age 6-12: start at 30mg qd; increase by 10mg q week up to 70mg qd as needed

Methylphenidate

- **Formulations**
  - Methylphenidate (Ritalin)
  - Methylphenidate extended or continuous release (Ritalin SR, Ritalin LA, Concerta ER, Metadate CD)
  - Methylphenidate Transdermal Patch ((Daytrana)
  - Dexmethylphenidate (Focalin)
  - Dexmethylphenidate extended release (Focalin XR)
- **Indications**
  - ADHD
- **Mechanism of action**
  - Norepinephrine and Dopamine synaptic release
  - Norepinephrine and Dopamine reuptake inhibitor
- **Alerts, Warnings, Precautions**
  - Sudden death in those with pre-existing cardiac abnormalities
  - Adults: sudden death, stroke, MI reported
  - Increased risk of hypertension, seizures, suppression of growth
  - Psychiatric: emergence of mania, psychosis, aggression
- **Contraindications**
  - In those with anxiety, tension, agitation
  - Within 2 weeks of stopping MAOI
- **Methylphenidate Dosing**
  - Age 6 and over: start 5mg bid; increase 5-10mg q week until response
  - Adults: start 5mg bid or tid; increase 5-10mg q week until response
  - Doses over 60mg qd not recommended

Atomoxetine (Strattera)

- **Indications**
  - ADHD in Children, Adolescents, and Adults
- **Mechanism of Action**
  - SNRI
- **Black Box Warning**
  - Suicidal thoughts in Children and Adolescents: Pooled results from 12 trials (over 2200 patients) revealed a greater risk of suicidal ideation early during treatment in those receiving STRATTERA compared to placebo. The average risk of suicidal ideation in patients receiving STRATTERA was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred.
- **Alerts & Warnings**
  - Severe Liver Injury (W)
  - Serious Cardiovascular Events, including Sudden Death (W)
  - Emergence of New Psychotic or Manic Symptoms
  - Contraindicated in Narrow Angle Glaucoma
- **Drug-Drug Interactions**
  - Avoid with MAOIs
  - Administer with caution systemically-administered beta-2-agonists; they may increase pulse and blood pressure

  - Metabolized by CYP2D6; decrease dose when giving with fluoxetine, paroxetine, quinidine and other 2D6 inhibitors; CYP2D6 inhibitors increase Atamoxetine's AUC by 6-8 fold
- **Dosing**
  - In individuals up to 70 kg
    - Start 0.5mg / kg and after 3 days increase to 1.2 kg / kg
  - In individuals over 70 kg
    - Start 40mg and after 3 days increase to 80mg qd, either single of divided dose. Increase to 100mg qd if insufficient response
  - Hepatic Insufficiency
    - If moderate: decrease to 50% of starting and target dose
    - If severe: decrease to 25% of starting and target doses

Guanfacine Extended Release (Intuniv)

- **Indications**
  - ADHD in Children & Adolescents ages 6-17 years
- **Mechanism of Action**
  - Alpha 2_A agonist
- **Warnings**
  - Hypotension, Bradycardia & Syncope
  - Sedation & Somnolence
  - Pregnancy Category B
- **Dosing**
  - If switching from immediate-release guanfacine, discontinue that treatment, and titrate with Guanfacine Extended Release (Intuniv) according to this schedule.
  - Begin at a dose of 1 mg qd and adjust in increments of no more than 1 mg/week.
  - Maintain the dose at 1-4 mg once daily, depending on clinical response and tolerability.
- **Drug-Drug Interactions**
  - CYP 3A4 inhibitors (ketoconazole, grapefruit) may increase guanfacine levels
  - CYP 3A4 inducers (rifampin) may decreae guanfacine levels
  - Valproic acid levels may be increased when co-administered with guanfacine

Note: Pemoline – removed from US market due to its association with life-threatening hepatic failure

Dementia Medications

Donepezil (Aricept)

- **Indications**
  - Dementia of Alzheimer Type, Mild to Moderate
  - Dementia of Alzheimer Type, Severe
- **Mechanism of Action**
  - Reversible inhibitor of Acetylcholinesterase
  - Increases levels of acetylcholine by inhibiting its degradation
- **Alerts & Warnings**
  - Anesthesia: As a Cholinesterase Inhibitor, it is likely to exaggerate Succinylcholine-type muscle relaxation during anesthesia

  - Cardiovascular Conditions, including risk of bradycardia or heart block
  - Digestive Conditions, including risk of increased gastric acid secretion and risk of ulcer
  - Genitourinary Conditions, including bladder outflow obstruction
  - Neurological Conditions, including seizures
  - Pulmonary: Use with caution in those with Asthma or Obstructive Pulmonary Disease
- **Dosing**
  - Start 5mg q evening; increase to 10mg if insufficient response

Rivastigmine (Exelon)

- **Formulations:** capsules, oral solution, patch
- **Indications**
  - Dementia of Alzheimer's Type, Mild to Moderate
  - Dementia associated with Parkinson's Disease (DPD), Mild to Moderate
- **Mechanism of Action**
  - Reversible inhibitor of Acetylcholinesterase
- **Alerts and Warnings**
  - Gastrointestinal: nausea, vomiting, weight loss, anorexia, peptic ulcers, GI bleeding
  - Anesthesia: As a Cholinesterase Inhibitor, it is likely to exaggerate Succinylcholine-type muscle relaxation during anesthesia
  - Cardiovascular Conditions, including risk of bradycardia or heart block
  - Genitourinary Conditions, including bladder outflow obstruction
  - Neurological Conditions, including seizures
  - Pulmonary: Use with caution in those with Asthma or Obstructive Pulmonary Disease
- **Oral Dosing**
  - DAT: start at1.5 mg bid; increase by 1.5mg bid q 2 weeks up to 6mg bid
  - DPD: start at1.5 mg bid; increase by 1.5mg bid q 4 weeks up to 6mg bid
- **Patch Dosing**
  - Apply Exelon Patch 4.6mg / 24hrs for 4 weeks and increase to 9.5mg / 24hrs.

Galantamine (Razadyne)

- **Formulations**
  - Galantamine immediate release (IR) as tablets and oral solution
  - Galantamine ER
- **Indication**
  - Dementia of Alzheimer's Type, Mild to Moderate
- **Mechanism of Action**
  - Reversible inhibitor of Acetylcholinesterase
- **Alerts and Warnings**
  - Anesthesia: As a Cholinesterase Inhibitor, it is likely to exaggerate Succinylcholine-type muscle relaxation during anesthesia
  - Cardiovascular Conditions, including risk of bradycardia or heart block
  - Digestive Conditions, including risk of increased gastric acid secretion and risk of ulcer
  - Genitourinary Conditions, including bladder outflow obstruction
  - Neurological Conditions, including seizures
  - Pulmonary: Use with caution in those with Asthma or Obstructive Pulmonary Disease
- **Dosing**

  - Galantamine IR: start 4mg bid; increase in 4 weeks (minimum) to target maintenance dose of 8mg bid; increase to 12mg bid in 4 weeks if inadequate response
  - Galantamine ER (Razadyne ER): Start at 8mg qd; increase in 4 weeks (minimum) to target maintenance dose of 16mg; increase to 24mg qd in 4 weeks if inadequate response
  - Hepatic Insufficiency: dose no higher than 16mg qd
  - Renal Insufficiency: dose no higher than 16mg qd
- **Drug-Drug Interactions**
  - Metabolized by CYP2D6 and CYP3A4: dose usually does NOT need to be adjusted when given with CYP2D6 and CYP3A4 inhibitors (e.g., ketocanozole) or in poor metabolizers

Memantine (Namenda)

- **Formulations:** tablets and oral solution
- **Indication**
  - Dementia of Alzheimer Type, Moderate-Severe
- **Mechanism of Action**
  - Persistent activation of central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate is hypothesized to contribute to Alzheimer's Disease. Memantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist which binds preferentially to the NMDA receptor-operated cation channels.
- **Alerts and Warnings**
  - No Alerts and Warnings
- **Dosing**
  - Start 5mg qd; target maintenance dose is 20mg qd as bid doses; increase by 5mg qd every week until target
  - Severe Renal Failure: target dose is 5mg bid
  - May be prescribed in combination with the Acetylcholinesterase inhibitors (e.g., Aricept)

Caprylic Triglyceride (Axona)

- **Formulations:** A medical Food, a powder mixed with water
- **Indication**
  - Dementia of Alzheimer Type, mild to moderate
- **Mechanism of Action**
  - Glucose is the primary source of energy for the brain. Alzheimer's disease (AD) patients exhibit a decline in the ability to metabolize glucose in the brain. Inadequate glucose leads to damage resulting in impaired memory and cognition and brain shrinkage. These metabolic defects in the brain often appear 10 to 20 years earlier than other Alzheimer's symptoms.
  - Caprylic Triglyceride (Axona) is converted by the liver into ketone bodies, which provide an alternative fuel for brain cells. Ketone bodies are naturally occurring compounds that are produced mainly by the liver from fatty acids during periods of extended fasting. Ketone bodies have been demonstrated to protect neurons.

  - Axona is a specially formulated medical food intended for the clinical dietary management of the metabolic processes associated with mild-to-moderate AD
  - Axona safely increases plasma concentrations of ketone bodies (predominantly BHB), which can provide an alternative energy source for the brains of AD patients
  - Clinical trials have shown that Axona improves cognitive function in some AD patients
  - Axona is administered under physician supervision and dispensed by prescription
- **Alerts and Warnings**
  - None
  - Axona's adverse events are primarily limited to the GI tract
- **Dosing**
  - Axona is administered orally once a day, as a powder to be mixed with water or other foods/liquids. Administer after a meal, preferably breakfast or lunch
- **Drug-Drug Interactions**
  - Axona does not interact with medications and can be taken with commonly prescribed AD medications
- **What Is a Medical Food?**
  - A Medical Food is an FDA-regulated product, in a relatively new category of medical protocols defined by Congress as part of the Orphan Drug Act. A Medical Food is formulated to be consumed or administered enterally under the supervision of a physician and is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. Medical Foods can be prescription products, but are different than drugs or dietary supplements (also called nutraceuticals) in several aspects, such as their claims. Claims for both Medical Foods and drugs must be supported by solid laboratory and clinical data. Medical Food ingredients have Generally Recognized As Safe (GRAS) designation, the highest FDA standard of safety given to foods. Medical Foods, sometimes prescribed in addition to drugs, nonetheless represent an entirely different scientific and medical approach to managing diseases.

Note on above medications for the Dementias: There is no evidence that they arrest or slow the progression of the disease process.

Substance Use Disorder Medications

Acamprosate (Campral)

- **Indication**
  - Maintenance of abstinence from alcohol in patients with Alcohol Dependence
  - Acamprosate is hypothesized to restore the balance between glutamate, an excitatory neurotransmitter, and GABA, an inhibitor neurotransmitter
- **Warnings**
  - No package insert warnings
  - Precautions: Suicide: Adverse events related to suicidal behaviors were more common in acamprosate-treated patients than in those treated with placebo.
- **Contraindication**
  - **Avoid in severe renal failure**
- **Dosing**

- 666mg tid without regard to meals (comes in 333mg capsules)
- Start treatment as soon as possible after alcohol withdrawal and establishment of sobriety
- Maintain med in event of relapse
- In moderate renal insufficiency (30-50 mL/min): dose of 333mg tid
- In severe renal insufficiency: do NOT prescribe
- Not hepatically metabolized

Disulfiram (Antabuse)

- **Indication**
  - Disulfiram is an aid in the management of selected chronic alcohol patients who want to remain in a state of enforced sobriety so that supportive and psychotherapeutic treatment may be applied to best advantage.
- **Mechanism of Action**
  - Disulfiram blocks the oxidation of alcohol at the stage of acetaldehyde (preventing further oxidation into acetate) causing buildup of acetaldehyde. The 5-10 times increased levels of acetaldehyde cause the Alcohol-Disulfiram Reaction.
- **Boxed Warning**
  - Disulfiram should never be administered to a patient when the patient is in a state of alcohol intoxication. The physician should instruct relatives accordingly. The patient should be educated regarding the alcohol-disulfiram reaction and be strongly cautioned against the surreptitious consumption of alcohol while taking the medication.
  - Alcohol-Disulfiram Reaction, even small amounts, produces flushing, throbbing in head and neck, respiratory problems, nausea, copious vomiting, sweating, thirst, chest pain, palpitation, dyspnea, hyperventilation, tachycardia, hypotension, syncope, marked uneasiness, weakness, vertigo, blurred vision, and confusion. In severe reactions there may be respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions, and death.
- **Cautions with Concurrent Conditions**
  - Due to accidental Alcohol-Disulfiram Reaction, Disulfiram should be used with EXTREME CAUTION in patients with Diabetes Mellitus, Hypothyroidism, Epilepsy, cerebral damage, nephritis, and hepatic cirrhosis or insufficiency.
  - Avoid in pts with severe myocardial disease, or coronary artery occlusion
  - Avoid in pts with psychosis
  - Use in Pregnancy: Disulfiram use has not been established in pregnancy
- **Drug-Drug Interactions**
  - Avoid with metronidazole, paraldehyde. alcohol, or alcohol-containing preparations, such as cough syrups or sleep tonics
- **Dosing**
  - 250mg qd (range of 125-500mg qd); continued until pt fully rehabilitated.

Naltrexone (Revia, Vivitrol)

- **Formulations**
  - Immediate release tablet (Revia)
  - Extended release injectable suspension (Vivitrol)
- **Indications**
  - Treatment of Alcohol Dependence

  - Treatment of Opioid Dependence
  - Blockade of the effects of exogenously ingested opioids
- **Mechanism of Action**
  - Pure opioid antagonist that reversibly blocks opioid effects
  - Naltrexone is a synthetic congener of oxymorphone
- **Warnings**
  - Hepatocellular damage if given in excessive doses
  - **Contraindicated in cases of acute hepatitis or liver failure**
  - Unintended Precipitation of Abstinence: to prevent occurrence of an opioid abstinence syndrome, patients should be opioid-free for a minimum of 7-10 days prior to starting naltrexone. If the physician believes there is a risk of precipitating abstinence syndrome, a naloxone challenge should be administered.
  - Attempt to overcome Blockade: Patients may attempt to overcome the opioid blocking effect of naltrexone by ingesting large amounts of exogenous opioids. As a consequence, the patient may suffer from life-threatening opioid intoxication.
  - Ultra-Rapid Opioid Withdrawal: The use of naltrexone has not been established in Ultra-Rapid Detoxification Programs.
- **Contraindications**
  - Avoid in pts currently dependent on opioids or has taken opioids (including appropriate use as an analgesic) in the last 7-10 days
  - Avoid in pts in acute opioid withdrawal
  - If any question that patient may have ingested opioids, perform the **Naloxone Challenge Test** (Inject Naloxone 0.2mg IV or 0.8mg SQ; observe for 30s for withdrawal; if none present, may Rx Naltrexone)
- **Dosing**
  - Naltexone IR: 50mg qd
  - Vivitrol: 380mg IM injection q 4 weeks

Buprenorphine

- **Formulations**
  - Buprenorphine + Naloxone (Bunavail, Suboxone, Zubsolv)
  - Buprenorphine (Subutex)
- **Indications**
  - Treatment of Opioid Dependence
- **Note**
  - Buprenorphine is a Schedule III narcotic under the Controlled Substances Act
  - It can only be dispensed by physicians who've met certifying requirements and have notified the Dept of Health and Human Services of their intent to prescribe.
  - Naloxone is inactivated by gastric acid when Suboxone is taken orally and thus plays no pharmacodynamic effect. It is added to minimize IV or IM use, in which naloxone may precipitate opioid withdrawal.
- **Mechanism of Action**
  - Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. In non-opioid-dependent subjects, BNP leads to opioid agonist effects which are limited by a ceiling effect.
  - Naloxone is an antagonist at the mu-opioid receptor. Naloxone has no clinical effect when Suboxone is taken sublingually. **Naloxone is included so that if buprenorphine**

+naloxone is abused and injected IV or taken IM, the naloxone causes opioid antagonist effects, and thus precipitating acute opioid withdrawal.
    - When buprenorpine alone or buprenorphine+naloxone are taken sublingually, they are clinically equivalent.
- **Warnings**
    - Respiratory depression
    - In case of overdose the primary management should be the re-establishment of adequate ventilation with mechanical assistance if required.
    - CNS depression
    - Dependence
    - Hepatitis and hepatic events: Cases of hepatitis have occurred.
    - Head injury and Increased Intracranial Pressure: Buprenorphine, like other powerful opioids may elevate cerebrospinal fluid pressure.
    - Opioid Withdrawal Effects
- **Dosing**
    - For Suboxone and Subutex: target is 12-16mg qd sublingually.
    - Buprenorphine without Naloxone is preferred during induction.
    - Induction with buprenorphine is started when objective signs of opioid withdrawal are seen.
    - Buprenorphine+naloxone is preferred for maintenance treatment (for unsupervised administration).
    - Titration (done quickly to minimize pt dropout and opioid withdrawal symptoms)
        - Day 1: Buprenorphine 8mg sl qd
        - Day 2: Buprenorphine 16 sl qd
        - Day 3: Buprenorphine+naloxone 16mg sl qd
- **Drug-Drug Interactions**
    - Buprenorphine is metabolized by CYP3A4. If CYP3A4 inhibitors are given, monitor closely. Dose decreases may be indicated.

Varenicline (Chantix)

- **FDA Indication**
    - Varenicline is a tablet used as an aid to smoking cessation treatment.
- **Mechanism of Action**
    - Partial agonist selective for α4β2 nicotinic acetylcholine receptor subtypes
- **Warnings**
    - Neuropsychiatric Symptoms, including changes in behavior, agitation, depressed mood, suicidal ideation and suicidal behavior.
    - Adverse effects were headache, nausea, insomnia, and abnormal dreams.
    - Pregnancy Category: C
- **Dosing**
    - Patient sets a date to stop smoking and then starts Varencline one week before that date.
        - Days 1 - 3: 0.5 mg once daily
        - Days 4 - 7: 0.5 mg twice daily
        - Day 8 – to end of treatment: 1 mg twice daily
    - For patients who remain abstinent after 12 weeks, may add another 12 week course to increase rate of long-term abstinence.

- Special populations: No dose change with hepatic impairment. No dose changes in the elderly but monitor effects due to decreased renal function.
- No meaningful drug-drug interactions.

Flumazenil (Romazicon)

- **Indication**
  - Flumazenil is an IV medication that is indicated for the complete or partial reversal of the sedative effects of benzodiazepines in cases 1) where general anesthesia has been induced and/or maintained with benzodiazepines, 2) where sedation has been produced with benzodiazepines for diagnostic and therapeutic procedures, and 3) for the management of benzodiazepine overdose.
- **Boxed Warning**
  - The use of Flumazenil has been associated with the occurrence of **seizures.**
  - Seizures are most frequent in patients who have been on benzodiazepines for long-term sedation or in overdose cases where patients are showing evidence of serious cyclic antidepressant overdose.
  - Practitioners should individualize the dosage of Flumazenil and be prepared to manage seizures.
- **Warnings**
  - Hypoventilation: Patients who have received Flumazenil for the reversal of benzodiazepine effects (after conscious sedation or general anesthesia) should be monitored for resedation, respiratory depression , or other residual benzodiazepine effects for an appropriate period (up to 120 minutes) based on the dose and duration of effect of the benzodiazepine employed.
- **Dosing** (administered IV in solution)
  - Reversal of conscious sedation
    - Adults: 0.2 mg IV over 15s; wait 45s; if needed another 0.2mg IV over 15s; may repeat up to total dose of 1.0mg
    - Peds: 0.01mg/kg IV over 15s; repeat up to 4 doses
  - Reversal of general anesthesia for adults: 0.2 mg IV over 15s; wait 45s; repeat up to 4 additional times every 60s.
  - Reversal of Benzodiazepine overdose in adults: 0.2 mg IV over 30s; wait 30s; repeat 0.3mg IV over 30s; further doses of 0.5mg IV over 30s can be given up to cumulative dose of 3mg.

LAAM or Levomethadyl Acetate Hydrochloride (ORLAAM)

- **Legacy Medication**
  - LAAM is a synthetic opioid agonist and was indicated in the management of opioid dependence.
  - LAAM has been off US market since August 2004 for causing torsades de pointes. Patients receiving it were switched to the use of Methadone.

Second Generation Antipsychotics

Clozapine (Clozaril)

- **FDA Indications**

  - Treatment Resistant Schizophrenia
  - Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorders (Clozaril brand only)
- **Mechanism of Action**
  - High affinity for D4 receptors (most antipsychotics work at D2)
  - Clozapine acts as an antagonist at adrenergic, histaminergic, cholinergic, and serotonergic receptors
- **Boxed Warnings**
  1. Agranulocytosis
     - Risk of agranulocytosis in unmonitored pts is 1-2%
     - Risk in monitored patients is 0.35%
  2. Seizures
  3. Myocarditis
  4. Other Adverse Pulmonary and Cardiac Effects (orthostatic hypotension, respiratory and cardiac arrest)
  5. Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- **Alerts & Warnings**
  - Hyperglycemia & Diabetes Mellitus
  - Cerebrovascular Adverse Events, including Strokes, in Elderly Patients with Dementia-Related Psychosis
  - Increased Risk of Death in Elderly Patients
  - Neuroleptic Malignant Syndrome
  - Tardive Dyskinesia
- **Dosing**
  - Start 12.5mg qd or bid; increase by 25mg qd up to target of 300-450mg qd in about 2 weeks. Schedule as bid doses.
  - Maintenance dose: increase as needed up to 600-900mg qd. Do not exceed 900mg qd. Median maintenance dose in treatment resistant pts was 600mg qd.
    - Seizure risk doubles above 600mg qd.
  - Treatment termination: decrease med over 12 weeks
  - Restarting after termination. If pt stopped meds for 2 days or longer, begin at 12.5mg qd or bid. You may be able to titrate up more quickly than initial titration.
- **Drug-Drug Interactions**
  - Take caution with Benzo's since cardiac arrest has occurred in combination.
  - These may increase Clozapine level: cimetidine, caffeine, ciprofloxacin, erythromycin, fluvoxamine
  - These may decrease Clozapine level: carbamazapine, phenytoin, rifampin, tobacco smoke

Risperidone (Risperdal)

- **Formulations**
  - Risperdal tablets, oral solution, and disintegrating tablets; Risperdal Consta
- **FDA Indications**
  - Schizophrenia in adults and adolescents
  - Bipolar Disorder, Manic & Mixed Episodes, Acute Treatment in children-adolescents 10 to 17 years of age & adults

  - Risperidal Consta: Maintenance Treatment (either as monotherapy or as adjunctive therapy with lithium or valproate) for Bipolar I Disorder
  - Irritability Associated with Autistic Disorder in children and adolescents 5-16 years of age.
- **Mechanism of Action**
  - Antagonist at D2 and $5HT_{2A}$
- **Boxed Warning**
  - Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- **Alerts & Warnings**
  - Hyperglycemia & Diabetes Mellitus
  - Cerebrovascular Adverse Events, including Strokes, in Elderly Patients with Dementia-Related Psychosis
  - Increased Risk of Death in Elderly Patients
  - Neuroleptic Malignant Syndrome
  - Tardive Dyskinesia
- **Dosing**
  - Adults: Start 2mg qd to target of 4-8mg qd
  - Adolescents: Start 0.5-1mg qd to target of 1-6mg qd
  - Children: Start 0.25-0.5mg qd to target of up to 2.5mg qd
  - Elderly, Debilitated, with Hepatic or Renal Impairment: Start 0.5mg bid. Increase as needed by 0.5mg bid
- **Drug-Drug Interactions**
  - Risperidone is metabolized by CYP2D6: take caution in concurrent use with CYP2D6 inhibitors: fluoxetine and paroxetine will increase risperidone levels by up to 9 fold

Paliperidone (Invega)

- **Formulations**
  - Extended Release Tablets (Invega): 1.5, 3, 6, 9 mg
  - Depot Injectable (Invega Sustenna)
- **FDA Indications**
  - Schizophrenia, acute and maintenance treatment
  - Schizoaffective Disorder, monotherapy or adjunct to mood stabilizer (tablets only)
- **Mechanism of Action**
  - Antagonist at the D2, $5HT_{2A}$ receptors (also at Histamine H1 and Adrenergic α1 and α2)
- **Boxed Warning**
  - Increased mortality in elderly patients with dementia-related psychosis
- **Alerts & Warnings**
  - QT Prolongation
  - Cerebrovascular adverse events, including strokes, in elderly patients with dementia-related psychosis
  - Hyperglycemia & Diabetes Mellitus
  - Neuroleptic Malignant Syndrome
  - Tardive Dyskinesia
  - Gastrointestinal – avoid in patients with severe GI narrowing
- **Dosing of Tablets (Invega)**
  - Prescribe 6mg qd. No dose titration is required. Increase to 12mg qd if needed no sooner than 5 days from initiation.

  - Renal Impairment
    - Moderate: top dose is 6mg qd
    - Severe: prescribe 3mg qd
  - Note: Invega tablets must be swallowed whole with liquid. They cannot be chewed.
- **Dosing of Depot Injectable (Invega Sustenna)**
  - Initiate Invega Sustenna with a dose of 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle.
  - The recommended **monthly** maintenance dose is 117 mg; some patients may benefit from lower or higher maintenance doses within the recommended range of 39 mg to 234 mg based on individual patient tolerability and/or efficacy.
  - Following the second dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.
- **Drug-Drug Interactions**
  - Low drug-drug interactions. Paliperidone is not substantially metabolized by CYP450 enzymes.

Olanzapine

- **Formulations**
  - Zyprexa, ZYDIS oral disintegrating tablets, Zyprexa injection
- **FDA Indications**
  - Schizophrenia
  - Bipolar Disorder: mixed and manic episodes; acute treatment; either as monotherapy or in combination with Lithium or Depakote
  - Bipolar Disorder: maintenance treatment
  - Zyprexa IM is indicated for agitation associated with Schizophrenia or Mania.
- **Mechanism of Action**
  - Antagonist to Serotonin $5HT_{2A/2C}$, $5HT_6$, Dopamine D_{1-4}, Histamine H_1, and Adrenergic α_1 receptors
- **Boxed Warning**
  - Increased mortality in elderly patients with dementia-related psychosis
- **Alerts & Warnings**
  - Hyperglycemia & Diabetes Mellitus
  - Cerebrovascular Adverse Events, including Strokes, in Elderly Patients with Dementia-Related Psychosis
  - Increased Risk of Death in Elderly Patients
  - Neuroleptic Malignant Syndrome
  - Tardive Dyskinesia
  - Orthostatic Hypertension
- **Dosing**
  - Schizophrenia: Start 5-10mg qd. Increase by 5mg per day increments up to 20mg qd as needed.
  - Mania: Start 15mg qd; increase to 20 mg qd as needed
  - Combination with Lithium or Depakote: Start 10mg qd
  - IM dosing: Start 10mg IM; repeat every 2-4 hrs up to total dose of 30mg IM.
- **Drug-Drug Interactions**
  - Olanzapine is metabolized by CYP1A2 and several other enzymes. Carbamazepine increases clearance by 50%. May need to increase olanzapine dose.

- Caution with antihypertensives due to Olanzapine's adrenergic α_1 receptor antagonism

Olanzapine-Fluoxetine Combo (Symbyax)

- **FDA Indications**
  - Bipolar Depression
- **Boxed Warning**
  - Increased Risk of Suicide in Children & Adolescents
  - Increased Mortality In Elderly Persons With Dementia-Related Psychosis
- **Alerts & Warnings**
  - Life-threatening Serotonergic Syndrome when used with Triptan Medications.
  - Persistent Pulmonary Hypertension of the Newborn
  - Hyperglycemia & Diabetes Mellitus
  - Cerebrovascular adverse events, including strokes, in elderly patients with dementia-related psychosis
  - Neuroleptic Malignant Syndrome
  - Tardive Dyskinesia
  - Orthostatic Hypertension
- **Dosing**
  - Start 6mg/25mg tablet (Olanzapine/Fluoxetine). Increase to 18mg/75mg as needed

Quetiapine (Seroquel)

- **Formulations**
  - Seroquel, Seroquel XR
- **FDA Indications**
  - Schizophrenia
  - Bipolar Disorder, depressive episodes, acute treatment
  - Bipolar Disorder, manic episodes, acute treatment
  - Bipolar Disorder, maintenance treatment as adjunct
- **Mechanism of Action**
  - Antagonist at Dopamine D1 and D2, and Serotonin $5HT_{1a}$ and $5HT_2$, (Also at Histamine H1, and Adrenergic α1 and α2)
- **Boxed Warnings**
  - Increased Risk of Suicide in Children & Adolescents
  - Increased Mortality In Elderly Persons With Dementia-Related Psychosis
- **Alerts & Warnings**
  - Neuroleptic Malignant Syndrome
  - Tardive Dyskinesia
  - Hyperglycemia & Diabetes Mellitus
  - Cataracts
- **Dosing**
  - Bipolar Depression: Start: 50mg hs on day 1 and increase by 100mg each subsequent day up to 300mg qhs. Patients increased up to 600mg daily showed no additional benefit.
  - Bipolar Mania: Start at 100mg on day 1 and increase by 100mg each subsequent day up to 400 mg. Give bid schedule. Increase further to 800mg daily as needed.
  - Schizophrenia: Start 25mg bid. Increase by increments of 25-50mg bid until target dose of 300-400mg daily is reached. Increase up to 800mg daily as needed.

  - In Hepatic Impairment: Start 25mg daily and increase by 25-50mg daily until target dose is reached.
- **Drug-Drug Interaction**
  - Phenytoin increases quetiapine elimination. May need to increase it when given concurrently with phenytoin.

Ziprasidone (Geodon)

- **Formulations**
  - Geodon, Geodon injection
- **FDA Indications**
  - Schizophrenia
  - Bipolar Disorder, manic & mixed episodes, acute treatment
  - Ziprasidone Intramuscular: Acute agitation in schizophrenic patients
- **Mechanism of Action**
  - Antagonist at the D2, $5HT_{2A}$, and $5HT_{1D}$ receptors
  - Agonist at the 5HT1A receptor
  - Serotonin and norepinephrine reuptake inhibitor
- **Boxed Warnings**
  - Increased mortality in elderly persons with dementia-related psychosis
- **Alerts & Warnings**
  - QT Prolongation and risk of sudden death
  - Hyperglycemia & Diabetes Mellitus
  - Neuroleptic Malignant Syndrome
  - Tardive Dyskinesia
- **Dosing**
  - Schizophrenia: Start 20mg bid with food. Increase by increments of 20mg bid up to 100mg bid as needed.
  - Mania: Start 40mg bid with food. Increase to 60-80mg bid on second day
  - IM dose: 10-20mg IM for agitation up to 40mg per day.
- **Drug-Drug Interaction**
  - Ziprasidone is metabolized by CYP3A4. Its levels will decrease with carbamazepine and increase with ketoconazole.
  - Ziprasidone did little effect on metabolism of other drugs
  - Avoid with prolongers of QTc interval: dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, **mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide**, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus.

Aripiprazole (Abilify)

- **Formulations**
  - Abilify tablet, oral disintegrating tablet, oral solution, IM injection
  - Abilify Maintena long-acting injection
- **FDA Indications**
  - Schizophrenia, acute treatment for adults and adolescents
  - Bipolar Disorder, manic & mixed episodes, acute & maintenance treatment
  - Agitation Associated with Schizophrenia or Bipolar Disorder

  - Major Depressive Disorder, adjunctive treatment
  - Irritability Associated with Autistic Disorder
- **Mechanism of Action**
  - Partial agonist at Dopamine D_2 and Serotonin 5-HT_{1A} receptors, and antagonist at Serotonin 5-HT_{2A} receptor
- **Boxed Warning**
  - Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- **Alerts & Warnings**
  - Hyperglycemia & Diabetes Mellitus
  - Cerebrovascular adverse events, including strokes, in elderly patients with dementia-related psychosis
  - Neuroleptic Malignant Syndrome
  - Tardive Dyskinesia
- **Dosing**
  - Start 10-15mg qd. Increase to 30mg qd as needed but no earlier than 2 weeks.
  - Peds Dose for Bipolar (age 10-17): Start 2mg qd, increase to 5mg qd in 2 days and to target of 10mg qd in 2 days. Max of 30mg qd.
  - For Depression Adjunct: Start at 2-5mg qd and increase to target of 15mg qd in 5mg increments qweek.
  - For Autism: Initiate at 2 mg/day. Increase to 5 mg/day with subsequent increases to 10 mg/day or 15 mg/day if needed. Dose adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week.
  - For agitation associated with Schizophrenia or Bipolar Disorder: 9.75mg IM
- **Drug-Drug Interactions**
  - When given with CYP3A4 inhibitors (ketoconazole), reduce aripiprazole dose to half.
  - When given with CYP3A4 inducers (carbamazepine) double the dose.
  - When given with CYP2D6 inhibitors (fluoxetine, paroxetine, quinidine) reduce aripiprazole dose to half.
  - Caution with antihypertensives due to aripiprazole's adrenergic α_1 receptor antagonism.

Iloperidone (Fanapt)

- **Formulations**
  - Tablets: 1, 2, 4, 6, 8, 10, 12mg
- **FDA Indications**
  - Schizophrenia, acute treatment for adults; approved 2009
- **Mechanism of Action**
  - Partial agonist at Dopamine D_2 and Serotonin 5-HT_{1A} receptors
- **Boxed Warning**
  - Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- **Warnings & Precautions**
  - QTc Prolongation: Iloperidone increased QTc interval by 9msec at dose of 12mg bid. QTc prolongation was increased by use of CYP450 2D6 and 3A4 inhibitors.
  - Hyperglycemia & Diabetes Mellitus
  - Weight Gain
  - Seizures
  - Orthostatic Hypotension and Syncope

  - Cerebrovascular adverse events, including strokes, in elderly patients with dementia-related psychosis
  - Neuroleptic Malignant Syndrome
  - Tardive Dyskinesia
- **Dosing**
  - Starting dose: 1mg bid (to minimize orthostasis); Target dose: 6-12mg bid; Titration schedule each day of first week: 1mg bid, 2mg bid, 4mg bid, 6mg bid, 8mg bid, 10mg bid, 12,mg bid
  - When patient stops meds for 3 days or longer, restart by following titration schedule.
  - Avoid in patients with hepatic impairment.
- **Drug-Drug Interactions**
  - Avoid with medications that prolong the QTc interval: Class Ia and III anti-arrhythmics
  - Avoid with medications that inhibit metabolism of iloperidone: CYP450 2D6 and 3A4 inhibitors.

Asenapine (Saphris)

- **Formulations**
  - Sublingual Tablets
- **FDA Indications**
  - Schizophrenia, acute treatment for adults; approved 2009
  - Bipolar 1 Disorder: acute treatment for manic or mixed episodes
- **Mechanism of Action**
  - Antagonist at Dopamine D_2 and Serotonin 5-HT_{2A} receptors
- **Boxed Warning**
  - Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- **Warnings & Precautions**
  - QTc Prolongation: Asenapine increased QTc interval by 2-5msec at doses of between 5mg bid to 20mg bid.
  - Hyperglycemia & Diabetes Mellitus
  - Weight Gain
    - Pts with initial BMI < 23: 22% with ≥ 7 percent weight gain
    - Pts with initial BMI 23-27: 13% with ≥ 7 percent weight gain
    - Pts with initial BMI > 27: 9% with ≥ 7 percent weight gain
  - Seizures: between 0% and 0.3% in studies
  - Orthostatic Hypotension and Syncope
  - Cerebrovascular adverse events, including strokes, in elderly patients with dementia-related psychosis
  - Neuroleptic Malignant Syndrome
  - Tardive Dyskinesia
- **Dosing**
  - Starting & Target Dose for Schizophrenia: 5mg bid. May be increased to 10mg bid
  - Starting Dose for Bipolar Disorder: 10mg bid. May decrease to 5mg bid if adverse effects occur.
  - Avoid in patients with severe hepatic impairment. The levels of asenapine increased 7 fold as compared to healthy subjects. No dosage adjustments are necessary in mild to moderate hepatic impairment.
  - No dose adjustments necessary in renal impairment.

- **Drug-Drug Interactions**
    - Avoid in combination with other drugs that prolong QTc such as Class 1A antiarrhythmics (e.g., quinidine, procainamide), Class 3 antiarrhythmics (e.g., amiodarone, sotalol), antipsychotics (e.g., ziprasidone, chlorpromazine, thioridazine), and antibiotics (e.g., gatifloxacin, moxifloxacin).

Lurasidone (Latuda)

- **Formulations**
    - Tablets: 20, 40, 80, 120mg
- **FDA Indications**
    - Schizophrenia, acute treatment for adults; approved 2010
- **Mechanism of Action**
    - Antagonist at Dopamine D_2, Serotonin 5-HT_{2A}, Serotonin 5-HT_7 receptors
    - Agonist at Serotonin 5-HT_{1A}
- **Boxed Warning**
    - Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- **Warnings & Precautions**
    - Hyperglycemia & Diabetes Mellitus
    - Weight Gain
    - Seizures
    - Orthostatic Hypotension and Syncope
    - Cerebrovascular adverse events, including strokes, in elderly patients with dementia-related psychosis
    - Neuroleptic Malignant Syndrome
    - Tardive Dyskinesia
- **Dosing**
    - Starting dose: 40mg qd with food; Target dose: 40-160mg qd;
    - In patients with renal or hepatic impairment: starting dose is 20mg qd and dose not to exceed 80mg qd.
    - With CYP 3A4 inhibitors
- **Drug-Drug Interactions**
    - Metabolized through CYP 3A4. Decrease dose to 80mg qd when used concurrently with medications that inhibit 3A4 such asketoconazole or grapefruit.CYP 3A4 inducers, such as carbamzapine or St. John's Wort can lower lurasidone levels and concurrent use should be avoided.

Monitoring Protocol for Patients on Second Generation Antipsychotics

The following is the protocol developed by the American Diabetes Association and the American Psychiatric Association for monitoring patients on second generation antipsychotics (SGA).

Baseline Measures:

- Personal / Family History
- Weight
- Waist Circumference
- Blood Pressure
- Fasting blood glucose

- Fasting lipid profile

Monitoring protocol for patients on SGAs*

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

Go to the link below to access this entire ADA/APA article along with the tables that describe the protocol:

http://care.diabetesjournals.org/cgi/content/full/27/2/596#T3

As a reminder, here are the World Health Organization Guidelines for the Metabolic Syndrome, one of the adverse effects of SGAs.

The Metabolic Syndrome

- **Hypertension**: Current antihypertensive therapy and/or BP >140/90 mmHg
- **Dyslipidemia**: Plasma triglycerides >1.7 mmol/L (150 mg/dL) and/or HDL <0.9 mmol/L (35 mg/dL) in men and <1.0 mmol/L (<40 mg/dL) in women
- **Obesity**: BMI >30 kg/m^2 and/or waist-to-hip ratio >0.90 in men and >0.85 in women
- **Glucose**: Type 2 diabetes or Impaired Glucose Tolerance (IGT)
- **Microalbuminuria** = overnight urinary albumin excretion rate >20 mg/min (30 mg/g creatinine)

- **Requirements for diagnosis**: Type 2 diabetes or IGT and any 2 of the above criteria; if Normal Glucose Tolerance, must demonstrate 3 other disturbances

First Generation Antipsychotics (AKA Neuroleptics or Conventional Antipsychotics)

- **List of First Generation Antipsychotics Currently Available in the US**
  - Chlorpromazine (Thorazine)
  - Fluphenazine (Prolixin)
  - Haloperidol (Haldol)
  - Loxapine (Loxitane, Adasuve)
  - Molindone (Moban)
  - Perphenazine (Trilafon)

  - Pimozide (Orap)
  - Prochlorperazine (Compazine)
  - Trifluoperazine (Stelazine)
  - Thioridazine (Mellaril)
  - Thiothixene (Navane)
- **FDA Indications for First Generation Antipsychotics**
  - Schizophrenia, acute and maintenance treatment for all of the above
  - Loxapine (Adasuve brand only) additionally for acute treatment of agitation associated with Schizophrenia or Bipolar I Disorder
  - Prochlorperazine (Compazine) additionally for severe nausea and vomiting
- **Mechanism of Action**
  - D2 antagonists
  - Low Potency Medications also have strong antagonist effects on Histamine H1 and Adrenergic α1 and α2. This leads to sedation and orthostatic hypotension.
- **Boxed Warning**
  - FDA Boxed Warning: "Clinical studies indicate that antipsychotic drugs of both types [conventional and atypical] are associated with an increased risk of death when used in elderly patients treated for dementia-related psychosis."
- **Alerts & Warnings**
  - QT Prolongation: Thioridazine (Mellaril) rarely used due to prominent QTc prolongation.

First Generation Antipsychotic	Brand Name	Chlorpromazine Equivalent Doses (mg)	Starting Dose (mg)	Target Dose (mg)
LOW POTENCY Chlorpromazine	Thorazine	100	50-100	200-1600
MID POTENCY Loxapine Perphenazine	 Loxitane Trilafon	 12 8	 10-25 4-8	 60-100 16-32
HIGH POTENCY Fluphenazine Haloperidol Pimozide Thiothixene Trifluoperazine	 Prolixin Haldol Orap Navane Stelazine	 2 2 1 5 5	 1-2 1-5 1-2 2-5 2-5	 2-20 2-20 2-10 5-30 5-50

Notes

- Chlorpromazine Dose Equivalents is defined as the number of milligrams of the medication that is considered therapeutically equivalent to 100mg of Chlorpromazine. So, for example, a dose of 2mg of haloperidol equals 100mg of Chlorpromazine
- Table above does not include all the first generation antipsychotics available. It is limited to the meds that remain most commonly in use today.

Antidepressant Medications

Fluoxetine (Prozac)

- **Formulations** (pulvules, oral solution, weekly capsules)
- **FDA Indications**
    - Major Depressive Disorder in children, adolescents & Adults
    - Obsessive Compulsive Disorder in children, adolescents & Adults
    - Panic Disorder
    - Bulimia Nervosa
    - Premenstrual Dysphoric Disorder (Sarafem brand fluoxetine)
- **Mechanism of Action:** SSRI
- **Warnings**
    - See Boxed Warnings and Warnings at end of section to apply to all these antidepressants
    - Avoid with Thioridazine due to CYP 450 inhibition. May result in ventricular arrhythmia and sudden death.
    - Risk of rash or urticaria
- **Dosing**
    - Adults: start 20mg qd; Children 10-20 mg qd
    - Increase up to 80mg qd for adults and 60mg children
    - Bulimia: titrate to target dose of 60mg qd; only this dose effective in decreasing binging
- **Drug-Drug Interactions**
    - Avoid with MAOIs
    - Avoid with Pimozide
    - Avoid with Triptans due to risk of Serotonergic Syndrome
    - **Fluoxetine is a CYP2D6 Inhibitor**: Avoid with TCAs like Desipramine may lead to TCA toxicity
    - Avoid with Thioridazine

Sertraline (Zoloft)

- **FDA Indications**
    - Major Depressive Disorder
    - Premenstrual Dysphoric Disorder
    - Obsessive Compulsive Disorder for children, adolescents & adults
    - Panic Disorder
    - Social anxiety Disorder
    - Post Traumatic Stress Disorder
- **Mechanism of Action:** SSRI
- **Warnings**
    - See Boxed Warnings and Warnings at end of section to apply to all these antidepressants
- **Dosing**
    - Start 25-50mg qd; increase to 200mg qd

Paroxetine (Paxil and Paxil CR)

- **FDA Indications**

  - Major Depressive Disorder
  - Premenstrual Dysphoric Disorder
  - Obsessive Compulsive Disorder
  - Panic Disorder
  - Generalized Anxiety Disorder
  - Social anxiety Disorder
  - Post Traumatic Stress Disorder
- **Mechanism of Action:** SSRI
- **Warnings**
  - See Boxed Warnings and Warnings at end of section to apply to all these antidepressants
  - Avoid with Thioridazine due to CYP 450 inhibition. May result in ventricular arrhythmia and sudden death.
  - Paroxetine has been linked to fetal heart defects due to exposure in the first trimester.
- **Dosing**
  - Start 10-20mg qd; increase up to 50-60mg qd (upper dose depends on specific disorder)
  - In OCD and Panic Disorder, target dose is 40mg qd; increase to 60mg qd
- **Drug-Drug Interactions**
  - **Paroxetine is a CYP2D6 and CYP3A4 inhibitor**: Avoid with TCAs like Desipramine which may lead to TCA toxicity
  - Avoid with Thioridazine – see above

Escitalopram (Lexapro)

- **FDA Indications**
  - Major Depressive Disorder (adults and adolescents 12-17 years of age)
  - Generalized Anxiety Disorder in adults
- **Mechanism of Action:** SSRI. Escitalopram is the S-entantiomer of racemic citalopram.
- **Warnings**
  - See Boxed Warnings and Warnings at end of section to apply to all these antidepressants
- **Dosing**
  - Starting and target dose: 10mg qd. If lack of response, increase to 20mg qd.
  - Dose Adjustment: Use same dose in elderly patients, in patients with hepatic impairment and patients with mild-moderate renal impairment.
- **Drug-Drug Interactions**
  - Avoid with MAOIs
  - Avoid with pimozide (Orap) due to QTc prolongation

Bupropion (Wellbutrin)

- **Formulations**
  - Wellbutrin, Wellbutrin SR, Wellbutrin XR
- **FDA Indications**
  - Major Depressive Disorder
  - Smoking cessation (Zyban brand)
- **Mechanism of Action**
  - Unknown. Clinical action presumed to be mediated by norepinephrine and dopamine.

  - Bupropion is relative weak dopamine and norepinephrine reuptake inhibitor.
- **Warnings**
  - See Boxed Warnings and Warnings at end of section to apply to all these antidepressants
  - Seizure risk:
    - Wellbutrin SR up to doses of 300mg qd: 0.1%
    - Doses over 300mg to 400mg qd: 0.4%
- **Contraindications**
  - Avoid in pts with seizure disorder
  - Avoid in pts with current or prior diagnosis of Bulimia Nervosa or Anorexia Nervosa
  - Avoid in pts undergoing benzodiazepine withdrawal (seizure risk)
  - Avoid with MAOIs
- **Dosing (Wellbutrin SR)**
  - Start 150mg qd. Increase to target of 150mg bid in 4 days minimum.
  - May increase to 200mg bid in 4 weeks if needed.
  - In Severe Hepatic Impairment: prescribe no more than 100mg qd.
- **Drug-Drug Interactions**
  - Bupropion inhibits CYP2D6 (although it itself is not metabolized by this enzyme). Therefore, Bupropion administration may increase meds metabolized by CYP2D6. It increased the AUC of Desipramine by 2-5 fold.
  - Bupropion toxicity is enhanced by the MAOI med, phenelzine
  - Caution in use with levodopa and amantadine due to increased adverse effects

Mirtazapine (Remeron)

- **Formulations:** tablet, sol tab
- **FDA Indications**
  - Major Depressive Disorder
- **Mechanisms of Action**
  - Antagonist of presynaptic α2 adrenergic inhibitory autoreceptors
  - Antagonist of (Serotonin) 5-HT_2 and 5-HT_3 receptors (thus leading to low sexual and GI adverse effects)
  - Also, mirtazapine is a potent Histamine H1 antagonist (leading to sedation) and peripheral α1 adrenergic antagonist (leading to orthostasis)
- **Warnings**
  - See Boxed Warnings and Warnings at end of section to apply to all these antidepressants
- **Dosing**
  - Start 15mg qhs. Target dose is 15-45mg qhs. Increase q 1-2 weeks.
  - Severe Renal and Hepatic Impairment: metabolism and clearance are decreased. Therefore, consider lower dose.
- **Drug-Drug Interactions**
  - Low CYP450 enzyme interactions
  - Caution in concurrent use with Benzodiazepines due to sedative effects

Venlafaxine (Effexor and Effexor XR)

- **Formulations**
  - Immediate release and extended release
- **FDA Indications**
  - Major Depressive Disorder
  - Panic Disorder (XR only)
  - Generalized Anxiety Disorder (XR only)
  - Social Anxiety Disorder (XR only)
- **Mechanism of Action:** SNRI
- **Warnings**
  - See Boxed Warnings and Warnings at end of section to apply to all these antidepressants
  - Risk of development of sustained hypertension.
- **Dosing**
  - Venlafaxine: start 75mg qd. Titrate to 225mg qd as needed. May increase up to 375mg qd if response is inadequate
  - Venlafaxine XR: Start 75mg qd with food either morning or evening. Titrate to 225mg qd as needed
  - In moderate hepatic impairment reduce dose to half.
  - In mild-moderate renal impairment reduce dose by 25%.
  - In dialysis patients, reduce dose by 50%.
- **Drug-Drug Interactions**
  - Minor CYP450 enzyme effects. No dose adjustments recommended.

Desvenlafaxine (Pristiq)

- **FDA Indications**
  - Major Depressive Disorder
- **Mechanism of Action:** SNRI; active metabolite of venlafaxine.
- **Warnings**
  - See Boxed Warnings and Warnings at end of section to apply to all these antidepressants
  - Risk of development of sustained hypertension.
- **Dosing**
  - Start and target: 50mg qd; may increase to 400mg qd max
  - In severe or end-stage renal impairment dose up to 50mg qod
  - In hepatic disease, no dose adjustment necessary; however dose escalation greater than 100mg qd is not recommended.
- **Drug-Drug Interactions**
  - Minor CYP450 enzyme effects. No dose adjustments recommended.

Duloxetine (Cymbalta)

- **FDA Indications**
  - Major Depressive Disorder
  - Generalized Anxiety Disorder
  - Diabetic Peripheral Neuropathic (DPN) Pain.
- **Mechanism of Action:** SNRI

- **Warnings**
  - See Boxed Warnings and Warnings at end of section to apply to all these antidepressants
- **Dosing**
  - Start 20mg bid. Increase to target of 60mg daily either as qd or bid schedule.
  - May increase to total daily dose of 120mg qd (approved for DPN Pain and GAD)
  - Avoid in pts with Hepatic Insufficiency
  - Avoid in end stage renal disease
- **Drug-Drug Interactions**
  - Duloxetine is metabolized by CYP1A2 and CYP2D6.
  - CYP1A2 inhibitors (fluvoxamine) increased duloxetine AUC 6 fold
  - CYP2D6 inhibitors (fluoxetine, paroxetine, quinidine) increased duloxetine levels by 60%
  - Duloxetine increased levels of other meds metabolized by CYP2D6. Desipramine AUC increased 3 fold when given with duloxetine.

Levomilnacipran (Fetzima)

- **FDA Indications**
  - Major Depressive Disorder
- **Mechanism of Action**
  - SNRI
- **Main Side Effects**
  - Nausea, constipation, tachycardia, hyperhidrosis, urinary hesitation
- **Warnings**
  - See Boxed Warnings and Warnings at end of section to apply to all these antidepressants
- **Dosing**
  - Target dose is 40-120 mg qd
  - Treatment should be titrated: initial dose 20 mg qd for 2 days, then increase to 40 mg qd. Based on response and tolerability, dose can be increased by 40mg qd every 2 or more days up to 120mg qd.
- **Drug-Drug Interactions**
  - Levomilnacipran is metabolized by CYP 3A4 and its levels can increase with strong 3A4 inhibitors (e.g., ketoconazole). However, no clinically significant change in exposure to Levomilnacipran occurred with 3A4 inducers (e.g., carbamazepine).

Vilazodone (Viibryd)

- **FDA Indications**
  - Major Depressive Disorder
- **Mechanism of Action:** SSRI and partial agonist at 5HT1A post-synaptic receptor
- **Main Side Effects**
  - Nausea, diarrhea, vomiting, insomnia
- **Warnings**
  - See Boxed Warnings and Warnings at end of section to apply to all these antidepressants
- **Dosing**

  - Target dose is 40 mg qd
  - Treatment should be titrated: initial dose 10 mg qd for 7 days, then 20 mg qd for additional 7 days, and then increase to 40 mg qd
- **Drug-Drug Interactions**
  - Vilazodone is metabolized by CYP3A4.
  - CYP3A4 inhibitors (ketoconazole, grapefruit, erythromycin) increase vilazodone levels
  - When used with CYP3A4 strong inhibitors, reduce vilazodone dose to 20mg qd. If used with moderate CYP3A4 inhibitors (erythromycin), may reduce to 20mg qd if patient has intolerable side effects.

Vortioxetine (Brintellix)

- **FDA Indications**
  - Major Depressive Disorder
- **Mechanism of Action**
  - SSRI, agonist at 5HT1A and antagonist at 5HT3 post-synaptic receptors
- **Main Side Effects**
  - Nausea
- **Warnings**
  - See Boxed Warnings and Warnings at end of section to apply to all these antidepressants
- **Dosing**
  - Target dose is 20 mg qd
  - Treatment should be titrated: initial dose 10 mg qd, then increase to 20 mg qd as tolerated. Dose can be decreased to 5mg qd if higher doses not tolerated.
- **Drug-Drug Interactions**
  - Vortioxetine is metabolized by several CYP 450 enzymes, including 2D6 and 3A4. Although it does not substantially inhibit or induce metabolism of other drugs, other drugs can affect metabolism of Vortioxetine. Reduce the dose to half when using concurrent 2D6 inhibitors (e.g., fluoxetine, paroxetine, bupropion) and consider increasing the dose with strong CYP inducers (e.g., carbamazepine, phenytoin)
  - Avoid or use caution with other serotonergic medications

Nortriptyline (Pamelor)

- **FDA Indications**
  - Major Depressive Disorder
- **Mechanism of Action:** Nortriptyline has SNRI effects
- **Warnings**
  - See Boxed Warnings and Warnings at end of section to apply to all these antidepressants
- **Dosing**
  - Dose according to plasma levels: 50-150 ng/dl
  - Usual adult dose: 75-100mg daily in divided doses or once daily
- **Drug-Drug Interactions**
  - Nortriptyline is metabolized by CYP2D6. Avoid 2D6 inhibitors: fluoxetine, paroxetine, quinidine, cimetidine
- **Overdose**

- TCAs may be lethal in overdosage due to their cardiac membrane stabilizing properties that cause widening of QRS complex and heart block.
- Features of overdose: confusion, restlessness, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia
- Management of Overdose
    - Secure airway: intubate if consciousness impaired
    - Establish IV
    - Initiate cardiac monitoring
    - GI decontamination: gastric lavage and activated charcoal.
    - Administer IV sodium bicarbonate to maintain the serum pH in the range of 7.45 to 7.55.
    - Rarely hemoperfusion may be used to remove drug from plasma

Boxed Warnings for All the Above Antidepressants

- Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children, adolescents and adults up to age 24 with Major Depressive Disorder (MDD) and other psychiatric disorders

Warnings / Precautions for the Above Antidepressants

- Depressive worsening and risk of suicide in adults
- Screening for patients with Bipolar Disorder: Use of antidepressants may increase risk of a manic or mixed episode.
- Serotonin Syndrome or Neuroleptic Malignant Syndrome: All SSRIs and SNRIs increase risk of Serotonin Syndrome or states clinically similar to NMS either when used alone or in combination with other medications. The use of SSRIs and SNRI is contraindicated with concurrent use of MAOIs.
- Pregnancy: Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. A particular risk is Persisting Pulmonary Hypertension of the Newborn, which is associated with antidepressant exposure after 20 weeks gestation.
- Bleeding: All SSRIs and SNRIs increase the risk of bleeding due to serotonin's effect of decreasing platelet adhesion. Concomitant use with aspirin, NSAIDs, warfarin and other anticoagulants can increase the risk of abnormal bleeding.
- Hyponatremia: All SSRIs and SNRIs increase hyponatremia risk, in many cases related to SIADH (Syndrome of Inappropriate Antidiuretic Hormone Secretion).
- Antidepressant Discontinuation Syndrome: particularly when abrupt, symptoms can include agitation, irritability, anxiety, confusion, parasthesias (including electric shock sensations), headache, dizziness, insomnia, and hypomania.

Additional Individual Risks

- Fluoxetine, Fluvoxamine, and Paroxetine Additional Risk: Use with Thioridazine due to CYP 450 inhibition may result in ventricular arrhythmia and sudden death.
- Fluvoxamine Additional Risks: Potential interactions with Terfenadine, Astemizole, Cisapride, and Pimozide, and Tizanidine by increasing levels of these medications.

Monoamine Oxidase Inhibitors

Phenelzine (Nardil)

- **FDA Indications**
  - "Atypical depression" described as mixed anxiety and depression with phobic or hypochondriacal features
  - "Nardil should rarely be the first antidepressant drug used. Rather, it is more appropriate for patients who have failed to respond to other drugs more commonly used in these conditions."
- **Mechanism of Action:** nonselective MAOI
- **Warnings**
  - See Boxed Warnings and Warnings at end of section to apply to all these antidepressants
- **Dosing**
  - Starting dose: 1 tablet (15mg) tid.
  - Early phase treatment: increase to 60mg daily and up to 90mg daily as a tid dosing schedule.
  - Maintenance treatment: dose may be decreased over several weeks to a maintenance dose that may be as low as one tablet a day.
  - Avoid in patients with pheochromocytoma, congestive heart failure, renal or hepatic impairment.
- **Drug-Drug Interactions**
  - Serotonergic Syndrome: avoid MAOIs with serotonergic drugs: SSRIs and SNRIs
  - Hypertensive Crisis (Noradrenergic Syndrome): avoid MAOIs with Sympathomimetics
    - Features of Hypertensive Crisis: elevated blood pressure with occipital headache that may radiate frontally, photophobia, neck stiffness, palpitations, chest pain, nausea, vomiting, and cold sweats. Intracranial bleeding has occurred.
    - Treatment of Hypertensive Crisis: stop MAOI and administer phentolamine 5mg IV.
    - Prescribed Drugs to Avoid: amphetamines, methylphenidate, dopamine, epinephrine, methyldopa, L-Dopa, L-trypophan, L-tyrosine, Guanethidine, sinus or cold meds that may contain pseudoephedrine
    - Drugs of Abuse to Avoid: amphetamine, cocaine, ecstasy
    - Tyramine-rich Foods to Avoid: protein-rich foods that have undergone protein breakdown, causing production of tyramine (tyramine is a catecholamine that enters the body and is normally metabolized by Monoamine Oxidase, which is inhibited by the MAOI): aged cheeses, dry sausage, pickled herring, sauerkraut, beer, wine, liver, yeast, fava beans, and yogurt.
  - Caution MAOI with antihypertensives due to possibly exaggerated hypotensive effect.

Use of MAOIs

The American Psychiatric Association Practice Guidelines state that due to dietary restrictions and potentially serious side effects, MOAIs should be reserved for "patients who do not respond to other treatments." Since the number of failed trials is not defined by the APA guidelines, another source with more specific information was found.

According the VA Criteria for Use (included below), MAOIs for use in MDD should be reserved for patients who either failed two previous antidepressant trials or who have a history of previous response to MAOIs. Other criteria need to be met also.

These are the MAOI's that have an FDA indication for MDD. (List ordered as follows: generic name, brand name, starting dose, usual target doses).

Medication	Brand Name	Starting Dose	Target Dose
Isocarboxazid	Marplan	20mg qd	30-60mg qd
Phenelzine	Nardil	15mg qd	30-90mg qd
Tranylcypromine	Parnate	10mg qd	30-60mg
Selegiline Transdermal System*	Emsam	3mg/24hours	6-12mg/24hours

* Note that Selegiline Transdermal Patches should not be cut to provide lower doses

Since you may not be familiar with the use of transdermal systems, I reprint the pertinent section from the package insert later in this guide.

VA Criteria For Use For MAOIs For Major Depressive Disorder

In order to receive an MAOI for the treatment of major depressive disorder, patients should meet the following:

1. Have failed to achieve remission (the absence of depressive symptoms or the presence of minimal depressive symptoms) after trials of two different antidepressants at therapeutic doses for at least 6 weeks)
OR
2. Have demonstrated a therapeutic response to an MAOI in the past.

PLUS ALL of the following must be met:

- The patient has no current contraindications to an MAOI (e.g., designated opiates, serotonin-active medications) See Next Section.
- The patient has not taken another antidepressant for a minimum of 2 - 5 weeks (see individual antidepressant labeling for specific washout period) prior to starting an MAOI.
- The patient demonstrates an understanding of and is willing to comply with the required dietary, herbal, and over-the-counter medications restrictions while taking an MAOI.
- The clinician-prescriber is willing or the facility has a system in place to answer the patient's questions about the medication 24 hours a day to avoid drug-drug and drug-food interactions.

Contraindications to MAOI Use

Dietary sources rich in tyramine

- Meat, Poultry and Fish
    - Air dried, aged, and fermented meats, sausages, salamis
    - Pickled herring
    - Spoiled or improperly stored meat, poultry or fish, including liver.

- Vegetables
    - Broad bean pods, e.g., fava bean pods
- Dairy (milk products)
    - Aged cheeses, e.g., parmesan, cheddar
- Beverages
    - All tap beer, and other non-pasteurized beer
- Other
    - Concentrated yeast extract
    - Sauerkraut
    - Most soy products including soy sauce and tofu
    - OTC supplements containing tyramine

Medications which increase the risk of serotonin syndrome or hypertensive (noradrenergic) crisis

- Antidepressants
    - SSRIs – citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
    - SNRIs – desvenlafaxine, duloxetine, venlafaxine
    - Tricyclics – amitriptyline, imipramine, desipramine, nortriptyline, clomipramine, doxepin
    - Mirtazapine
    - Bupropion
    - Other MAOIs (isocarboxazid, phenelzine, tranylcypromine, selegiline)
    - St. John's Wort
- Analgesics
    - Meperidine
    - Tramadol
    - Methadone
    - Propoxyphene
- Anticonvulsants
    - Carbamazepine
    - Oxcarbazepine
- Stimulants, including amphetamines
    - Cough/Cold Products containing Dextromethorphan
    - Decongestants containing pseudoephedrine or phenylephrine
- Buspirone
- Cyclobenzaprine

Antidepressants: Switch or Augment?

A common dilemma (and frequent exam question) relates to when is it most appropriate to switch and when to augment an antidepressant.

Switch if after an optimized trial (i.e., achieving a high FDA approved dose and adequate duration on the med, such as 6-8 weeks for an adult, or longer for an older adult and assuring full compliance) the response is low or non-existent.

My rule of thumb is if I don't see about a 25% improvement, I switch. If I get greater than a 25% improvement I augment. That's how I define non-response and response. But clinician have differing cut-off points.

- **Lithium**:
  - This is the most studied augmenting agent. It may convert 35-60% of non-responders to responders.
  - Dose at 450-900mg qd for a blood level of 0.4-0.8 mmol.
  - If no response aim for a higher blood level, as you would for Bipolar Disorder.
- **T3 (Triiodothyronine)**
  - Fewer side effects than lithium and yet is equally effective.
  - In a recent study response was 43% of previous non-responders.
  - T3 may cause tachycardia. Get an EKG prior to initiation for older or medically ill adults.
  - Start at 12.5mcg (half a 25 mcg tab).Target dose to 25-50 mcg (note micrograms).
- **Pindodol:**
  - The 5-HT_{1A} postsynaptic antagonist pindolol accelerates the onset of action of antidepressants by preventing negative feedback to the presynaptic 5-HT_{1A} receptor.
  - Dose it at 2.5 to 7.5 mg qd.
  - Adverse effects are low (about 10%) and include nausea, diarrhea, and mild heart rate decreases.
- **Buspirone:**
  - Benign side effect profile.
  - Dose it at 15-30mg qd in divided doses.
- **Note:**
  - When you add a second antidepressant, such as bupropion to an SSRI that is called combination therapy.

Mood Stabilizers

Lithium

- **Formulations**
  - Eskalith, Eskalith CR, Lithobid
- **FDA Indications**
  - Bipolar Mania, Acute Treatment
  - Maintenance therapy of subsequent mood episodes in those with a history of a manic episode.
- **Mechanism of Action**
  - Lithium alters sodium transport in nerve and muscle cells. It is hypothesized to effect a shift towards intraneuronal metabolism of catecholamines.
- **Boxed Warning**
  - Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy
- **Warnings**

  - Lithium should generally not be given to patients with **significant renal or cardiovascular disease, severe debilitation or dehydration, or sodium depletion** since the risk of lithium toxicity is very high in these patients.
  - Chronic lithium therapy may be associated with diminution of renal concentrating ability, occasionally presenting as Diabetes Insipidis, with polyuria and polydypsia.
  - Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have been reported in patients on chronic lithium therapy.
  - Assess baseline kidney function prior to starting lithium therapy.
  - Encephalopathic Syndrome has occurred in a few patients on lithium and a neuroleptic. This syndrome is characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, and BUN.
- **Dosing**
  - Start at 600-900mg qd in divided doses. Titrate based on serum level. Most pts will be stabilized on doses up to 1800mg qd.
  - Trough serum level target is 0.6-1.2mEq/L (draw trough level within an hour of the upcoming dose)
  - Maintenance dose is equal to the stabilizing dose.
- **Drug-Drug Interactions**
  - Diuretic-induced sodium loss can lead to reduced lithium clearance and higher lithium levels.
  - NSAIDS including Cox-2 inhibitors, Metronidazole, ACE Inhibitors can increase lithium levels.
- **Overdose**
  - Features: nausea, vomiting, diarrhea, weakness, fatigue, severe tremor, muscle fasciculations, clonus, choreoathetosis, lethargy, confusion, stupor, coma, seizures, cardiovascular collapse.
  - Note: toxicity does not correlate well with serum lithium level. There are acute poisonings, chronic poisonings, and acute-on-chronic poisonings.
  - Management
    - Obtain lithium level and then repeat in 2 hours to note trend
    - Obtain head CT if mental status changes to rule out other etiologies.
    - Obtain EKG: Lithium may cause arrhythmias including complete heart block
    - Decontaminate GI: gastric lavage, activated charcoal
    - Provide hemodialysis
    - Give IV fluids to increase renal elimination

Valproate (Depakote)

- **Formulations**
  - Depakote, Depakote XR, Depakene Capsules and Syrup, Depakon Injection
- **FDA Indications**
  - Bipolar Mania, Acute Treatment
  - Migraines (Prophylaxis, not acute treatment)
  - Epilepsy (Complex Partial Seizures, Simple or Complex Absence Seizures)
- **Mechanisms of Action**
  - Unknown but hypothesized to increase GABA concentrations
- **Boxed Warnings**
  - **Hepatotoxicity**

    - **Pancreatitis**
    - **Teratogenicity** - Usage in Pregnancy
        - Congenital Malformations
        - Neural Tube Defects
        - Other Pregnancy-Related Abnormalities
- **Alerts & Warnings**
    - Urea Cycle Disorders
    - Somnolence in the Elderly
- **Dosing**
    - Start: 750mg qd in divided doses
    - Increase to achieve response or serum level of 50-125 µg / ml
- **Drug-Drug Interactions**
    - Lamotrigine: Valproate increases Lamotrigine elimination half-life from 26 hrs to 70 hrs; decrease Lamotrigine dose to half and extend its titration to twice the duration
    - Topiramate: co-administration led to hyperammonemia with or without encephalopathy
    - Clonazepam: co-administration induced absence seizures in those with a seizure history
    - Amitriptyline: co-administration has led to rare TCA toxicity
    - Phenobarbital: co-administration inhibits metabolism of phenobarbitol; monitor for toxicity
    - Ethosuximide: co-administration inhibits metabolism of ethosuximide; monitor toxocity

Carbamazepine and Carbamazepine XR (CBZ)

- **Formulations**
    - Immediate-release tablets, extended-release tablets, oral suspension
- **FDA Indications**
    - Bipolar Mania and Mixed Episodes, Acute Treatment (Equetro brand only)
    - Epilepsy (Partial Complex Seizures, Generalized Tonic-Clonic Seizures, Mixed Seizures)
    - Trigeminal Neuralgia
- **Mechanisms of Action**
    - Mechanism of action is unknown
    - CBZ reduces pain induced by stimulation of the infraorbital nerve in cats & rats.
    - CBZ depresses thalamic potential and bulbar and polysynaptic reflexes
- **Boxed Warnings**
    - **Aplastic Anemia and agranulocytosis have occurred**.
    - Although reports of transient or persistent decreased platelet or white blood cell counts are not uncommon in association with the use of carbamazepine, data are not available to estimate accurately their incidence or outcome. However, the vast majority of the cases of leukopenia have not progressed to the more serious conditions of aplastic anemia or agranulocytosis.
    - Because of the very low incidence of agranulocytosis and aplastic anemia, the vast majority of minor hematologic changes observed in monitoring of patients on carbamazepine are unlikely to signal the occurrence of either abnormality. Nonetheless, complete pretreatment hematological testing should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

- **Warnings**
    - In pregnancy: **CBZ can cause fetal harm when ingested by a pregnant woman**.
    - General
        - Patients with a history of an adverse hematologic reaction may be at particular risk.
        - Severe dermatologic reactions, including Stevens-Johnson Syndrome, may occur.
        - In patient with a seizure disorder should not have CBZ discontinued abruptly.
        - Coadministration of CBZ and Delaviridine may lead to loss of virologic control
- **Dosing**
    - Ages under 6: start 10-20mg / kg qd suspension using tid or qid schedule; usually maintenance not to exceed 35mg / kg.
    - Ages 7-12: start 100mg bid; increase by 100mg qd using bid schedule for carbamazepine EX and tid or qid schedule for IR. Generally do not exceed 1000mg qd.
    - Ages 13 to Adult: start 200mg bid; increase by 100mg qd using bid schedule for carbamazepine EX and tid or qid schedule for IR. Generally do not exceed 1000mg qd for ages 13-15 and 1200mg qd for ages over 15.
    - For Trigeminal Neuralgia: start 100mg bid
    - Pregnancy: D
- **Drug-Drug Interactions**
    - Avoid CBZ suspension with liquid chlorpromazine. It may result in an orange rubbery precipitate in the stool.
    - CBZ is metabolized by **CYP3A4**
        - **CYP3A4 inhibitors may increase CBZ levels** (cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, fluvoxamine, loratadine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, **ketaconazole,** acetazolamide, verapamil, grapefruit juice, protease inhibitors, **valproate**).
        - **CYP3A4 inducers may lower CBZ levels** (cisplatin, doxorubicin HCl, felbamate, rifampin, phenobarbital, phenytoin, primidone, methsuximide, theophylline)
        - **CBZ may increase other med levels** (clomipramine, phenytoin, primidone)
        - **CBZ may lower other med levels** (acetaminophen, alprazolam, felodipine, cyclosporine, corticosteroids (e.g., prednisolone, dexamethasone), clonazepam, clozapine, dicumarol, doxycycline, ethosuximide, haloperidol, lamotrigine, levothyroxine, methadone, methsuximide, midazolam, olanzapine, **oral contraceptives**, oxcarbazepine, phensuximide, phenytoin, praziquantel, protease inhibitors, risperidone, theophylline, tiagabine, topiramate, tramadol, **TCA's** (e.g., imipramine, amitriptyline, nortriptyline), valproate, warfarin, ziprasidone

Lamotrigine (Lamictal)

- **Formulations:** Lamotrigine tablets; chewable tablets
- **Indications**
    - Maintenance treatment in Bipolar I Disorder (to delay the time of occurrence of a subsequent mood episode in patients treated for an acute mood episode with standard therapy).
    - Epilepsy: Adjunctive and Monotherapy

        - Adjunctive: Partial Seizures, Generalized Seizures of Lennox-Gastout Syndrome, and Primary Tonic-Clonic Generalized Seizures in adults and children
        - Monotherapy: Partial Seizures
- **Boxed Warnings**
    - Serious rashes requiring hospitalization and discontinuation of treatment have been reported in association with the use of Lamictal, including **Stevens-Johnson Syndrome**. (also known as Toxic Epidermal Necrolysis).
    - Rate of serious rashes: 1 in 1000
    - Highest risk in first 2-8 weeks of treatment
    - Risk Factors for the Prediction of the Development of Serious Rashes
        - Age is the only identified one.
        - There are suggestions that the following may predict development of rash
            - Coadministration with Valproic Acid and Sodium Divalproex.
            - Exceeding the recommended initial dose
            - Exceeding the recommended dose escalation
    - Because it is not possible to predict which cases of rash will be serious, Lamictal should ordinarily be discontinued at the first sign of rash.
- **Warnings**
    - Acute Multiorgan Failures have occurred
    - Blood Dyscrasias have occurred
    - In patients with epilepsy, withdrawal seizures may occur on abrupt discontinuation
- **Dosing**
    - For Bipolar Disorder, start 25mg qd. Increase to target of 200mg qd. See titration schedule in the table below
    - Maintenance dosing for women taking Estrogen-Containing Oral Contraceptives: increase lamotrigine dose up to twice normal target dose.
    - Severe Hepatic Impairment: decrease Lamotrigine to half
    - Note that Lamotrigine has complex drug-drug interactions and its dosing is based on use of concurrent anti-epilepsy drug (AED). Below is a table for patients with Bipolar Disorder.
        - Remember that Valproate SLOWS Lamotrigine metabolism and lamotrigine dose and titration should be cut in half. Other AED's SPEED Lamotrigine metabolism. The middle column is the "normal" titration schedule

Lamotrigine Treatment	For Patients Taking Valproate‡	For Patients Not Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Rifampin† and Not Taking Valproate‡	For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Rifampin† and Not Taking Valproate‡
Weeks 1 and 2	25 mg every other	25 mg daily	50 mg daily

	day		
Weeks 3 and 4	25 mg daily	50 mg daily	100 mg daily, in divided doses
Week 5	50 mg daily	100 mg daily	200 mg daily, in divided doses
Week 6	100 mg daily	200 mg daily	300 mg daily, in divided doses
Week 7	100 mg daily	200 mg daily	up to 400 mg daily, divided doses

Sleep-Related Medications

Hypnotic Agents

Hypnotic Agent	Brand Name	Usual Dose (hs)	Onset (min)	Half Life (hours)	Daytime Sedation	FDA Indication	Notes
Flurazepam	Dalmane	15-30mg 7.5	30-60	47-100	High	SI & SM*	
Quazepam	Doral	-30mg	30-60	39 - 200	High	SI & SM	
Estazolam	Prosom	1-2 mg	15-60	10 - 24	Medium	SI & SM	
Temazepam	Restoril	7.5-30mg	45-60	3 - 18	Medium	SI & SM	
Triazolam	Halcion	.125-.25mg	15-30	1.5 - 6	Low	SI	
Zolpidem	Ambien	5-10mg	15-30	2.5	Low	SI	Ambien CR dose: 6.25-12.5mg
Zaleplon	Sonata	5-10mg	15-30	1	Low	SI	
Eszopiclone	Lunesta	2- 3 mg	45 - 60	6	Low	SI & SM	Lunesta in elderly: 1-2mg elderly
Ramelteon	Rozerem	8mg qhs	30	1 - 2.6	Low	SI	Melatonin agonist Not after fatty meal

* SI: Sleep Initiation; SM: Sleep Maintenance

Modafinil (Provigil) & Armodafinil (Nuvigil)

- **FDA Indications**: Modafinil and armodafinil are indicated to improve wakefulness in patients with excessive daytime sleepiness related to:
    - Narcolepsy
    - Obstructive Sleep Apnea
    - Shift Work Sleep Disorder
- **Mechanism of Action**
    - Unknown but similar to that of the stimulants: it promotes wakefulness, increased locomotor activity, euphoric effects, and changes in perception and mood similar to the stimulants. Considered to activate more discrete brain region than stimulants.

  - Modafinil is a racemic mixture of the R- and S-enantiomers whereas Armodafinil is the active R-enantiomer.
- **Alerts and Warnings**
  - Patients with abnormal levels of sleepiness who take Provigil should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking PROVIGIL, should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity. Prescribers should also be aware that patients may not acknowledge sleepiness or drowsiness until directly questioned about drowsiness or sleepiness during specific activities.
- **Dosing**
  - Modafinil
    - 200mg qd (up to 400mg tolerated but no evidence of additional benefit)
  - Armodafinil
    - 150-250mg qd for sleep apnea and narcolepsy and 150mg for shift work sleep disorder.
  - Both
    - In Shift Work Sleep Disorder, take 1 hr before start of shift
    - Severe hepatic impairment: decrease dose to half
- **Drug-Drug Interactions**
  - Modafanil may increase TCA levels in the 7-10% of pts deficient in CYP2D6
  - No pharmacokinetic alterations when given with the stimulants

Sodium Oxybate (Xyrem)

- **FDA Indications**:
  - Narcolepsy
  - Obstructive Sleep Apnea
  - Shift Work Sleep Disorder
- **Boxed Warnings**
  - Xyrem should not be used with alcohol or other CNS depressants.
  - Sodium oxybate is GHB, a known drug of abuse. Abuse has been associated with some important central nervous system (CNS) adverse events (including death). Even at recommended doses, use has been associated with confusion, depression and other neuropsychiatric events. Reports of respiratory depression occurred in clinical trials. Almost all of the patients who received sodium oxybate during clinical trials were receiving CNS stimulants.
  - Important CNS adverse events associated with abuse of GHB include **seizure, respiratory depression and profound decreases in level of consciousness, with instances of coma and death**. For events that occurred outside of clinical trials, in people taking GHB for recreational purposes, the circumstances surrounding the events are often unclear (e.g., dose of GHB taken, the nature and amount of alcohol or any concomitant drugs).
  - Xyrem is available through the Xyrem Success Program, using a centralized pharmacy
    - The Success Program provides the required prescription form
    - Provides educational materials to prescriber and patient
    - Once signed, Xyrem is shipped to the patient.
    - Patient follow-up recommends every 3 months.

- **Warnings**
  - Due to Xyrem's rapid onset of action, it should only be ingested at bedtime.
  - Xyrem's use with alcohol may potentiate CNS depressant effects.
  - Xyrem is a CNS depressant with the potential to impair respiratory drive.
  - **Overdose: life-threatening respiratory depression** has been reported.
  - Confusion / Neuropsychiatric Adverse Events: including psychosis, paranoia, hallucinations, agitation, and depression.
  - Use in the Elderly: Monitor closely.
- **Dosing**
  - Start 2.25mg at bedtime **while seated in bed** and 2.25mg 2 ½ to 4 hours later
  - Increase to response up to 9mg (4.5mg divided doses) by increasing by 1.5mg qd.
  - Hepatic Insufficiency: decrease dose to half
  - Schedule III drug
- **Drug-Drug Interactions**
  - Avoid with CNS depressants due to cumulative effects

Ropinirole (Requip & Requip XR)

- **Formulations**
  - Immediate-release tablets, extended-release tablets
- **FDA Indications**
  - Restless Leg Syndrome
  - Parkinson's Disease
- **Mechanism of Action**
  - Nonergot dopamine agonist
- **Alerts and Warnings**
  - Falling asleep during activities of daily living, including driving.
  - Syncope and orthostatic hypotension
  - Hallucinations (in Parkinson's Patients only)
  - Pregnancy Category C
- **Dosing**
  - Take tablet of 0.25 mg qd 2-3 hours before bedtime. For additional relief, increase dose to 1mg qd by end of first week and up to 4mg qd by 0.5mg increments each week.

Pramipexole (Mirapex)

- **FDA Indications**
  - Restless Leg Syndrome
  - Parkinson's Disease
- **Mechanism of Action**
  - Nonergot dopamine agonist
- **Alerts and Warnings**
  - Falling asleep during activities of daily living, including driving.
  - Orthostatic hypotension
  - Hallucinations (in Parkinson's Patients only)
  - Pregnancy Category C
- **Dosing**

- Take tablet of 0.125 mg qd 2-3 hours before bedtime. For additional relief, increase dose every 4-7 days to 0.25mg qd and to 0.5mg qd.
- Special Populations: increase titration steps to every 14 days in renal impairment

Additional Precautions For Both Requip & Mirapex

- Rebound May Occur With Use
  - The phenomenon of increased RLS symptoms in the early morning
- Augmentation May Occur With Use
  - The phenomenon of increased RLS symptoms in the evening or afternoon and / or spread of RLS symptoms to additional extremities
- Increase of Urges With Use of Dopaminergic Agents
  - Reported increased urges to gamble, engage in sex and other compulsive behaviors

Medications for the Treatment of Substance Use Disorders

Buprenorphine with naloxone (Suboxone)

- **FDA Indications**
  - Buprenorphine/naloxone sublingual tablet is indicated for the maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.
  - NOTE: Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.
- **Mechanisms of Action**
  - Buprenorphine: kappa-opioid antagonist and mu-opioid partial agonist/antagonist.
  - Naloxone: a potent mu-opioid antagonist that precipitates opioid withdrawal in any individual currently under the influence of an opioid agonist. Naloxone is used in uncontrolled environments to minimize its abuse potential.
  - When buprenorphine is used sublingually as prescribed it produces opioid agonist effects that are mild (display a ceiling effect) as compared to full agonists such as morphine.
  - When buprenorphine/naloxone is taken sublingually as prescribed, the addition of naloxone does not appreciably alter the subjective opioid agonist effects of buprenorphine even though naloxone levels are detectable in the plasma.
  - When buprenorphine/naloxone is administered intravenously to opioid dependent individuals, the naloxone produces opioid antagonists effects, precipitating acute withdrawal symptoms. However, buprenorphine/naloxone still has an abuse potential, primarily among persons with lower level dependence or among those who use buprenorphine as their primary opioid of abuse.
- **Alerts and Warnings**

  - Since Buprenorphine with and without naloxone has an abuse potential, patients need to be cautioned to store these meds securely. Additionally, patients need to be told that giving or selling buprenorphine is against the law.
  - Since buprenorphine is a mu-opioid partial agonist it can induce opioid agonist intoxication. Patients should be cautioned to avoid use of machinery or driving during dose induction or change, until they can reasonably predict their response to the medication.
  - Signs of buprenorphine overdose, whether deliberate or accidental, are those of opioid-agonism: pinpoint pupils, sedation, hypotension, respiratory suppression and possible death
  - Buprenorphine when combined with another CNS depressant, such as a benzodiazepine or alcohol, is more likely to lead to respiratory suppression and can result in death.
  - Management of buprenorphine overdose may include administration of naltrexone and naloxone.
  - Buprenorphine passes into breast milk and should be avoided in breast-feeding patients.
- **Dosing**
  - Buprenorphine/naloxone sublingual tablets: 2mg/0.5mg and 8mg/2mg.
  - Starting dose: 2mg/0.5mg with titration by 2mg/0.5mg until withdrawal symptoms resolve. Target dose is 16mg/4mg qd with a range from 4mg/1mg up to 24mg/6mg qd, administered as a single daily dose.
- **Drug-Drug Interactions**
  - Buprenorphine levels may increase when used concurrently with CYP 3A4 inhibitors, such as, ketoconazole, erythromycin, grapefruit, HIV protease inhibitors. Conversely, buprenorphine levels may decrease with CYP 3A4 inducers, such as carbamazepine, although this has not been studied.

Naltrexone Extended Release Injection (Vivitrol)

- **FDA Indications**
  - Treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of naltrexone ER. This medication should only be used as part of a comprehensive management program that includes psychosocial interventions.
- **Mechanism of Action**
  - Naltrexone is an opioid antagonist, with highest affinity for the mu-opioid receptor
  - Naltrexone ER (Vivitrol) is a microsphere extended release formulation of naltrexone for intramuscular administration. This formulation of naltrexone has an elimination half-life of between 5-10 days.
  - Naltrexone does not diminish alcohol withdrawal symptoms.
- **Contraindications**
  - Patients receiving opioid analgesics
  - Patients with opioid dependence
  - Patients in acute opioid withdrawal
  - Patients with positive urine toxicology for opioids or those who have failed a prior naloxone challenge test (i.e., have continued to use alcohol or opioids during administration of oral naloxone).
- **Alerts, Warnings and Precautions**

  - Hepatic disease: Naltrexone may cause hepatotoxicity in excessive doses. The margin of separation between a standard dose and a dose that can lead to hepatic damage may be five-fold or less.
  - Eosinophilic Pneumonia: one case was reported after start of naltrexone ER
  - Unintended precipitation of opioid withdrawal
  - Opioid overdose following an attempt to overcome opioid blockade. (Note that the package insert states that Vivitrol is not intended in the treatment of opioid dependence.)
  - Depression and suicide: the rate of suicidal ideation and behaviors in subjects administered naltrexone ER were low but higher than in patients receiving placebo. Rates of reported depression were also higher in subjects receiving naltrexone ER as compared to controls.
- **Dosing**
  - 380 mg IM injection q 4 weeks in a gluteal site. If a patient misses or delays a dose, the medication should be administered as soon as possible.
  - Special populations
    - Hepatic disease: naltrexone is contraindicated in patients in acute hepatitis or liver failure. Other hepatic disease is relative contraindication.
    - Pregnancy category C
    - Naltrexone is excreted into mild of lactating mothers.

Acamprosate (Campral)

- **FDA Indications**
  - Indicated to maintain abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation.
  - Treatment with acamprosate should be part of a comprehensive management program that includes psychosocial interventions.
- **Mechanism of Action**
  - The mechanism of action of acamprosate is not fully understood. During chronic alcohol use, there occurs a compensatory increase in excitatory neurotransmission and decrease in inhibitory neurotransmission. During abstinence, this imbalance leads to malaise and other uncomfortable emotions and sensations. Acamprosate is believed to help restore the normal balance between excitatory and inhibitory neurotransmission.
- **Alerts, Warnings and Precautions**
  - Depression and suicide: the rate of suicidal ideation and behaviors in subjects administered acamprosate were low but higher than in patients receiving placebo. Completed suicides occurred in 3 of 2272 (0.13%) patients in the pooled acamprosate group from all controlled studies and 2 of 1962 patients (0.10%) in the placebo group.
- **Dosing**
  - Two 333mg tablets (666mg total each dose) tid.
  - Treatment should be initiated as soon as possible after patient achieves abstinence from alcohol. Administration should be continued during relapses.
  - Special populations
    - Renal disease: for patients with moderate renal impairment, dose should be cut in half to 333mg tid. In patients with severe renal disease (creatinine clearance $\leq$ 30ml /min) acamprosate is contraindicated.

- Pregnancy category C
- Acamprosate is excreted into mild of lactating mothers.

Other Psychotropic Medications

Dextromethorphan and Quinidine (Nuedexta)

- **FDA Indications**
  - Pseudobulbar Affect
- **Mechanism of Action**
  - Dextromethorphan: uncompetitive NMDA (glutamate) antagonist and sigma-1 agonist
  - Quinidine: anti-arrhythmic
  - Mechanism of beneficial effect is unknown
- **Alerts and Warnings**
  - Quinidine is a CYP450 2D6 inhibitor
  - Concomitant use with quinidine, quinine, or mefloquine.
  - Patients with a history of quinidine, quinine or mefloquine-induced thrombocytopenia, hepatitis, or other hypersensitivity reactions.
  - Use with an MAOI or within 14 days of stopping an MAOI. Allow 14 days after stopping NUEDEXTA before starting an MAOI.
  - Prolonged QT interval, congenital long QT syndrome, history suggestive of torsades de pointes, or heart failure.
  - Complete atrioventricular (AV) block without implanted pacemaker, or patients at high risk of complete AV block.
  - Concomitant use with drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine or pimozide).
- **Dosing**
  - Capsule strength: Dextromethorphan hydrobromide 20 mg and Quinidine sulfate 10 mg.
  - Take one capsule qd for one week
  - Then take one capsule q12 hours thereafter

Part 4: Additional Board-Pertinent Information

Antidepressant Use During Pregnancy

- Rates of depression during pregnancy and post-partum period: 10-15%
    - Two thirds of these are women experiencing a recurrence of depression and one third are experiencing their initial episode.
    - Previously, it was believed that pregnancy protected women against depression. It is now known that that is not true.
- Relapse rates during pregnancy for women with previous depression:
    - WITHOUT medication: 67%- 75%
    - WITH medication: 31%
- Risks to fetus and mother from maternal DEPRESSION
    - Depressed pregnant mothers gain less weight
    - Depressed pregnant mothers are more likely to use drugs, including alcohol and tobacco
    - Depressed pregnant mothers have higher rates of miscarriage, premature delivery, and pre-eclampsia
    - Newborns have smaller head circumferences, lower weights, and APGAR scores
- Risks associated with *IN UTERO* ANTIDEPRESSANT EXPOSURE
    - SSRI's and SNRI's after the 20 week of pregnancy can lead to higher rates of **Persistent Pulmonary Hypertension of the Newborn** (PPHN). PPHN is the result of elevated pulmonary vascular resistance to the point that venous blood is diverted to some degree through fetal channels (ductus arteriosus and foramen ovale) into the systemic circulation and bypassing the lungs, resulting in systemic arterial hypoxemia. The risk of developing PPHN with SSRI exposure after the 20th week of pregnancy is approximately six times that of non-exposed newborns.
    - Paroxetine has been linked to fetal heart defects due to exposure in the first trimester.
    - Bupropion has NOT been associated with increased risk of birth defects or of impaired development.
    - When pregnant mother takes an SSRI antidepressant through the time of delivery, the newborn may experience withdrawal symptoms. These include jitteriness, poor sleep, increased muscle tone, tremors, feeding problems. Some infants are transferred to a high risk nursery until these symptoms resolve.
    - Some pregnant women choose to decrease and stop the SSRI in the third trimester to avoid risk of pulmonary hypertension and of the newborn's medication withdrawal symptoms.
    - Two studies looked at the long-term effects on children at the ages of 16 months and 7 years of age of in utero exposure to fluoxetine. No effects were found.
    - Use of tricyclics is generally not recommended during pregnancy
- Use of Antidepressant while BREASTFEEDING
    - Fluoxetine levels in breast-mild are estimated to be 10-20% of that found in the mother's blood
    - Most studies did not find adverse effects on breast-fed infant exposed to fluoxetine but some small studies and case reports found that a small number of infants experienced irritability, diarrhea, vomiting, and disrupted sleep.

- Levels of other SSRI's are lower in breastmilk and may be better choices. Consider sertraline or paroxetine.

Mood Stabilizer Use During Pregnancy

- Rates of relapse of Bipolar Disorder During pregnancy:
  - WITHOUT medication: 67%
  - WITH medication: 35%
- General Management
  - perform pregnancy tests on all your female patients of child-bearing age prior to starting them on a medication.
  - Encourage all female patients of child-bearing age who are on psychotropics to maintain adequate contraception.
  - The safest pregnancies are those that are planned. Note that stopping a mood stabilizer after discovering that the patient is pregnant, perhaps five weeks into the pregnancy, may already be too late.
  - Meds that decrease levels of oral contraceptives and that can lead to unplanned pregnancy
    - Carbamazepine, Oxcarbazepine, Topiramate.
  - All female patients of child-bearing age on valproate should receive folate supplements.
- Engage all you female patients of child-bearing age in a discussion of possible approaches in the event the patient becomes pregnant. The three possibilities are:
  - Continue medications throughout pregnancy
  - Discontinue medications for the duration of pregnancy
  - Discontinue medications for the first trimester only, during which teratogenic risk is greatest.
- **First Trimester – The Danger Period**: First-Trimester exposure to Lithium, valproate, or carbamazepine increases the rate of birth defects.
  - Lithium: Epstein's anomaly with lithium occurs at a rate of 1-2 per 1000 which is about 12-20 times greater risk than in the general population. At delivery lithium levels can rise dramatically due to fluid shifts. Thus, dose should be lowered or medication stopped prior to expected delivery date.
  - Valproate: Neural tube defects occur at a rate of 3-5%. The rate of craniofacial, cardiac and limb abnormalities is also increased.
  - Carbamazepine: Neural tube defects occur at a rate of 1%. And the rate of craniofacial abnormalities is also increased.
  - Other meds: No teratogenic abnormalities have been found with haloperidol, perphenazine, trifluoperazine, or thiothixene. These first generation antipsychotics may be good alternatives to other mood stabilizers. Less is known about teratogenic risk with newer anti-convulsants and second generation antipsychotics.
  - Monotherapy: monotherapy is strongly preferred since use of more than one medication increases risk of birth defects. For example, a 2002 study found 5 out of 50 (10%) neonates had a major birth defect after exposure to valproate and Lamotrigine, a rate that is probably elevated.
- Fetal Monitoring: Patients on lithium, valproate or carbamazepine should receive the following.
  - Maternal serum levels of alpha-fetoprotein prior to the 20^{th} week of pregnancy
  - If alpha-fetoprotein levels are elevated, targeted sonography (to assess for neural tube defects) and amniocentesis should be performed

  - Level 3 ultrasound should be performed to assess for possible cardiac defects (which are increased also with valproate).
  - Serum levels of medications need to be closely monitored since changes in blood volume, hepatic metabolism and renal excretion all occur during the course of pregnancy.
- ECT: ECT remains a relatively safe mood stabilizing alternative to medications.

Ketoconazole Drug-Drug Interactions

- Ketoconazole is a Potent Inhibitor of **CYP 450 3A4**. For example, its inhibiting effects on drugs metabolized by CYP 3A4 is 100 stronger than that of Fluoxetine. The psychiatric medications whose levels may increase with concurrent administration with Ketoconazole include but are not limited to:
  - Alprazolam
  - Diazepam
  - Midazolam
  - Triazolam
  - Carbamazepine
  - Haloperidol
  - Clozapine
  - Clomipramine
  - Fluvoxamine
  - LAAM
  - Methadone

How to Use EMSAM

1. **EMSAM** should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh or the outer surface of the upper arm. A new application site should be selected with each new patch to avoid re-application to the same site on consecutive days. Patches should be applied at approximately the same time each day.
2. Apply the patch to an area of skin that is not hairy, oily, irritated, broken, scarred or calloused. Do not place the patch where your clothing is tight which could cause the patch to rub off.
3. After you have selected the site for your patch, wash the area gently and thoroughly with soap and warm water. Rinse until all soap is removed. Dry the area with a clean dry towel.
4. Just before you apply the patch, remove it from the pouch. Remove half of the protective backing and throw it away. Try not to touch the exposed side (sticky side) of the patch, because the medicine could come off on your fingers.
5. Press the sticky side of the patch firmly against the skin site that was just washed and dried. Remove the second half of the protective liner and press the remaining sticky side firmly against your skin. Make sure that the patch is flat against the skin (there should be no bumps or folds in the patch) and is sticking securely. Be sure the edges are stuck to the skin surface.
6. After you have applied the patch, wash your hands thoroughly with soap and water to remove any medicine that may have gotten on them. Do not touch your eyes until after you have washed your hands.
7. After 24 hours, remove the patch. Do not touch the sticky side. As soon as you have removed the patch, fold it so that the sticky side sticks to itself.

8. Throw away the folded patch so that children and/or pets cannot reach it.
9. Wash your hands with soap and water.
10. If your patch falls off, apply a new patch to a new site and resume your previous schedule.
11. Only one EMSAM patch should be worn at a time.
12. Avoid exposing the EMSAM application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

Dear Colleague, thanks for reviewing work that is periodically updated. I would appreciate your feedback on how to make this manuscript more useful to you as a study aid.

My email is DrJack@AmericanPhysician.com

Warmest regards,

Jack Krasuski, MD