Spring 1-1-2008

Antidepressant Medications

Amir A. Afkhami
George Washington University - School of Medicine and Health Sciences

6.2 Antidepressant Medications

Amir Afkhami, MD, PhD

HISTORY

The first effective antidepressant, **iproniazid phosphate**—a **monoamine oxidase inhibitor** (MAOI)—was originally developed to treat tuberculosis, but was observed to have antidepressant effects. It was marketed to treat depression in 1958. Iproniazid was later replaced by **imipramine**—originally developed to treat psychotic disorders in the 1950s—a less hepatotoxic drug and the first drug in the long line of tricyclic antidepressants (TCAs). The tricyclics were followed by the more tolerated serotonin reuptake inhibitors (SSRIs), beginning with fluoxetine hydrochloride (Prozac), which was approved for the treatment of depression in December 1987.

GENERAL FACTS AND PRINCIPLES OF DEPRESSION AND ANTIDEPRESSANT TREATMENT

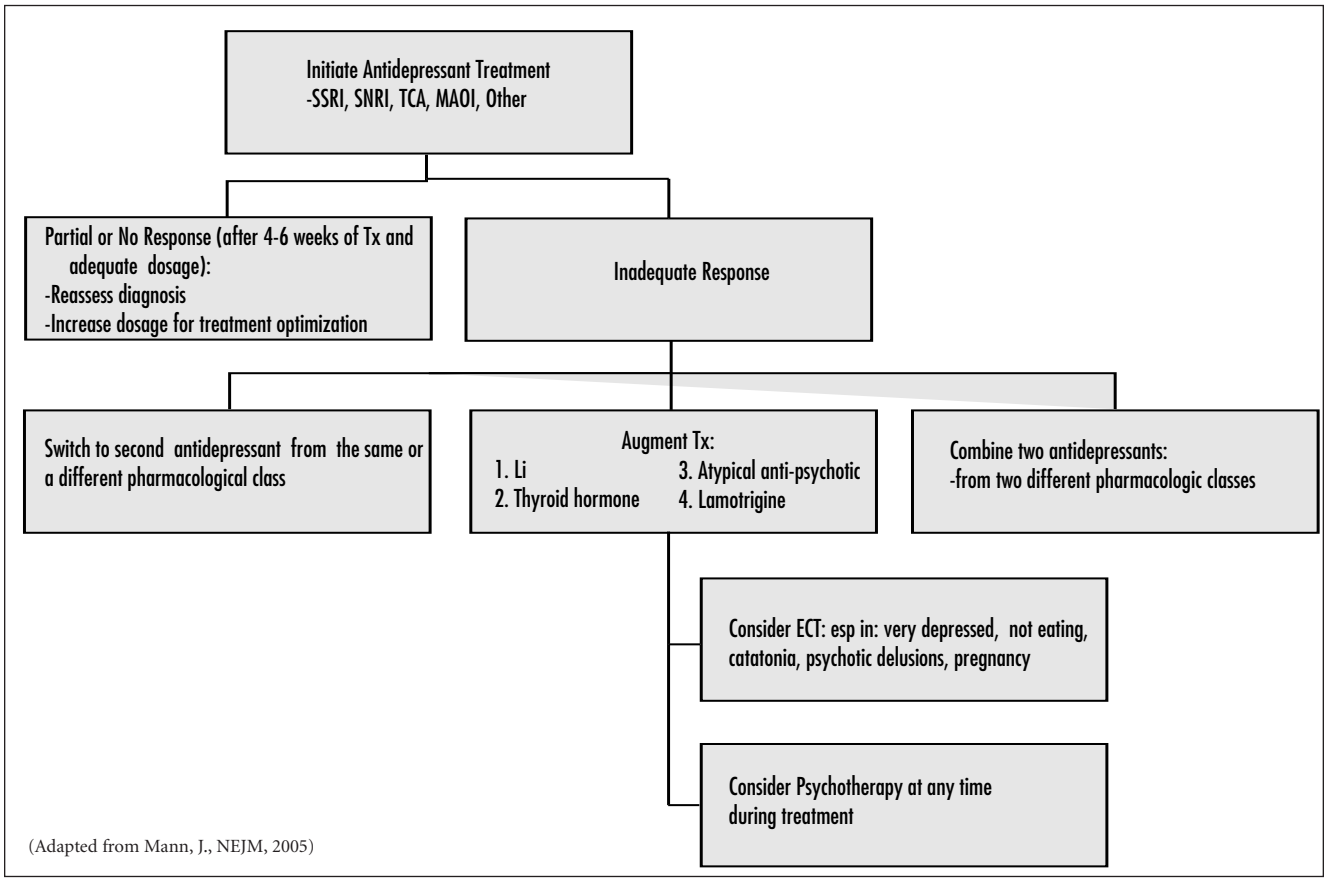
- Approximately half to two thirds of patients with major depression will improve with antidepressant treatment **when treated with an adequate dose of any antidepressant after eight weeks of treatment.**
- Even **without** therapy, the **majority** of patients with major depression recover within **6-12 months**.
- Suicidality remains a major risk factor in patients with major depression and **10-15% of patients with severe major depression eventually commit suicide**, with the risk of suicide increasing after the initial lifting of depression and return of energy.
- The use of antidepressant medication approximately **doubles** the chance that a depressed patient will recover within **two to four months.**
- The main causes of failed antidepressant trials are due to the use of **inadequate dosage** and/or an **inadequate time** for the medication to take effect.
- Antidepressants should be maintained at their **maximum recommended dosage** with **minimum adverse side-effects** and should be tried for at least **four to six weeks** before evaluating effectiveness.
- Discontinuation of Antidepressant treatment during the first 30 days of treatment is more common among **racial minorities,** and **economically** and e**ducationally disadvantaged** populations.
- In general, most antidepressants increase synaptic serotonin, norepinephrine, or dopamine principally by inhibiting their reuptake and metabolism. These first messengers then trigger a signal transduction cascade.
- Lithium, thyroid hormone (T3) and other agents may be used to augment the effect of antidepressants.
- The combination of antipsychotics and antidepressants can be used in patients who have depression with psychotic features.
- **Electroconvulsive therapy** (ECT) is the most efficacious treatment for subtypes of **severe depression and/or depression refractory to pharmacotherapy** (see chapter on "Somatic Treatments").
- Classes of Antidepressants include: selective **serotonin reuptake inhibitors** (SSRIs), **serotonin-norepinephrine reuptake inhibitors** (SNRIs), **heterocyclic and tricyclic antidepressants** (TCAs), **monoamine oxidase inhibitors** (MAOIs), norepinephrine-reuptake inhibitors (NRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), atypical **antidepressants,** and stimulants. (Atypical antipsychotics and anticonvulsants have antidepressant effects, commonly used in combination with antidepressants)

Table 1. Classification, Dose Range, and Side Effects of Antidepressants

Functional Classification Generic (trade name)	Standard Dosage Range (mg/day)	Half Life (hr)	Insomnia & Agitation	Sedation	Hypotension	Anticholinergic Effects	Nausea & GI effects	Sexual Dysfunction	Weight Gain
Selective Serotonin-Reuptake Inhibitors (SSRIs)									
Fluoxetine (Prozac)	5-40	84 (7-10 days for active metabolite)	Moderate	None/Mild	None/Mild	None/Mild	Moderate	Moderate	Mild
Paroxetine (Paxil)	5-80	15-20	Moderate	None/Mild	None/Mild	Mild	Moderate	Moderate	Moderate
Serteraline (Zoloft)	25-150	24 (2-4 days for active metabolite)	Moderate	None/Mild	None/Mild	None/Mild	Moderate	Moderate	Mild
Fluvoxamine (Luvox)	25-300	16-20	Moderate	None/Mild	None/Mild	None/Mild	Moderate	Moderate	Mild
Citalopram (Celexa)	20-40	35	Moderate	None/Mild	None/Mild	None/Mild	Moderate	Moderate	Mild
Escitalopram (Lexapro)	10-20	30	Moderate	None/Mild	None/Mild	None/Mild	Moderate	Moderate	Mild
Selective Serotonin Norepinephrine-Reuptake Inhibitors (SNRIs)									
Venlafaxine (Effexor)	75-375	5 (10 hrs for active metabolite)	Moderate	None/Mild	None/Mild	None/Mild	Moderate	Moderate	None/Mild
Milnacipran (Ixel)	50-200	8	Moderate	None/Mild	None/Mild	None/Mild	Moderate	Moderate	None/Mild
Duloxetine (Cymbalta)	40-120	12	Mild/Moderate	Mild	None/Mild	Mild	None/Mild	None/Mild	None/Mild
Tricyclic Antidepressants (TCAs)									
Tertiary Amine TCA's									
Amitrptyline (Elavil)	25-300	10-50	None/Mild	Severe	Moderate	Severe	None/Mild	Mild	Moderate
Dothiepin (Dothep)	25-300	11-40	None/Mild	Severe	Moderate	Moderate	None/Mild	Mild	Moderate
Clomipramine (Anafranil)	50-250	20-50	Mild	Severe	Moderate	Moderate	Mild	Mild	Moderate
Imipramine (Tofranil)	25-150	5-25	Moderate	Moderate	Moderate	Moderate	None/Mild	Mild	Moderate
Secondary amine TCAs and Tetracyclic Antidepressants [Nonselective Norepinephrine –Reuptake Inhibitors]									
Desipramine (Norpramine)	25-300	12-24	Moderate	None/Mild	Moderate	Mild	None/Mild	Mild	Mild
Nortriptyline (Pamelor)	25-150	18-44	Mild	Mild	Mild	Mild	None/Mild	Mild	Mild
Maprotiline (Ludiomil)	50-200	21-25	Moderate	None/Mild	Mild	Mild	None/Mild	Mild	Moderate
Monoamine Oxidase Inhibitors (MAOIs)									
Phenelzine (Nardil)	7.5-60	1.5-4	Moderate	Mild	Moderate	Mild	Mild	Moderate	Mild
Tranylcypromine (Parnate)	5-60	4.4-8	Moderate	Mild	Moderate	Mild	Mild	Moderate	Mild
Isocarboxazid (Marplan)	20-60	2.5	Moderate	None/Mild	Moderate	Mild	Mild	Moderate	Moderate
Selegiline (Eldepryl)	5-10	2	Mild	None/Mild	Mild	Mild	Mild	Mild	Mild
Moclobemide (Manerix)	300-600	1.5-4	Mild	None/Mild	Mild	Mild	Mild	None/Mild	None/Mild
Mixed-Action and Newer Agents									
Bupropion (Wellbuterin)	75-450	4-24	Moderate	None/Mild	None/Mild	Mild	None/Mild	None/Mild	None/Mild
Mirtazapine (Remeron)	7.5-60	20-40	None/Mild	Severe	Mild	None/Mild	None/Mild	None/Mild	Severe
Nefazodone (Serzone)	50-600	2-18	None/Mild	Moderate	Mild	Mild	Mild	None/Mild	Mild
Trazodone (Desyrel)	50-600	4-9	None/Mild	Severe	Mild	None/Mild	Mild	Moderate	Mild

Adapted from Mann, J., *NEJM*, 2005

ALGORITHM FOR ACUTE TREATMENT OF MAJOR DEPRESSION



(Adapted from Mann, J., NEJM, 2005)

MECHANISM OF ANTIDEPRESSANT ACTION

The mechanism of action of antidepressant medications is not precisely known, however, the "monoamine hypothesis" of depression stems in part from the **serotonin, norepinephrine** and **dopamine** augmenting effects of antidepressants. The modulation of serotonin, which is produced in the neurons of the **raphe nuclei** of the brain-stem, appears to be central to both the pathology and treatment of depression. The most effective antidepressant medications appear to increase synaptic levels of monoamines, produce down-regulation of post-synaptic receptors and trigger a cascade of signal transduction effects that ultimately lead to changes in gene regulation.

CLASSES OF ANTIDEPRESSANTS

SSRIs

Mechanism of Action

- **Inhibit the reuptake of serotonin** (5-hydroxytryptamine or 5-HT) at the synaptic cleft.
- Initial high levels of serotonin in the cleft will not only activate post-synaptic receptors, but also stimulate autoreceptors of pre-synaptic cells thereby **transiently decreasing serotonin production.** Neurons adapt to the high levels of serotonin in the cleft and autoreceptors are down regulated thereby not interfering with serotonin production.
- Changes in receptor adaptation and signal transduction in animal models occur over several weeks and it is believed that these effects mediate the effects of antidepressants and explain why SSRIs take several weeks to take effect.

Primary Indication

- The primary indication of SSRIs is for the treatment of **major depressive disorder (MDD).**
- **All SSRIs are equally effective** in treating depression, although they differ enough from one another that failure to respond to one SSRI doesn't predict failure to a different SSRI.
- SSRIs are the **safest alternative** in depressed patients with **cardio-vascular comorbidities.**

Indications for Specific SSRIs

- **Fluoxetine** is approved by the FDA for treatment of:
  - Acute major depressive disorder (adult and pediatric), recurrent major depressive disorder, bulimia nervosa, obsessive-compulsive disorder, panic disorder, and premenstrual dysphoric disorder.
  - Also effective in treating MDD associated with alcoholism, MDD associated with diabetes, seasonal affective disorder, posttraumatic stress disorder, obesity, hot flashes, migraine headache prophylaxis, and fibromyalgia.
- **Paroxetine** is approved by the FDA for treatment of:
  - Acute major depressive disorder (adults), generalized anxiety disorder, and social phobia.
  - Also effective in treatment of interferon-induced major depressive disorder, diabetic neuropathy, premature ejaculation, and vasovagal syncope.
- **Sertraline** is approved by the FDA for treatment of:
  - Acute major depressive disorder (adults), recurrent major depressive disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, and social anxiety disorder.
  - Also effective in treating major depressive disorder s/p myocardial infarction, major depressive disorder associated with Alzheimer's dementia, generalized anxiety disorder, premature ejaculation, and dysthymic disorder.
- **Fluvoxamine** is approved by the FDA for treatment of:
  - Obsessive-compulsive disorder (adult and pediatric).
- **Citalopram** is approved by the FDA for treatment of:
  - Acute major depressive disorder (adults).
  - Also effective in the treatment of panic disorder, prostatodynia, and social anxiety disorder, MDD associated with stroke, diabetic neuropathy, dysthymic disorder, headache, impulsive aggressive disorder, obsessive-compulsive disorder, panic disorder, pathologic crying, pathologic gambling, posttraumatic stress disorder, and premenstrual dysphoria syndrome.
- **Escitalopram** is approved by the FDA for treatment of:
  - Acute major depressive disorder (adults) and generalized anxiety disorder.

Adverse Effects

(See also Table 1)

Gastrointestinal GI: Side effects are common, including nausea, cramping, diarrhea, bloating, and abdominal pain.

Cardiovascular: May cause bradycardia, normalization of heart rate variability, which may be cardio-protective. Sertraline is extensively studied (SADHEART trial, Glassman et al., JAMA, 2002), proven effective post-myocardial infarction and with unstable angina, with no adverse cardiac effects.

Hematologic: Decrease platelet aggregation, increase bleeding time, leading to easy bruising and risk for GI and other bleeding, particularly in the elderly and when combined with non-steroidal anti-inflammatory drugs (NSAIDS).

Hepatic: Mild AST, ALT elevations possible.

Metabolic and Endocrine: In women, galactorrhea may occur with some SSRIs, due to serotonin down-regulation of dopamine.

Sexual Dysfunction: Decreased libido and delayed or no orgasm are the most common. Dysfunction of erection or engorgement less common.

Neurologic and Neuropsychiatric: SSRIs can cause neuromuscular irritability and extrapyramidal side effects, including worsening of tremor and rigidity in disorders such as Parkinson's Disease and spastic cerebral palsy. Serotonin Syndrome, caused by excessive serotonin (such as occurs with high-dose SSRIs or SSRIs in combination with MAOI's and other agents that potentiate serotonin function), is characterized by delirium, neuromuscular irritability, seizures and autonomic instability signs. It is clinically similar to NMS. Apathy or blunting of emotions is also common with long-term SSRI treatment, thought to be secondary to dopamine down-regulation with SSRIs.

Pregnancy and Lactation: (see section on Women's Mental Health and Reproductive Psychiatry). SSRIs are all Pregnancy class C medications. Recent evidence suggests risk for persistent pulmonary hypertension in neonates when mothers treated in third trimester with SSRIs. Paroxetine recently implicated in an increased risk of birth defects, particularly VSDs and ASDs. SSRIs may cause discontinuation symptoms in neonates. SSRIs all pass into breast milk, though levels of sertraline in nursing infants minimal.

Overdose: Generally safe in overdose.

Suicide Risk: SSRIs now carry "black box" warnings due to increased risk of suicidality (suicidal thinking and behavior) in children and adolescents being treated with these agents. An FDA review of a total of 24 antidepressant trials involving over 4400 patients showed a greater risk of suicidality during the first months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. Other relevant recommendations from the FDA include:

- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.

TCAs

Mechanism of Action

- TCAs block the **Norepinephrine** and 5-HT presynaptic transporter sites and to a lesser extent the Dopamine reuptake transporter.
- **Clomipramine** is predominantly a **5-HT reuptake inhibitor,** whereas **desipramine, nortriptyline,** and **protriptyline** are predominantly **NE reuptake inhibitors** and **amitriptyline, doxepin, imipramine,** and **trimipramine** are largely **equal in inhibiting both** the **NE** and the **5-HT** reuptake mechanism.

Indications

- The primary indication of TCAs, except clomipramine, is for the treatment of Major Depressive Disorder.
- **Clomipramine** is FDA approved for the treatment of **obsessive-compulsive disorder.**

Special Indications

- Panic disorder, social phobias, post traumatic stress disorder, reducing binging and purging in bulimia nervosa, refractory pain syndromes (diabetic neuropathy, fibromyalgia, fibrositis, rheumatoid arthritis, central pain).
- Effective in the treatment of **premature ejaculation.**
- Imipramine and clomipramine are effective in treating **catapleptic episodes** associated with narcolepsy.

Adverse Effects

Anticholinergic: Blurred vision, urinary retention, constipation, dry mouth are not dose dependent. The estimation of anticholinergic potency are as follows: **amitryptyline** > **trimipramine** > **doxepin** > **imipramine** > **desipramine** > **nortriptyline.**

Cardiovascular: Orthostatic hypotension is the most serious complication, due to anti a-1 adrenergic effects. TCAs are class I (quinidine-like) antiarrhythmics, causing **decreased conduction through the A-V node** and resulting in **Q-T prolongation.**

- In patients with preexisting first degree atrioventricular (AV) block there is a risk of complete block and therefore ECG monitoring is required in this patient population.
- TCAs should not be used in patients with cardiovascular disease and should be avoided in post-MI patients in whom TCAs are associated with increased risk of morbidity and mortality.

Dermatologic: Cutaneous vasculitis, urticaria, and photosensitivity.

Hematologic: Benign eosinophilia and leucopenia transiently occur in the first few weeks of therapy. Agranulocytosis, although rare, is a medical emergency and can be fatal so CBC should be monitored in this patient group.

Hepatic: AST, ALT, Alk Phos, or even bilirubin elevations are not uncommon. AST or ALT elevation with values three times the upper limit of normal are worrisome and the TCA should be discontinued.

Metabolic and Endocrine: In women, **Galactorrhea** and **amenorrhea,** which are dose dependent, have been reported. Weight gain has also been reported with TCAs.

Neurologic and Psychiatric: Acute delirium, as a result of TCA's anticholinergic properties, has been reported and can be treated with **physostigmine.** This effect is more common in the elderly and African Americans and is dose dependent (more common in higher doses). A fine resting tremor has also been observed. TCA's can lower the seizure threshold. Switching from depressed to manic or hypomanic states has been reported in bipolar depressed patients.

Sexual Dysfunction: Primarily erectile dysfunction. **Imipramine > desipramine > clomipramine > amitriptyline > protriptyline** in decending order cause disturbances in sexual function.

Pregnancy and Lactation: (see Chapter on Women's Mental Health and Reproductive Psychiatry) Imipramine, amitriptyline, nortriptyline associated with congenital anomalies (category D).

Overdose: The most serious consequence of TCA overdose relate to their cardiovascular effects. Superventricular tachycardia, multifocal PVCs, ventricular tachycardia, flutter, or fibrillation can result in severe hypotension or shock. ECG abnormalities in overdose include prolonged PR interval, widened QRS complex, QT prologation, T-wave flattening or inversion, ST-segment depression, right bindle branch block, complete heart block, or cardiac standstill. Treatment for overdose includes **alkalization** of serum in addition to cardiac monitoring and **ventilatory and pressor** support.

- The **combined** use of **TCA** and **MAOIs** are **counter indicated.**

SNRIs and Newer Mixed Agents

Mechanism of Action

- SNRIs **block monoamine transporters** more selectively than TCAs and without the potential adverse cardiac-conduction effects of TCAs.
- **Duloxetine** and **Venlafaxine** block both serotonin and norepinephrine reuptake. At lower dosages (i.e., <200 mg/day) **Venlafaxine** appears to be more selective for serotonin **transporter; at higher dosages, the noradrenergic effects become more prominent.**
- **Bupropion** blocks the reuptake of norepinephrine and dopamine. It has no serotonergic activity. It is indicated for the treatment of major depressive disorder and smoking cessation.

Indications

- In some studies, Venlafaxine appears to demonstrate **superior efficacy** and **higher rates of remission** in s**evere depression** as compared to SSRIs such as fluoxetine or TCAs. This is still an open issue.

- Venlafaxine and duloxetine are effective for the treatment of chronic pain, diabetic neuropathy, and pain occurring as part of primary or secondary depression. Only Duloxetine has FDA approval for diabetic peripheral neuropathy.
- **Buproprion** is associated with less nausea, diarrhea, somnolence, and **sexual dysfunction** than SSRIs. Bupropion is also effective in treating SSRI-induced sexual dysfunction. In fact, cases of spontaneous and prolonged orgasm on buproprion have been documented in the literature.

Adverse Effects

Generally, side effects are similar to those associated with SSRIs.

- Dose dependent increases in systolic and diastolic blood pressure have been reported in patients on venlafaxine, and bupropion.
- Buproprion has been documented to cause seizures at doses >400mg/day. It should not be used in patients with epilepsy and bulimia.

MAOIs

Mechanism of Action

- MAOIs inhibit the activity of **monoamine oxidase,** an enzyme that breaks down cathecholamine and indolamine neurotransmitters, thereby **increasing** levels of **neurepinephrine, dopamine,** and **serotonin neurotransmitters.**
- Earlier MAOIs inhibited monoamine oxidase irreversibly but newer MAOIs such as **moclobemide** are **reversible inhibitors.**
- Two **isoforms** of MAO have been identified—these are: **MAO-A** & **MAO-B. MAO-A** preferentially degrades s**erotonin, melatonin, epinephrine, and norepinephrine** whereas MAO-B preferentially targets **phenylethylamine, dopamine, and benzylamine.** Newer MAOIs like selegiline (Ensem patch) target the MAO-B more selectively. Drugs that block gastrointestinal MAO-A, l**ike the earlier MAOIs, require patients to be on a low tyramine diet because dietary tyramine is metabolized by MAO-A in the gut.**

Indications

- MAOIs are indicated for typical Major Depressive Disorder and atypical depression. They are preferentially more effective than TCAs in the treatment of atypical depression.

Special Indications

- Panic disorder, social phobia, neurodermatitis, treatment resistant narcolepsy, migrane headaches, and idiopathic hypotension.

Adverse Effects

Allergic: Maculopopular rashes, red-green blindness with optic atrophy (rare).

Cardiovascular: Conduction abnormalities such as **QTc interval shortening,** orthostatic hypotension.

Hypertensive Crisis: The consumption of foods or other products containing pressor amines or sympathomemetic agents together with MAOIs have resulted in critical hyperadrenergic states characterized by **elevations in both systolic and diastolic blood pressures** with potentially dire consequences such as fatal strokes, cardiac arrhythmias, or cardiac failure. **Tyramine containing foods,** most commonly aged cheeses and red wine, are frequently implicated in this complication. Other amines or precursors to amines such as histamine, dopamine, levodopa, and tyrosine may also be implicated. Sympathomimetics such as amphetamines and ephedrine and TCAs can also precipitate this complication when used in conjunction with MAOIs.

- Patients on MAOIs should therefore be on **tyramine-restricted diets** and avoid over the counter remedies that may contain **sympathomimetics** such as phenylephrine based cold remedies. In addition, a **washout** of at least **14 days** should be in effect when switching MAOIs to prevent potential hypertensive crises.

Neurologic: Peripheral sensory neuropathy—probably as a result of **pyridoxine deficiency** secondary to phenelzine. Other effects include ataxia, hyperacusis, hyperritability, muscle tension, myoclonic jerks, carple tunnel syndrome, and in its most severe form seizures, coma, or death. Anorgasmia and impotence have been reported with phenelzine. Phenelzine and tranylcypromine have been associated with daytime drowsiness.

Psychiatric: Similar to TCAs "flipping" from depression to mania or hypomania can occur with MAOIs.

Overdose: Potentially fatal, symptoms may not be evident for 6 to 12 hrs. after ingestion. These include flushing, diaphoresis, tachycardia, hypertension, mental confusion, increased deep tendon reflexes, involuntary movements, seizure.

Teratogenicity and Excretion in Breast Milk: FDA **category C,** MAOIs are counterindicated during pregnancy and tranylcypromine is known to be excreted in breast milk.

REFERENCES

1. Benjamin J. Sadock, MD; Virginia A. Sadock, MD, Eds., *Kaplan & Sadock's Comprehensive Textbook of Psychiatry* (Philadelphia: Lippincott Williams & Wilkins, 2000), Vol. II, pp. 2432-2516.
2. *The American Journal of Psychiatry* [special issue on Depression and its treatment] 163; 1: 1-155.
3. Paul J. Perry, Bruce Alexander, Barry I. Liskow, and C. Lindsay DeVane, *Psychotropic Drug Handbook,* 8th ed. (Philadelphia: Lippincott Williams & Wilkins, 2007).
4. J. John Mann, "The Medical Management of Depression," *The New England Journal of Medicine,* 353; 17: 1819-1834.
5. Glassman AH, O'Connor CM, Califf RM et al.: Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 2002; 288:701-9.