Antidepressants
The Old and The New

October, 1998

In 1958 researchers discovered that imipramine had antidepressant activity. Since then, a number of antidepressants have been developed with a variety of pharmacological mechanisms and side effect profiles.

PHARMACOLOGY & CLASSIFICATION

The mechanism of action for antidepressants is not entirely clear; however they are known to interfere with neurotransmitters.

Tricyclic antidepressants (TCAs) block the reuptake of both norepinephrine (NE) and serotonin (5HT). The relative ratio of their effect on NE versus 5HT varies. The potentiation of NE and 5HT results in changes in the neuroreceptors and is thought to be the primary mechanism responsible for the antidepressant effect. In addition to the effects on NE and 5HT, TCAs also block muscarinic, alpha, adrenergic, and histaminic receptors. The extent of these effects vary with each agent resulting in differing side effect profiles.

Selective serotonin-reuptake inhibitors (SSRIs) block the reuptake of 5HT and increase synaptic 5HT transmission. They have little or no effect on other neurotransmitters. The lack of activity at muscarinic and histaminic receptors results in fewer anticholinergic (ACH) and sedative effects.

Monoamine oxidase inhibitors (MAOIs), phenelzine (Nardil®) and tranylcypromine (Parnate®) inhibit the enzymatic breakdown of 5HT and NE. They are usually reserved for atypical or resistant depression due to their toxicity profile.

Moclobemide (Manerix®) is the first reversible inhibitor of monoamine oxidase A (RIMA). This unique mechanism results in a good tolerability profile and unlike traditional MAOIs, there is no need to restrict dietary tyramine. Although not available in the USA, substantial use elsewhere, including Europe has found moclobemide to be safe and effective.

Nefazodone (Serzone®) has a unique dual mechanism of action. Like the SSRIs, it blocks the reuptake of 5HT; however, it also antagonizes the 5HT2 receptor. The 5HT2 blockade may reduce the stimulating effects seen with the SSRIs. Nefazodone is structurally and pharmacologically similar to trazodone (Desyrel®) although it binds much less to α1 receptors. These agents do not have significant ACH effects. They cause some sedation, have positive effects on sleep, and decrease anxiety.

Venlafaxine (Effexor®), a serotonin-norepinephrine reuptake inhibitor (SNRI), has activity similar to the TCAs without the usual ACH, sedative, or hypotensive side effects. Higher doses can actually cause a small increase in BP which may be useful in elderly patients with orthostatic hypotension. A long-acting (XR) formulation is now available for once daily dosing.

HIGHLIGHTS

- All antidepressants show similar efficacy in the treatment of depression when used in adequate dosages. Choosing the most appropriate agent depends on specific patient variables, concurrent diseases, concurrent drugs, and cost.
- Non-TCA antidepressants such as the SSRIs have become first line agents in the treatment of depression due to their relative safety and tolerability. Each has its own advantages and disadvantages for consideration in individualizing therapy.
- TCAs may be preferred in patients who do not respond to or tolerate other antidepressants, have chronic pain or migraine, or for whom drug cost is a significant factor.
- Secondary amine TCAs (desipramine and nortriptyline) have fewer side effects than tertiary amine TCAs.
- Maintenance therapy at full therapeutic dosages should be considered for patients at high risk for recurrence.

Cost (FYI):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Dosage</th>
<th>Cost</th>
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<tbody>
<tr>
<td>Venlafaxine</td>
<td>XR</td>
<td>150mg po od</td>
<td>$ 740 /yr</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>SR</td>
<td>75mg po bid</td>
<td>$1,420 /yr</td>
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Buproprion SR (Wellbutrin®) has recently been approved in Canada. It is unique in its ability to affect both dopamine (DA) and NE without significant effects on 5HT or other neurotransmitters. It has been effective in TCA nonresponders.

COMPARATIVE EFFICACY

All antidepressants are more effective than placebo in the treatment of major depression and response rates of ~70% are generally reported. Although several new antidepressants have been developed, none have proven to be more effective than the TCAs. There is currently no evidence that one antidepressant is more efficacious than another. When considering efficacy, it is important to remember:

- Onset of action is delayed and a minimum trial of 6 weeks at an adequate dosage is recommended to fully assess efficacy. (40% of those who respond do so only after 4 weeks of therapy!)
- TCAs studies often used doses ~200mg/day of amitriptyline.
- SSRIs have a flat dose-response curve. There is seldom any advantage in dosing higher than the usually effective minimum dose.
- TCAs, venlafaxine, and nefazodone appear to have an ascending dose-response curve, thus higher doses are usually associated with increased efficacy. One advantage with the TCAs over the newer agents is that plasma levels, which have some correlation to efficacy, are readily available.
- Nonresponders may respond to an agent from a different class.
- TCAs require titration up to therapeutic doses; whereas, newer agents generally allow for the immediate initiation of therapeutic
doses; however, patients with anxiety, or a fear of side effects, cautious titration is recommended for even non-TCAs to minimize side effects and increase the likelihood of compliance.

**COMPARATIVE SAFETY**
The overall incidence of side effects with the TCAs is similar to the SSRIs; however, the types of effects are quite different.5 Whereas, TCAs are associated with dry mouth, constipation, blurred vision, and dizziness, the SSRIs can cause a higher incidence of nausea, anorexia, diarrhea, anxiety, agitation, insomnia, nervousness, and sexual dysfunction. Most current literature considers the SSRIs to be better tolerated than TCAs, especially when used at the minimally effective dose.1 One meta-analysis has disputed this however, arguing that dropout rates (~32%) are not significantly different for either group.1

The **secondary amine** TCAs, desipramine (Norpramin®) and nortriptyline (Aventyl®) are generally better tolerated than the tertiary amine TCAs. Desipramine has the lowest incidence of ACH side effects while nortriptyline is least likely to cause orthostatic hypotension. If TCAs are used in elderly patients, desipramine or nortriptyline may be preferred.9 Newer agents may be good alternatives in patients who do not tolerate other antidepressants. Venlafaxine has side effects similar to the SSRIs. Moclobemide also has a relatively low incidence of side effects compared to other antidepressants. Side effects can sometimes be minimized by starting with **low initial doses** and increasing gradually to the usual effective dose. (Adverse effects and Precautions are further compared in Tables 1, 2, and the Comparison Chart.)

**Safety in overdose** is also a significant factor in choosing an antidepressant. The SSRIs have proven to be much safer than TCAs in overdose.2 TCAs may cause neurological and cardiovascular complications; whereas, SSRIs are unlikely to do so. Venlafaxine, nefazodone, and moclobemide are also less toxic than a TCA in overdose.

**Drug Interactions (DIs):** The TCAs are particularly subject to pharmacodynamic DIs with other drugs that have ACH and/or sedative properties. TCAs may also be affected by pharmacokinetic DIs as they are metabolized by the cytochrome P-450 (CYP) -2D6 isoenzyme.

The **SSRIs** inhibit various CYP isoenzymes and affect the metabolism of other drugs to various degrees. Fluoxetine and paroxetine are most likely and fluvoxamine is least likely to have significant effects on CYP. Fluvoxamine, however, will significantly affect other CYP isoenzymes such as 1A2. Sertraline causes less DIs overall but has moderate effects on CYP 2D6 and minimal effects on other isoenzymes. Venlafaxine's effects on the CYP system are thought to be minimal resulting in less DIs.

A serotonin syndrome (Table 1) can occur when one or more serotoninergic drugs are used. Several non-antidepressants having serotoninergic effects include buspirone, dihydroergotamine, lithium, L-dopa, opioids, selegiline, and sumatriptan.

Many serious DIs can occur with the MAOIs. Although moclobemide can have similar DIs, the potential to interact with antihypertensive medications is less.

When **switching antidepressants**, a washout period is usually required to avoid risks of toxicity (See Table 3). This is particularly important when changing to or from an MAOI. A washout period of 5-8 weeks is required for fluoxetine due to the long half life of both it and its active metabolite, norfluoxetine. Combinations of antidepressants may occasionally be used by specialists in carefully selected, difficult to treat patients.

**SELECTING AN ANTDEPRESSANT**
The current literature generally supports the use of non-TCAs as first line agents.2,7,12 One recent Canadian analysis concluded that when health related quality of life and costs borne by the patient were considered, an SSRI first strategy (replaced by a TCA if SSRI unsuccessful) was preferred.5 Subgroups of patients require special considerations for optimal drug selection (See Tables 2 and 4).

Patient specific considerations are important in choosing the most appropriate agent within a class. For example, fluoxetine may be preferred to the SSRI in patients with a history of poor compliance, or in whom cost is a significant factor. Paroxetine or nefazodone may be preferred in patients with a strong anxiety component. Patients with difficulty sleeping may benefit from the relative sedation of nefazodone or fluvoxamine. Fluvoxamine might be a poor choice in patients with sensitive stomachs due to the relatively higher incidence of GI upset. Venlafaxine may be useful in patients at risk of certain drug interactions, or those not tolerating the other agents. (See also Page 4 - Comparison Chart.)

**TREATMENT DURATION / MAINTAINANCE**
Evidence supports a total treatment of 1 year for first episodes (and perhaps longer in the elderly) to reduce the risk of relapse.13 Full therapeutic doses are recommended as relapse is more likely on lower doses.13 Patients should be considered for life-long maintenance therapy if they are at high risk for recurrence.14 Factors associated with increased risk include greater age of onset, number of episodes, rapid recurrence of episodes and concurrent dysthymic disorder (double depression). When **discontinuing**, it is preferable to taper the dosage over a prolonged period (e.g. 3-6 months) while monitoring for relapse.

**AUGMENTATION STRATEGIES**
Failure of an antidepressant trial at an adequate dose and trial period mandates a review of the diagnosis. Depressed patients not responding to at least two trials of an antidepressant may benefit from augmentation therapy. Augmentation has the advantages of avoiding antidepressant withdrawal symptoms while allowing for a more rapid response.15 Disadvantages include a more complex drug regimen, potential DIs, and cost.

Lithium augmentation has the most literature support.16 It enhances the synthesis and release of 5HT. Dosages are typically in the range of 600-900mg at bedtime and improvement is usually seen within 2 weeks.17 Most studies involve TCAs and there is some suggestion that lithium augmentation may not be as effective in patients on SSRIs, especially if they have already been tried at higher dosages. If used, monitoring of lithium levels, thyroid function, and renal function are required.

Thyroid supplements may also be effective in augmenting antidepressant therapy.18 A variety of mechanisms have been proposed including correction of subclinical hypothyroidism, potentiation of noradrenergic neurotransmission, and down-regulation of intracellular thyroid activity. Most of the literature suggests that T3 (liothyronine, Eltroxin®); however, T3 is no longer available.18,19 If T3 is tried, response may be seen within a few days, and should be evident within 3 weeks. Therapy also requires monitoring for thyrotoxicosis and periodic thyroid levels.

Other agents with limited evidence of augmentation potential include alprazolam, L-tryptophan, buspiron, pindolol, and anticonvulsants.

References available on request.
**The Rx Files: Antidepressants Oct/98**

**Supplementary Tables**

**Table 1: Adverse Effects: Management Options**

- **Dizziness** = check BP for orthostatic hypotension; mild symptoms may attenuate over several weeks; ↓ dose or switch agent; encourage adequate fluid intake & avoid excessive salt restriction; Floretine 0.1mg po od & titrate
- **Sedation/ feeling medicated/ foggy** = may attenuate over 1-2 weeks; give single dose 1-2 h prior to at bedtime; ↓ dose or choose alternative agent
- **Peripheral anticholinergic effects** = tolerance may develop over several weeks; switch to alternative agent; treatment options for some symptoms:
  - blurred vision - pilocarpine eye drops; methylcellulose drops for dry eyes
  - urinary hesitancy - brothanechol 25-50mg po tid-qid
  - abdominal cramps, nausea, diarrhea - adjust dose
  - dry mouth - sugarless gum; saliva substitutes (e.g. ORAL balance® Gel)
  - constipation - adequate hydration, activity, bulk forming laxatives
- **Weight gain** = modify & monitor diet & activity; switch to alternate agent
- **Sexual dysfunction** = distinguish etiology (drug versus illness); switch to alternate agent (venlafaxine, bupropion, nefazodone, moclobemide); adjust dose; other:
  - ↓ libido - neostigmine 7.5-15mg 30min prior to intercourse
  - impaired erection - brothanechol 10mg po tid
  - *nargosma - cyproheptadine (Periactin®) 4mg po qam
- **Myoclonus** = TCA toxicity; reassess dose/levels; clonazepam 0.25mg tid
- **Insomnia & anxiety (5HT related)** = ↓ dose; administer in am; + short course of trazodone 50-100mg hs; switch to alternate agent (e.g. nefazodone)
- **SIADH (syndrome of inappropriate antidiuretic hormone secretion)** (hyponatremia) = DC causative agent; fluid restriction (1 l/d)
- **Serotonin Syndrome** = (e.g. excitement, diaphoresis, rigidity, ↑ temp; ↑reflexes, THR, ↓BP) DC serotonergic agents; Tx: Periactin® 4mg po q4h

**Table 2: Precautions**

**TCAs:** benign prostatic hypertrophy, history of urinary retention, uncorrected angle closure glaucoma, history of seizure, post-MI - acute recovery phase, cardiovascular disease, cholinergic rebound upon withdrawal from high doses (dizziness, nausea, diarrhea, insomnia, restlessness, cardiac conduction delays, heart block; arhythmias)

**SSRIs:** hepatic dysfunction (↑ levels & half-life), irritable bowel syndrome, CNS overstimulation (e.g. serotonin syndrome) especially if used in combination with other serotonergic drugs (cryptophan, TCA, lithium, MAOI buspiron, sumatriptan, ondansetron); ↓ withdrawal syndrome: dizziness, GI upset, headache, agitation/restlessness, sleep disturbance (usually mild & transient; less common with fluoxetine)

**MAOIs:** hypertensive crisis can occur secondary to foods containing tyramine (e.g. HIGH ← unpasteurized cheese, cheddar, camembert, blue, yeast extract, herring, aged unpasteurized meats, broad bean pods; MODERATE ← avocado, meat extract, certain ales & beers, wines; LOW ← fruits, cream & cottage cheese, distilled spirits, chocolate); Contraindicated in: cerebrovascular / cardiovascular disease, pheochromocytoma, geriatric or debilitated, hx. of severe headache.

**Bupropion:** Contraindicated in patients with seizure disorder, history of bulimia or anorexia nervosa

**Pediatric Precautions:** Safety of antidepressants in children is not well established. Imipramine is indicated for use in children ≥6 years of age for the treatment of enuresis.

**Pregnancy:** Consider risk versus benefit! ECT & psychotherapy are non-drug options. TCAs & SSRIs, especially fluoxetine have the most clinical data to substantiate their safety. An increase in spontaneous abortions has been noted for fluoxetine. Use lowest dose and try to taper off 5-10 days before delivery.

**Elderly:** extra caution required; lower doses recommended

**Relative Seizure Risk:**

- HIGH ← maprotiline, amoxapine, clomipramine, bupropion
- MODERATE ← amitriptyline, imipramine, trimipramine, norpiripine, desipramine, doxepin, amitriptyline, imipramine, trimipramine, norpipirine, desipramine, doxepin, lowest = trazodone, SSR1S, MAOFS, moclobemide, venlafaxine

**Table 3: Switching Antidepressants:**

The most critical recommendations are in bold; risks of toxicity are greater with higher dosage regimens and inadequate washout period. Some urgent cases may necessitate shorter delays in switching.

| FROM                     | amitriptyline | clomipramine | doxepin | imipramine | desipramine | nortriptyline | venlafaxine | fluoxetine | paroxetine | sertraline | nefazodone | trazodone | phenergan | tranylcypromine | moclobemide |
|--------------------------|---------------|--------------|---------|------------|-------------|---------------|-------------|------------|------------|-----------|------------|-----------|-----------|-----------|---------------|-------------|
| amitriptyline            | 1*            | 1           | 1-7     | 7          | 1          |                |             |            |            |           |           |           |           |           |               |             |
| clomipramine             | 1*            | 1           | 7-14    | 7          | 1          |                |             |            |            |           |           |           |           |           |               |             |
| doxepin                  | 1*            | 1           | 1-7     | 1          | 7          | 1              |             |            |            |           |           |           |           |           |               |             |
| imipramine               | 1*            | 1           | 1-7     | 1          | 7          | 1              |             |            |            |           |           |           |           |           |               |             |
| desipramine              | 1*            | 1           | 1-7     | 1          | 7          | 1              |             |            |            |           |           |           |           |           |               |             |
| nortriptyline            | 1*            | 1           | 1-7     | 1          | 7          | 1              |             |            |            |           |           |           |           |           |               |             |
| venlafaxine              | 1*            | 3           | 7       | 3          | 1          |                |             |            |            |           |           |           |           |           |               |             |
| fluoxetine               | 35*           | 35          | 1       | 35         | 35         |                |             |            |            |           |           |           |           |           |               |             |
| paroxetine               | 1-7           | 7°↓         | 1       | 7°         | 1          | 10°↑          |             |            |            |           |           |           |           |           |               |             |
| sertraline               | 1-7           | 7°↓         | 1       | 10°↑       | 1          | 1              |             |            |            |           |           |           |           |           |               |             |
| nefazodone               | 1-3           | 3°          | 1       | 7°         | 1          | 1              |             |            |            |           |           |           |           |           |               |             |
| trazodone                | 1-7           | 7°↑         | 1       | 7°         | 2          | 2              |             |            |            |           |           |           |           |           |               |             |
| phenergan                | 10-14         | 14          | 10-14   | 14         |            | 14±           | 14±         | 2±         | 2±         |           |           |           |           |           |               |             |
| tranylcypromine          | 10-14         | 14          | 10-14   | 14         |            | 14±           | 14±         | 2±         | 2±         |           |           |           |           |           |               |             |
| moclobemide              | 2             | 2           | 2       | 2          | 2          | 2              |             |            |            |           |           |           |           |           |               |             |

**Table 4: Individualizing Therapy Considerations**

- Anxiety/Panic = SSRIs, nefazodone, (+/- benzoazaine)
- Anxiety, Comorbid = moclobemide; (? buspirone augmentation)
- Atypical* = moclobemide, MAOIs, SSRIs
- Bipolar* = mood stabilizer (+/- antidepressant)
- e.g. lithium, valproic acid, carbamazepine
- Cardiac Condition* = SSRIs, MAOIs, bupropion
- Chronic Pain/Neuropathy = amitriptyline, desipramine
- Elderly* = SSRIs (S.P,X,Z); 2° TCA’s; venlafaxine
- Migraine = amitriptyline, nortriptyline
- Obsessive Compulsive = venlafaxine (?BP; nortriptyline, SSRIs (ambulation, hydration, gradual dose titration)
- Orthostatic Hypotension = venlafaxine, trazodone, SSRIs, moclobemide, venlafaxine, trazodone, nefazodone, amitriptyline
- Phobic = moclobemide, MAOI, paroxetine?
- Psychotic = antipsychotic; (or amoxapine monox.)
- Seizure History = trazodone, SSRs, moclobemide, venlafaxine, trazodone, nefazodone, amitriptyline
- Sleep Disorder = bupropion
- Smoking Cessation = SSRIs, RIMA, venlafaxine, bupropion
- *Atypical depression defined as: mood reactivity; irritability; hyperomnia; hyperphagia; psychomotor agitation; hypersensitivity to rejection.

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<table>
<thead>
<tr>
<th>NAME</th>
<th>Generic / TRADE</th>
<th>RECEPTOR AFFINITY</th>
<th>5HT SELECTIVE</th>
<th>SSRIs SE in General</th>
<th>OTHER</th>
<th>COMMENTS &amp; ADDITIONAL USES</th>
<th>INITIAL &amp; MAX. DOSE</th>
<th>USUAL ADULT DOSE RANGE</th>
<th>$ per MONTH</th>
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<tr>
<td>Citalopram</td>
<td>CELEXA</td>
<td>(20, 40mg tab)</td>
<td>+</td>
<td>SSRI's SE in General nausea, anxiety, insomnia, tremor</td>
<td>+</td>
<td>no most anxiety &amp; stimulating of SSRIs</td>
<td>20mg am</td>
<td>20mg po od/am/am</td>
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<tr>
<td>Fluoxetine</td>
<td>PROZAC</td>
<td>(10,20mg cap &amp; 4mg/ml solution)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>no most anxiety; long half-life (5 wk washout)</td>
<td>10-20mg od</td>
<td>(10mg po od)‡ 20mg po od/am</td>
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<td>Fluvoxamine</td>
<td>LUVOX</td>
<td>(50,100mg tab)</td>
<td>0/+</td>
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<td>0</td>
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<td>40mg/d</td>
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<td>PAXIL</td>
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<td>+</td>
<td>+</td>
<td>Bellmania 50mg hs (insomnia, aggression); less cardiac effects than TCAs.</td>
<td>300mg/d</td>
<td>500mg &amp; 510hs</td>
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<td>BP, dizzy, headache,</td>
<td>+</td>
<td>may try entire dose at hs</td>
<td>50-100mg bid</td>
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<td>no dietary tyramine</td>
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<td>+++</td>
<td>BP, dizziness,</td>
<td>+++++</td>
<td>10-30mg hs for sleep disorders &amp; chronic pain</td>
<td>75mg po bid</td>
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<td>no gastrointestinal preclusion</td>
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<td>150mg po bid/cc</td>
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ACH = anticholinergic effects (dry mouth, constipation, urinary hesitancy, blurred vision); SED = sedation; 5HT = serotonin; NE = norepinephrine; DA = dopamine; TCA = tricyclic antidepressant; SSRI = selective 5HT reuptake inhibitor; MAOI = monoamine oxidase inhibitors; RIMA = reversible inhibitor of MAO-A. Cp = plasma levels avail.; $ = cost to patient in Saskatchewan for 30 days medication (includes markup & dispensing fee); OCD = obsessive compulsive disorder; ADD = attention deficit disorder; wt = weight; wk = week; Tx = treatment; SE = side effects; BP = blood pressure; HR = heart rate; GI = gastrointestinal; epi = epinephrine; DI = drug interactions; EDS = non-formulary in SK.; INITIAL DOSE: Lower initial doses are recommended for elderly patients, and those likely to be more sensitive to adverse effects. ‡ = initial or maintenance dose lower than the usual effective dose.