Antidepressants

The Old and The New

October, 1998 [iii]

In 1958 researchers discovered that imipramine had antidepressant activity.[1] 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$_1$ 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.[2] They have little or no effect on other neurotransmitters. The lack of activity at muscarinic and histaminergic 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.[3]

Nefazodone (Serzone®) has a unique dual mechanism of action. Like the SSRIs, it blocks the reuptake of 5HT; however, it also antagonizes the 5HT$_2$ receptor.[3] The 5HT$_2$ 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 α_1 receptors. These agents do not have significant ACH effects. They cause some sedation, have positive effects on sleep[4], and decrease anxiety.

Venlafaxine (Effexor®), a **serotonin-norepinephine reuptake inhibitor** (**SNRI**), has activity similar to the TCAs without the usual ACH, sedative, or hypotensive side effects.[3] 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): **venlafaxine XR** 150mg po od **$ 740 /yr**; (**Effexor®**) **Reg** 75mg po bid **$1,420 /yr**

Bupropion 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.[5] Although several new antidepressants have been developed, none have proven to be more effective than the TCAs.[6,3] 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!)
- TCA 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.[7,8] 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.[2]
- 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.[9] 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.[10] One meta-analysis has disputed this however, arguing that dropout rates (~32%) are not significantly different for either group.[11]

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.[8]

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 usually 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 serotonergic drugs are used. Several non-antidepressants having serotonergic effects include buspirone, dihydoergotamine, 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 ANTIDEPRESSANT

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 the preferred 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 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 T_3 (liothyronine) is more effective than T_4 (levothyroxine, *Eltroxin*®); however, T_3 is no longer available.[18,19] If T_4 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, buspirone, pindolol, and anticonvulsants.

References available on request.

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Supplementary Tables

Table1: Adverse Effects: Management Options [13,20,21]

- **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; Florinef 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** - bethanechol 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 - bethanechol 10mg po tid
  - •anorgasmia - 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 causitive agent; fluid restriction (1 l/d)
- **Serotonin Syndrome**[22] (e.g. excitement,diaphoresis,rigidity,↑ temp, ↑reflexes, ↑HR, ↓BP) D/C serotonergic agents; Tx: Periactin® 4mg po q4h

Table 2: Precautions[23]

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; arrhythmias)

SSRIs: hepatic dysfunction (↑ levels & half-life), irritable bowel syndrome, CNS overstimulation (e.g. ***serotonin syndrome***) especially if used in combination with other serotonergic drugs (tryptophan, TCA, lithium, MAOI, buspirone, sumatriptan, ondansetron)[24], withdrawal syndrome: dizziness, GI upset, headache, agitation/restlessness, sleep disturbance (usually mild & transient; less common with fluoxetine)[2,25]

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.[2,26,27]

Elderly: extra caution required; lower doses recommended **Relative Seizure Risk:**[28]

HIGH→ maprotiline, amoxapine, clomipramine, bupropion
LOW→amitripyline,imipramine,trimipramine,nortripyline,desipramine,doxe
LOWEST→ trazodone, SSRI'S, MAOI'S, moclobemide, venlafaxine

Table 3: Switching Antidepressants:
Recommended washout period (DAYS) in outpatients[29,30,31]

The more 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**	fluvoxamine	paroxetine	sertraline	nefazodone	trazodone	**phenelzine**	**tranylcypromine**	**moclobemide**	bupropion
amitriptyline	1*		1#		1-7†		7†	1†									
clomipramine	1*		1#		**7-14†**		7†	1†									
doxepin	1*		1#		1-7†		7†	1†									
imipramine	1*		1#		1-7†		7†	1†									
desipramine	1*		1#		1-7†		7†	1†									
nortriptyline	1*		1#		1-7†		7†	1†									
venlafaxine	1#				3†		7†	3†									
fluoxetine	**35**!		**35**!		**1**!		**35**!	**35**!									
fluvoxamine	1-7†		7†		1#		7†	1†									
paroxetine	1-7†		7†		1#		**10**†	1†									
sertraline	1-7†		7†		1#		**10**†	1†									
nefazodone	1-3†		3†		1#		7†	1†									
trazodone	1-7†		7†		1#		7†	2†									
phenelzine	**10-14**		**14**		**10-14**			**14**						**2**##		**14**	
tranylcypromine	**10-14**		**14**		**10-14**		**14**							**2**##		**14**	
moclobemide	**2**		**2**		**2**		**2**									**2**	

SWITCH TO ☞

* no washout required; use equivalent dose;
† taper first drug; start 2nd drug at a low dose;
\# taper first drug over 3-7 days prior to initiating 2nd drug;
taper if high dose; maintain dietary restrictions for 10 days;
! use lower doses of 2nd drug initially; longer tapering period (**8** weeks) may be required for high doses of fluoxetine

Table 4: Individualizing Therapy Considerations[32]

Anxiety/Panic	✔SSRIs, nefazodone, (+/- benzodiazepine)
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[33]	✔amitriptyline, desipramine,
Elderly[8,34,35]	✔SSRIs (S,P,X,Z); **2°** TCA's; venlafaxine
Migraine[36]	✔amitriptyline, nortriptyline
Obsessive Compulsive	✔SSRI (high dose), clomipramine
Orthostatic Hypotension	✔venlafaxine (↑BP); nortryptyline, SSRIs (ambulation, hydration, gradual dose titration)
Phobic	✔moclobemide, MAOI, paroxetine?
Psychotic	✔+ antipsychotic; (or amoxipine monotx.)
Seizure History	✔trazodone, SSRIs, moclobemide, venlafaxine
Sleep Disorders[37]	✔trazodone, nefazodone[3], amitriptyline
Smoking Cessation	✔bupropion
Weight Gain Avoidance[38]	✔SSRIs, RIMA, venlfaxine, bupropion

•***Atypical depression*** defined as: mood reactivity; irritability; hypersomnia; hyperphagia; psychomotor agitation; hypersensitivity to rejection.

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ANTIDEPRESSANT COMPARISON CHART [23,29,39,40,41]

Prepared by: Loren Regier, Brent Jensen - ***The Rx Files*** **- AUG/00**

NAME: **Generic** / TRADE	**RECEPTOR AFFINITY**	**SIDE EFFECTS** ACH.	SED.	OTHER	**COMMENTS & Additional Uses**		**INITIAL & MAX. DOSE**	**USUAL ADULT DOSE RANGE**	**$ per MONTH**
Citalopram CELEXA (20, 40mg tab) abr=**C**	**5HT SELECTIVE** SSRI's	+	+	**SSRIs SE in General** **nausea** {21%(F) - 36% (X)}, anxiety, insomnia {~14%}, agitation,anorexia,tremor somnolence {11-26%}, sweating, dry mouth, headache, dizziness, diarrhea {12% (F,P)-17% (S), constipation {13-18%} sexual dysfx.[42,43]	•avoid in pts prone to overdose •fewer CYP_{450} DI's of SSRIs	**Therapeutic Uses**: √ OCD (esp. F, X, P) √ Panic (esp. P,S) √ Anxiety (all) √ Bulimia nervosa (F) √ Pain syndromes √ diabetic neurop. (C) to deter use of EtOH •flat dose response curve (majority of patients responding do so at the **lowest effective dose**)	**20mg am** 60mg/d	20mg po od 40mg po od	**52.00** 52.00
Fluoxetine PROZAC (10,20mg **cap** & 4mg/ml **solution**) abr=**F**		0	0		•most anorexia & stimulating •long half-life (5 wk washout) •60mg **weekly** maintenance? [44]		10-20mg od 80mg/d	(10mg po od)† 20mg po od am 40mg po od am	27.00 **20.00** 31.00
Fluvoxamine LUVOX (50,100mg tab) abr=**X**		0/+	++		•most nauseating, constipating & sedating of the SSRI's		**25-50mg hs** 300mg/d	100mg po hs 150mg po hs 50am & 150hs	**39.00** 55.00 71.00
Paroxetine PAXIL (20,30mg tab) abr=**P**		+	+		•most anticholinergic of SSRIs		10-20mg am 50mg/d	20mg po od am 30mg po od am 40mg po od am	**64.00** 68.00 121.00
Sertraline ZOLOFT (25,50,100mg cap) abr=**S**		0	+		•most diarrhea & male sexual dysfx of SSRIs •fewer CYP_{450} DI's of SSRIs[45]		**25-50mg am** 200mg/d	100mg po od cc 50mg am &100mg pm 100mg po bid cc	**51.00** 97.00 95.00
Nefazodone SERZONE (100,150,200mg tab) abr-**Z**	**5HT Selective** $SSRI+5HT_2$ rec. antagonism	+	+++	As for SSRIs +: ↓ BP (nausea, dizziness, constipation)	•least stimulating serotonergic •no wt gain; less sex dysfx.,DI's •may try entire dose at hs[46]	•useful in anxiety & insomnia	50-100mg bid 600mg/d	100mg po bid 150mg po bid (300mg po hs)	64.00 **64.00** 64.00
Trazodone DESYREL (50,100mg tab) (150mg Dividose tab:50/75/100/150mg ✘)		**0**	++++	**↓↓ BP**, dizzy, headache, nausea; (α_1 blockade); **priapism** 1/6000, (Tx epi)	√dementia 50mg hs (insomnia, sundowning, aggression); less cardiac effects than TCAs	√ Panic, chr. pain √ **Sleep disorders:** 50-100mg hs	50mg bid 600mg/d	50mg po hs 100mg po bid pc 200mg po bid pc	12.00 22.00 **36.00**
Amitriptyline ELAVIL (10, 25, 50mg tab)	**5HT & NE EFFECTS** tertiary (**3°**) amine TCA's (not all-inclusive listing)	+++++	+++++	**General TCA SE**: ↑HR, ↓BP (Tx: fluid+/- Florinef), weight gain, sexual dysfx, sweating, rash, tremors, ECG abnormalities, seizures •fatal in overdose due to cardiac & neurologic toxicity. •2° amines generally **better tolerated** then 3° amines	•10-30mg hs for sleep disorders & chronic pain •Cp	**Therapeutic Uses** √ Pain Syndromes & sleep disorders[47] (esp. amitriptyline; but 2° TCAs also useful and may be better tolerated) √ Neuropathy √ Agitation & insomnia √ Panic √ Migraine prophylaxis[48] (esp. amitriptyline, nortriptyline) √ ADD (esp. desipramine)	10-25mg hs 300mg/d	50 mg po hs 200mg po hs	8.00 **11.00**
Clomipramine ANAFRANIL (10, 25, 50mg tab)		+++++	++++		•especially effective for **OCD** •Most serotonergic TCA; •Cp •higher risk of seizures		10-25mg hs 300mg/d	50 mg po hs 150mg po hs 200mg po hs	15.00 29.00 **36.00**
Doxepin SINEQUAN (10,25,50,75,100,150mg cap)		+++	++++		•Most histamine block; •Cp •√psychoneurotic/anxious dep.		10-25mg hs 300mg/d	50 mg po hs 200mg po hs	15.00 **24.00**
Imipramine TOFRANIL (10, 25, 50mg tab)		+++	+++		•Cp √ Childhood enuresis (age 6+)		10-25mg hs 300mg/d	50 mg po hs 150mg po hs 200mg po hs	8.00 10.00 **11.00**
Desipramine NORPRAMIN (10, 25, 50, 75,100mg tab) (50mg tabs better price in SK)	**NE > 5HT** secondary (**2°**) amine TCA's (not all inclusive list)	++	++		•Most NE activity •Least ACH side effects •Cp		10-25mg hs 300mg/d	50 mg po hs 150mg po hs (3x50mg) 200mg po hs (4x50mg)	15.00 26.00 **33.00**
Nortriptyline AVENTYL (10, 25mg cap)		+++	++		•Least hypotensive TCA •Cp (response rate higher at lower end of usual range[49])		10mg hs 150mg/d	25mg po hs 50mg po hs 100mg po hs	17.00 **25.00** 43.00
Venlafaxine EFFEXOR (**Reg**. 37.5, 75mg reg,) (**XR** 37.5mg, 75mg, 150mg caps) (contents of XR caps may be sprinkled)	**SNRI 5HT & NE** (also some DA)	+	+	•**As dose↑: ↑BP**, agitation, tremor, sweating, nausea {~37%}, sleep disturbances •caution: withdrawal effects	•initial nausea; "clean TCA" •side effects similiar to SSRIs; •no wt. gain; less sexual dysfx. •adjust dose for ↓ renal fx	√Generalized anxiety Useful BPAD	18.75-37.5mg bid 375mg/d	37.5mg po bid cc 75mg po bid cc 75mg **XR** po **daily** 150mg **XR** po **daily** 225mg **XR** po **daily**	63.00 **119.00** 6300 **66.00** 129.00
Bupropion SR WELLBUTRIN (100mg, 150mg tab)	**DA & NE**	0	0	agitation/insomnia/tremor, ↓appetite, GI upset, psychos.	•highest risk of seizures (~0.4%) •risk of abuse/dependence?	**=ZYBAN®**-→D/C smoking ,√ BPAD	100mg od am 450mg/d	100mg po bid 150mg po bid	45.00 **64.00**
MAOIs: non-selective & irreversible; ✓ atypical/refractory depression; enzyme effect ~10days; many DIs and food cautions (tyramine-hypertensive crisis risk)!; phenelzine *NARDIL* 15mg tab; tranylcypromine *PARNATE* 10mg tab									
Moclobemide MANERIX (100,150,300mg tab)	**RIMA** Selective & Reversible	+	0	Dry mouth, dizzy, headache, nausea, restless, tremor	•no dietary tyramine precaution •enzyme effect lasts ~24hrs	√Atypical, √Anxious-phobic, √Co-morbid anxiety	100mg bid 900mg/d	150mg po bid pc 300mg am&150pm pc 300mg po bid pc	**33.00** 46.00 64.00

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** = gastro-intestinal; **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

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Loren Regier, BSP, BA

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