Antidepressants, Other Review

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Overview

While effectiveness is generally comparable between classes and within classes of antidepressants, the adverse event and safety profiles of the older first generation agents (tricyclic antidepressants, oral monoamine oxidase inhibitors) have greatly reduced their use as first line agents. The second-generation antidepressants, a heterogeneous group of compounds, are now most commonly used as first- and second-line therapy for major depressive and related disorders.

The most commonly prescribed antidepressants, the selective serotonin reuptake inhibitors (SSRIs), are examined in a separate therapeutic class review. These agents, as their name implies, selectively block the reuptake of the neurotransmitter serotonin at the neuronal membrane. It is thought that this enhancement of serotonin activity is primarily responsible for their antidepressant effect.

Other second generation antidepressants exert their effects by inhibiting the reuptake and/or blocking the receptors of one or more of the neurotransmitters thought to be involved in the etiology of depression - dopamine, norepinephrine and serotonin. Another second-generation antidepressant is actually a transdermal form of an older class of antidepressants, the oral monoamine oxidase inhibitors (MAO-Is). This different route of administration results in a different pharmacodynamic and safety profile than the older oral MAO-Is.

Pharmacology[1,2,3,4,5,6,7,8,9,10]

The predominant therapeutic effects of each drug are indicated by a capitalized YES.

Mechanism of Action	TCAs	SSRIs	MAO-Is selegiline	NDRIs	Norepinephrine-Serotonin modulators	Serotonin modulators	SNRIs	Clinical and Physiological Effects
				bupropion	mirtazapine	nefazodone trazodone	duloxetine venlafaxine	
Acetylcholine receptor blockade	Yes	No	No	No	No	No	No	xerostomia, constipation, sinus tachycardia, memory impairment
Dopamine uptake inhibition	No	No	No	YES	No	No	No	antidepressant efficacy, euphoria, anti-Parkinson's activity, aggravation of psychosis
Histamine-1 receptor blockade	Yes	No	No	No	Yes	No	No	sedation, antipruritic effect
Monoamine oxidase inhibition	No	No	YES	No	No	No	No	antidepressant efficacy, acute hypertension
α_1 Norepinephrine receptor blockade	Yes	No	No	No	No	Yes	No	orthostatic hypotension, sedation
α_2 Norepinephrine receptor blockade	No	No	No	No	YES	No	No	antidepressant efficacy, sexual effects
Norepinephrine uptake inhibition	Yes	No	No	YES	No	No	YES*	antidepressant efficacy, blood pressure, tremors, diaphoresis
Serotonin uptake inhibition	Yes	YES	No	No	No	YES	YES*	antidepressant efficacy, nausea, loose stools, insomnia, anorgasmia
Serotonin receptor blockade	No	No	No	No	Yes	No	No	antinausea
Serotonin-2A receptor blockade	Yes	No	No	No	YES	YES	No	antidepressant efficacy, REM sleep, anxiolysis, anti-EPS
Serotonin-2C receptor blockade	No	No	No	No	YES	No	No	anxiolytic efficacy, appetite, motor restlessness

TCA – tricyclic antidepressant, NDRI – norepinephrine dopamine reuptake inhibitor, SNRI – serotonin norepinephrine reuptake inhibitor

A study performed by the manufacturer of duloxetine indicates that it more potently blocks serotonin and norepinephrine transporters in vitro and in vivo than venlafaxine.[11] Duloxetine has a 10-fold selectivity for serotonin and venlafaxine a 30-fold selectivity for serotonin.[12]

Indications

Drug	Mfr	Major Depressive Disorder (MDD)	Generalized Anxiety Disorder (GAD)	Social Anxiety Disorder (SAD)	Panic Disorder	Other Indications
bupropion IR	generic	X				
bupropion SR	generic	X				
bupropion ER (Wellbutrin XL)	GSK	X				prevention of major depressive episodes associated with seasonal affective disorder
duloxetine (Cymbalta)	Lilly	X				diabetic peripheral neuropathic pain
mirtazapine	generic	X				
nefazodone	generic	X				
selegiline (EMSAM)	BMS	X				
trazodone	generic	X				
venlafaxine IR	generic	X				
venlafaxine ER (Effexor XR)	Wyeth	X	X	X	X	

Pharmacokinetics

Drug	Protein Binding (%)	Half-Life (hr)	Active Metabolites
bupropion (Wellbutrin®, XL)[13,14,15]	84	21	erythrohydrobupropion, hydroxybupropion, threohydrobupropion (half-lives 20-37 hours)
duloxetine (Cymbalta®)[16]	>90	12	none
mirtazapine[17,18]	85	20 - 40	desmethyl metabolite
nefazodone[19]	>99	11 - 24	hydroxynefazodone, mCPP
selegiline (Emsam®)[20]	90	18-25	none
trazodone[21]	--	5 - 9	chlorophenylpiperazine, mCPP
venlafaxine (Effexor®, XR)[22,23]	27	5	O-desmethyl-venlafaxine (half life 11 hours)

bupropion: The peak plasma concentration of bupropion sustained-release (SR), the twice-daily dosage form, is 85 percent that of the immediate-release (IR) tablets.[24] The once-daily extended-release (ER) dosage form of bupropion (Wellbutrin XL) has been demonstrated to be equivalent to bupropion IR in terms of bioavailability and peak plasma concentrations. Studies have also shown bioequivalence of bupropion SR and bupropion ER.[25]

nefazodone: Food decreases the absorption and bioavailability of nefazodone by 20 percent. Liver cirrhosis increases its bioavailability by 25 percent. Nefazodone has a nonlinear pharmacokinetic profile due to autoinhibition via CYP450 3A.[26]

selegiline: Transdermal administration of selegiline results in significantly higher exposure to selegiline and lower exposure to its metabolites compared to oral dosing, where extensive first-pass metabolism occurs.[27]

venlafaxine: The ER dosage form (Effexor XR) has a slower rate of absorption and a lower peak plasma concentration than the IR dosage form (Effexor). The extent of absorption of the two dosage forms is equivalent.[28]

Clinical Trials

PubMed and the IFPMA Clinical Trials Portal were searched for English-language randomized human clinical trials of each of the drugs in this class. Additionally, manufacturers were requested to submit pertinent clinical data. The resulting studies were evaluated for validity, bias and importance. Studies of less than six weeks' duration were excluded since this short time frame may be insufficient to appropriately evaluate the effects of antidepressant agents. Smaller studies of MDD (fewer than 100 patients) were not included in this evaluation. Due to the high loss of patients in psychotrophic studies during follow-up, trials with more than 30 percent loss were not excluded on that basis. Studies focusing specifically on the elderly population or on inpatients were excluded because they are not applicable to the patient population under consideration. Studies that did not use the standard rating scales described below were also excluded. The majority of clinical drug trials are sponsored and/or funded by pharmaceutical manufacturers. While objective criteria were used to ensure that the studies included are free of bias, the potential influence of manufacturer sponsorship/funding must be considered.

EFFICACY SCALES

The two most common methods of reporting the efficacy results of antidepressant clinical trials are response rates and remission rates. Response is defined as a 50 percent reduction in severity of the depressive syndrome as measured by a standardized scale or a rating of much or very much improved as assessed by a global assessment method. Remission is a full resolution of the depressive syndrome such that the patient scores in the non-depressed range on such a standardized scale. In clinical trials of antidepressants, the percentage of patients who remit on placebo usually ranges from 20 to 30 percent while the remission rate on active drug is generally 45 to 60 percent. In most studies, response rates are 10 to 15 percent higher than the remission rate.

For MDD, two of the most commonly used standardized rating scales are the Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS).

HAM-D (Hamilton Depression Rating Scale) – This scale is used to assess the severity of MDD in patients already diagnosed with an affective disorder. It is the most widely used and accepted outcome measure for evaluating depression severity. The HAM-D is the standard depression outcome measure used in clinical trials presented to the Food and Drug Administration by pharmaceutical companies for approval of New Drug Applications. The standard HAM-D-21 contains 21 questions. The more commonly used HAM-D-17 excludes four questions relating to diurnal variation, depersonalization and derealization, paranoid symptoms and obsessional and compulsive symptoms. The remaining 17 questions are related to symptoms such as depressed mood, guilty feelings, suicide, sleep disturbances, anxiety levels and weight loss.[29] The HAM-D-17 provides ratings on current DSM-IV symptoms of depression, with the exceptions of hypersomnia, increased appetite and concentration/indecision.

MADRS (Montgomery Asberg Depression Rating Scale) – This scale measures the effect of treatment on depression severity and, as such, requires a baseline assessment before treatment with subsequent assessments during the course of treatment. The MADRS measures the severity of a number of symptoms, including mood and sadness, tension, sleep, appetite, energy, concentration, suicidal ideation and restlessness.[30]

Other standardized scales used in the evaluation of the drugs in this class include:

HAM-A (Hamilton Anxiety Rating Scale) – This is the most frequently used and accepted outcome measure for the evaluation of anxiety in clinical trials. The HAM-A consists of 14 items, each defined by a series of symptoms such as anxiety, tension, depressed mood, palpitations, breathing difficulties, sleep disturbances, restlessness and other physical symptoms.[31] It is included in the National Institute of Mental Health's Early Clinical Drug Evaluation Program Assessment Manual, designed to provide a standard battery of assessments for use in psychotropic drug evaluation.

CGI-I (Clinical Global Impression – Improvement) – This three-item scale assesses the patient's improvement or worsening.[32]

CGI-S (Clinical Global Impression – Severity) – This three-item scale assesses the clinician's impression of the current state of the patient's illness. The rater is asked to 'consider his total clinical experience with the given population'.[33]

PGI (Patient Global Impression – Improvement) – Patients use this scale to rate his/her own improvement.

VAS (Visual Analog Scale) – This is one of the most frequently used measurement scales in health care research, most commonly used for the measurement of pain.[34,35,36] This scale measures the intensity or magnitude of sensations and subjective feelings and the relative strength of attitudes and opinions about specific stimuli.

LSAS (Liebowitz Social Anxiety Scale) – This is a questionnaire whose objective is to assess the range of social interaction and performance situations those individuals with social phobia may fear and/or avoid. It is also a popular measurement tool used by researchers to evaluate the

efficiency of various social anxiety disorder treatments, including pharmacological trials. A modified social anxiety scale exists for children and adolescents.

SPIN (Social Phobia Inventory) – This self-assessment consists of questions which evaluate fear (of people in authority, of parties and social events, of being criticized, of talking to strangers, of doing things when people are watching, and of being embarrassed), avoidance (of talking to strangers, of speaking to people for fear of embarrassment, of going to parties, of being the center of attention, of making speeches, of being criticized, of speaking to authority), and physiological discomfort (blushing, sweating, palpitations, or shaking and trembling in front of other people).[37]

BPI (Brief Pain Inventory) – This questionnaire provides information on the intensity of pain (sensory dimension) as well as the degree to which pain interferes with function (reactive dimension). The BPI also asks questions about pain relief, pain quality, and the patient's perception of the cause of pain.

QLDS (Quality of Life in Depression Scale) - This is a 34-item depression-specific health-related quality of life instrument that assesses the ability and capacity of individuals to satisfy their daily needs.[38,39]

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) – This is a self-report measure designed to enable investigators to easily obtain sensitive measures of the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning.[40]

MAJOR DEPRESSIVE DISORDER (MDD)

bupropion IR and fluoxetine

Patients with MDD were, after a one-week placebo phase, randomly assigned to receive bupropion IR 225 to 450 mg/day or fluoxetine 20 to 80 mg/day for six weeks in a double-blind study.[41] The mean daily dose at the end of this 123 patient study was 382 mg for bupropion IR and 38 mg for fluoxetine. There were no statistically significant differences between treatments on any of the efficacy variables. Response based on HAM-D occurred in 63 percent of bupropion treated patients and 58 percent of fluoxetine treated patients (p=NS). Response based on CGI scores occurred in 68 and 58 percent of patients, respectively (p=NS). HAM-A improved by 59 percent for both treatment groups. There was no significant difference in the improvements in CGI-S and CGI-I. The incidence of treatment-emergent adverse events was low with no statistically significant differences between treatments. The manufacturer of bupropion IR funded this study.

bupropion IR and trazodone

After a one-week placebo lead-in, 124 outpatients with moderate to severe MDD were randomly assigned, in double-blind fashion, to receive bupropion IR 225 to 450 mg/day or trazodone 150 to 400 mg/day for six weeks.[42] Data from the 111 patients used in the efficacy analysis showed that the overall efficacy for each of the two drugs was similar. Improvement in the trazodone treatment group was significantly greater on day seven because of its effect on sleep. At the end of treatment, 58 percent of the bupropion treated patients and 46 percent of the trazodone treated patients were CGI responders. This is equivalent to an odds ratio (OR) for bupropion vs. trazodone of 1.38 / 0.82 = 1.62 indicating that, based on this study, the odds are 62 percent

better for achieving clinical response with bupropion compared with trazodone.[43] Anorexia and anxiety were reported significantly more often for the bupropion treatment group. Somnolence, appetite increase and edema were reported significantly more often in the trazodone treatment group.

bupropion SR and placebo

Investigators conducted a multicenter, randomized, double-blind, parallel-group study to evaluate the antidepressant efficacy and safety of bupropion SR in 362 outpatients with moderate-to-severe depression.[44] The study consisted of a one-week placebo phase followed by eight weeks of active treatment with bupropion SR 150 or 300 mg or placebo daily. By day 56, both bupropion SR treatments were more effective in relieving the symptoms of depression than was placebo. Patients in each active treatment group had significantly reduced symptoms by treatment day 56, as measured by the HAM-D-17, CGI-S and CGI-I scales ($p<0.05$ for all comparisons to placebo). Bupropion SR was well tolerated, with no serious adverse events reported, and no clinically significant changes in vital signs, laboratory test results or physical findings observed.

bupropion XL, escitalopram (Lexapro) and placebo

In two identical, double-blind RCTs, 830 patients with MDD were randomized to receive bupropion XL 300 to 450 mg, escitalopram 10 to 20 mg or placebo once daily for up to eight weeks.[45] Pooled data showed a significant difference between escitalopram and placebo, but not bupropion XL and placebo, in HAM-D-17 total scores. There was no significant difference between active treatments with respect to mean change in HAM-D-17, HAM-D-17 response or remission rates, percentage of patients much or very much improved on CGI-I or change in CGI-S.

duloxetine (Cymbalta) and placebo

Two-hundred sixty-seven adult patients with MDD were randomly assigned to receive duloxetine 60 mg/day or placebo in a nine-week, multi-center, double-blind, parallel-group clinical trial.[46] Duloxetine significantly improved the HAM-D-17 compared with placebo starting at week seven and continuing through the end of the study. Duloxetine also reduced overall pain as well as back, shoulder and time in pain while awake significantly more than placebo. PGI-I and QLDS were significantly improved by duloxetine. Response rates calculated using last-observation-carried forward (LOCF) were 35 and 50 percent for placebo and duloxetine treated patients, respectively ($p=0.017$). LOCF remission rates were 24 and 32 percent for placebo and duloxetine treated patients ($p=0.212$). The estimated probabilities of response were 42 and 65 percent for placebo and duloxetine treated patients ($p=0.004$). Estimated probabilities of remission were 28 and 43 percent for placebo and duloxetine treated patients ($p=0.064$). Discontinuations due to adverse events were more frequent for duloxetine-treated patients (12.5 percent) than for placebo-treated patients (4.3 percent). Nausea, dry mouth, dizziness, and constipation were more frequent for duloxetine than placebo. The manufacturer of duloxetine conducted this study.

A second nine-week study of 245 patients, similar to the one described above, found duloxetine 60 mg/day to be superior to placebo in improving HAM-D-17 starting at week two.[47] At the end of nine weeks, LOCF response rates were 23 and 45 percent for placebo and duloxetine treated patients, respectively ($p<0.001$). LOCF remission rates were 15 and 31 percent for placebo and duloxetine treated patients ($p=0.003$). The estimated probabilities of response were 29 and 62

percent for placebo and duloxetine treated patients (p<0.001). Estimated probabilities of remission were 16 and 44 percent for placebo and duloxetine treated patients (p<0.001). On the VAS for pain, only back pain was significantly reduced as compared to placebo (p<0.001) at the end of nine weeks. Discontinuation due to adverse events for duloxetine-treated patients was 13.8 percent as compared to 2.5 percent for placebo. The manufacturer of duloxetine conducted this study.

In a multicenter, double-blind study, 282 patients with MDD were randomized to receive duloxetine 60 mg or placebo daily.[48] Mean changes in the BPI (Brief Pain Inventory) Average Pain score, the primary efficacy measure, for duloxetine and placebo treated patients differed significantly at most visits, but were not significantly different at the end of the study. Mean changes at endpoint in the depression rating scales used (HAM-D-17, CGI-S, PGI-I) did not differ significantly between duloxetine and placebo treatment groups. Rates of discontinuation due to adverse events were 14.2 percent and 2.1 percent for duloxetine and placebo, respectively (p<0.001). Treatment-emergent adverse events reported at a significantly higher rate by duloxetine-treated patients and included nausea, dry mouth, fatigue and decreased appetite. The manufacturer of duloxetine sponsored this study.

mirtazapine and paroxetine

A total of 197 patients with MDD were randomized to 24 weeks of therapy with mirtazapine 30 to 45 mg/day or paroxetine 20 to 30 mg/day in a double-blind manner.[49] Both treatments were efficacious in improving depressive symptomatology, as assessed by group mean HAM-D-17, percentages of HAM-D responders and remitters and CGI responders. The mirtazapine group showed statistically significantly larger decreases from baseline in the group mean HAM-D-17 at weeks one, two and four. Statistically significant decreases with paroxetine were seen at weeks two and four. Mirtazapine had a significantly higher incidence of fatigue while paroxetine had significantly more patients complaining of increased sweating, headache and nausea.

mirtazapine and sertraline

In a double-blind, multicenter study, 345 patients with MDD were randomized to receive mirtazapine orally dissolving tablets 30 to 45 mg/day or sertraline 50 to 150 mg/day for eight weeks.[50] The primary efficacy variable, the mean change from baseline in the HAM-D-17, showed that mirtazapine was significantly (p<0.05) more effective than sertraline at all assessments during the first two weeks of the study. After this time, the HAM-D-17 was similar in both groups. Reduction in sleep disturbance was significantly greater in the mirtazapine group (p≤0.01). Both drugs also yielded similar effects in terms of HAM-D response, HAM-D remission rate, MADRS and CGI. Approximately two-thirds of the patients in each treatment group reported at least one adverse event; 13 percent of patients in the mirtazapine group and three percent of the sertraline group withdrew from the study due to adverse events.

nefazodone and placebo

A total of 165 outpatients with chronic MDD were enrolled in a randomized trial comparing nefazodone (maximum dose 600 mg/day) and placebo.[51] During this one-year study of maintenance treatment, a committee of research clinicians assessed the occurrence of major depressive episodes with the HAM-D and a blinded review of symptom exacerbations. At the end of one year, the probability of recurrence was 30.3 percent for nefazodone-treated patients and

47.5 percent for patients receiving placebo (p=0.043). Somnolence was significantly greater among the patients taking active medication (15.4 percent) compared with placebo (4.6 percent).

selegiline and placebo

Following a one-week placebo lead-in, 177 adults with MDD were randomly assigned to receive selegiline 6 mg/24 hours or placebo transdermally in a double-blind manner for six weeks.[52] The patients followed a tyramine-restricted diet during the medication trial and for two weeks after completion of treatment. At the conclusion of the trial, patients in the selegiline group showed significantly greater improvement than placebo in HAM-D-17 (p=0.01), MADRS (p=0.005) and CGI-S (p=0.007). Response rates based on HAM-D-17 were 38 percent for selegiline and 23 percent for placebo (p=0.04). Response rates based on CGI-S were 42 and 27 percent, respectively (p=0.03). Most responders showed improvement after one week of treatment. Five percent of patients in each group withdrew from the study due to adverse events. Application site reactions occurred in 36 percent of patients receiving selegiline and 17 percent of those receiving placebo (p=0.006). Otherwise, there was no significant difference in adverse event profiles of the two groups.

In a double-blind study, 289 adults with MDD (out of 365 enrollees) were randomized to receive selegiline 6 mg/24 hour or placebo transdermal patches daily for up to eight weeks.[53] Patients were not placed on tyramine-restricted diets. Selegiline was superior to placebo on the MADRS (p=0.001), but not on the HAM-D-17 or CGI-S. Side effects were similar in the two groups, with the exception of application site reaction, which occurred in 32 percent of the selegiline-treated patients and 15 percent of placebo treated patients (p=0.001).

In a similar study, 265 patients with MDD were randomized, in double-blind fashion, to receive selegiline 6 mg/24 hour or placebo transdermal patches for eight weeks.[54] Doses could be increased per protocol for patients who failed to show therapeutic response. Patients were not placed on tyramine-restricted diets. At the conclusion of this study, selegiline was superior to placebo as measured by the HAM-D-28 and MADRS ($p \leq 0.05$ for both comparisons endpoints).

trazodone and fluoxetine

Outpatients with current nonpsychotic major depressive episodes of at least four weeks duration were given single-blind placebo for one week, after which they were randomized to double-blind treatment with fluoxetine or trazodone for six weeks.[55] The median sustained doses in the 126 patients in the study were 250 mg/day for trazodone and 20 mg/day for fluoxetine. The HAM-D-21 improved similarly in both treatment groups ($p<0.001$ for each group compared to baseline). There were no differences between the groups in CGI-S, CGI-I or PGI-I. More fluoxetine-treated patients reported rhinitis and tremor ($p \leq 0.05$), and more trazodone-treated patients reported somnolence and dizziness ($p \leq 0.05$). More combined events suggesting activation (agitation, anxiety, nervousness, insomnia) were reported with fluoxetine (15.4 percent) than with trazodone (3.3 percent, $p \leq 0.05$). More combined events suggesting sedation (somnolence, asthenia) were reported with trazodone (42.6 percent) than with fluoxetine (21.5 percent, $p \leq 0.05$). Discontinuation rates for activation and sedation did not differ between treatments. The manufacturers of fluoxetine conducted this study.

venlafaxine IR and fluoxetine

In an eight week, multicenter, double-blind, parallel-group study, 382 outpatients with moderate to severe MDD for at least one month were randomized to treatment with venlafaxine IR 37.5 mg twice daily or fluoxetine 20 mg once daily.[56] Doses could be doubled after three weeks for poor response. Both drugs produced significant improvements from baseline in mean HAM-D and MADRS ($p<0.05$), but no significant differences were noted between groups. High response rates were noted with 81 percent in the venlafaxine group and 84 percent in the fluoxetine group achieving that endpoint. Remission was observed in 60 percent of the patients in each group. There were no significant differences in the occurrence of adverse events between groups. The manufacturer of venlafaxine IR funded this study.

In a double-blind study, 314 patients with MDD were randomized to venlafaxine 75 to 150 mg/day or fluoxetine 20 mg/day for eight weeks.[57] Both treatment groups significantly improved HAM-D, MADRS and CGI from baseline. While the HAM-D response at week six was higher in the venlafaxine group (72 percent) than the fluoxetine group (60 percent; $p=0.023$), there was no significant difference at the conclusion of the study. Significantly more patients reported nausea in the venlafaxine group (28 vs. 14 percent; $p=0.003$). The rate of withdrawal from the study due to adverse events was nine percent in the venlafaxine group and four percent in the fluoxetine group.

In a multicenter double-blind study, 341 patients with MDD and symptoms for more than two weeks were randomized to venlafaxine 75 mg/day or fluoxetine 20 mg/day, each given as fixed doses for 12 weeks.[58] Both treatments significantly improved MADRS, HAM-D-21 and CGI; there were no significant differences between groups. Response was noted in 55 percent of venlafaxine patients and 63 percent of fluoxetine patients. Remission occurred in approximately 35 percent of patients in each group. These low active-treatment remission rates are likely due to the use of a more conservative definition of remission (MADRS $\leq$6 rather than the more usual $\leq$10). There were no significant differences in adverse events between groups.

venlafaxine IR and sertraline

In a multicenter double-blind study, 147 patients with MDD were randomized to receive venlafaxine IR 37.5 mg twice daily or sertraline 50 mg once daily for eight weeks.[59] After two weeks, the doses could be increased to venlafaxine IR 75 mg twice daily or sertraline 50 mg twice daily. There were no significant differences between treatments in mean changes in HAM-D-21, MADRS or CGI-I, although each improved significantly from baseline. At the conclusion of the study, the HAM-D-21 response rate was higher in the venlafaxine group (83 percent) than in the sertraline group (68 percent; $p=0.05$). Similarly, HAM-D-21 remission rates were higher in the venlafaxine group than in the sertraline group (68 and 45 percent, respectively; $p=0.008$); this difference was more pronounced in patients who increased their dose. There was no significant differences observed between treatment groups for adverse events. The manufacturer of venlafaxine IR funded this study.

venlafaxine IR and venlafaxine ER (Effexor XR)

In a double-blind study, 287 patients with MDD were randomized to receive venlafaxine IR 37.5 mg twice daily, venlafaxine ER 75 mg once daily or placebo for a maximum of 12 weeks.[60] If the response was inadequate after two weeks of treatment, the daily dose of venlafaxine could be increased to 150 mg. Both dosage forms of venlafaxine were significantly superior to placebo

beginning at week two for the HAM-D and at week three for the MADRS. Significant improvement in CGI-S began at week six for venlafaxine IR and at week four for venlafaxine ER. Venlafaxine ER exhibited superiority over venlafaxine IR at week 12 for all efficacy variables.

venlafaxine ER (Effexor XR) and placebo

In an eight-week double-blind study, 191 patients with MDD were randomized to receive venlafaxine ER 75 to 225 mg/day or placebo.[61] Venlafaxine was significantly more effective than placebo beginning at week two on the CGI-S and at week four on the HAM-D and MADRS. This superiority continued through week eight. Nausea, insomnia and somnolence occurred more frequently with venlafaxine.

venlafaxine ER (Effexor XR) and escitalopram (Lexapro)

An eight-week, randomized, double-blind study compared the efficacy and tolerability of escitalopram to venlafaxine ER in 293 primary care patients with MDD.[62] The efficacy of escitalopram 10 to 20 mg was similar to venlafaxine ER 75 to 150 mg, based on mean change from baseline to week eight in MADRS. Response rates were 80 percent in the venlafaxine group and 77 percent in the escitalopram group (p=NS). Remission rates were 70 percent in each group, although sustained remission was attained nearly one week earlier in the escitalopram group compared to the venlafaxine group. More venlafaxine-treated patients had nausea, constipation, and increased sweating than patients treated with escitalopram ($p<0.05$ for each comparison). When treatment was completed after eight weeks, significantly more venlafaxine-treated patients had discontinuation symptoms ($p<0.01$).

In a randomized trial, 195 outpatients with MDD received one week of single-blind placebo treatment, followed by eight weeks of double-blind, fixed-dose treatment with either escitalopram or venlafaxine ER, rapidly titrated to 20 mg/day and 225 mg/day, respectively.[63] Mean changes from baseline to endpoint in MADRS for escitalopram and venlafaxine ER were similar. Response rates for the escitalopram and venlafaxine ER groups were 59 and 48 percent, respectively (p=NS). Remission rates at endpoint were 41 percent for escitalopram and 37 percent for venlafaxine ER (p=NS). The venlafaxine ER group had a higher incidence of treatment-emergent adverse events (85 percent) and discontinuation due to adverse events (16 percent) than the escitalopram group (68 and four percent, respectively; $p<0.05$ for both comparisons).

venlafaxine ER (Effexor XR) and fluoxetine

In a multicenter double-blind study, 301 patients with MDD were randomized to venlafaxine XR 75 to 225 mg/day, fluoxetine 20 to 60 mg/day or placebo; doses could be increased after two weeks.[64] At the eight-week endpoint, there were no significant differences between the two active treatments on HAM-D-21 or MADRS in the LOCF analysis. Both active treatments significantly improved HAM-D-21 compared to placebo. Only venlafaxine improved MADRS and CGI compared to placebo. Venlafaxine patients experienced significantly more dizziness and nausea than fluoxetine or placebo patients ($p<0.05$). The manufacturer of venlafaxine ER funded this study.

venlafaxine ER (Effexor XR) and sertraline

In an eight-week double-blind study, 163 subjects with MDD were randomized to receive venlafaxine ER 75 to 225 mg/day or sertraline 50 to 150 mg/day.[65] There were no significant differences in the effects of the two agents on Q-LES-Q (the primary endpoint), HAM-D, HAM-A or CGI-S. This lack of difference was also noted for two predetermined subgroups – patients with anxious depression and those with severe depression. Withdrawal due to adverse events occurred in 8.4 percent of venlafaxine patients and 3.8 percent of sertraline patients. The manufacturer of sertraline funded this study.

GENERALIZED ANXIETY DISORDER (GAD)

venlafaxine ER (Effexor XR) and placebo

In a double-blind study, 251 non-depressed outpatients with GAD requiring treatment were randomly assigned to receive either venlafaxine ER or placebo for 28 weeks.[66] The dosage of venlafaxine (75, 150 or 225 mg/day) was based on symptom response. During weeks six through 28, response rates in the venlafaxine XR group were at least 69 percent compared with 42 to 46 percent in the placebo group ($p<0.001$). By an evaluable-patient analysis, venlafaxine XR significantly improved all primary efficacy measures from week one or two through week 28, including the HAM-A, CGI-I and CGI-S ($p<0.001$ for all comparisons to placebo). The most common treatment-emergent adverse event was nausea, followed by somnolence and dry mouth.

In five multicenter, double-blind, clinical trials, 1,839 adult outpatients with GAD were randomized to receive fixed or flexible doses of venlafaxine ER 37.5 to 225 mg/day or placebo.[67] Three trials had a duration of eight weeks; two trials had a duration of 24 weeks. On the CGI-I, 66 percent of patients aged 60 years or older responded to venlafaxine ER compared to 41 percent of patients on placebo ($p<0.01$). For patients less than 60 years, comparable figures were 67 percent and 44 percent, respectively ($p<0.001$). In older adults, 23 percent of venlafaxine ER patients and 31 percent of placebo patients discontinued treatment prematurely; comparable figures for younger adult patients were 27 percent for the venlafaxine group and 28 percent for the placebo group, respectively. Discontinuations due to adverse events were 15 percent and 14 percent for venlafaxine ER and placebo, respectively, in older adults compared with 15 percent and eight percent for younger adults.

In a 24-week double-blind, parallel-group study, 244 primary care patients with GAD were randomized to receive venlafaxine ER 75 mg or placebo, each given daily.[68] After two weeks, the dose could be doubled if the physician considered the response poor. At 24 weeks, the HAM-A trended towards improvement in the venlafaxine group ($p=0.05$ compared to placebo). Remission rates measured at 24 weeks were 28 percent for the venlafaxine group and 19 percent for the placebo group ($p=0.11$).

SOCIAL ANXIETY DISORDER (SAD)

venlafaxine ER (Effexor XR) and placebo

A multicenter, double-blind trial examined the efficacy and safety of venlafaxine ER in the treatment generalized SAD.[69] Two hundred seventy-two outpatients were randomly assigned to receive either flexible dose venlafaxine ER 75 to 225 mg per day or placebo for 12 weeks.

Venlafaxine ER was significantly more effective than placebo as demonstrated by the LSAS at weeks four to 12. Both the CGI-S and CGI-I showed that venlafaxine ER was significantly more effective than placebo at weeks four to 12. Response rates were significantly higher in the venlafaxine ER group throughout the last eight weeks of the study.

A double-blind study evaluated the efficacy, safety and tolerability of venlafaxine ER in adult outpatients with generalized SAD.[70] Patients were randomly assigned to receive 12 weeks of treatment with a flexible dose of venlafaxine ER 75 to 225 mg per day or placebo. Data from 271 patients were analyzed for efficacy; 279 patients were analyzed for safety. Overall, 173 patients completed the study. Improvement on the LSAS was significantly greater with venlafaxine ER treatment than with placebo throughout the last six weeks of the study ($p<0.05$). CGI-S and SPIN were significantly better with venlafaxine ER from week eight through the completion of the study. Week 12 response rates based on LSAS were significantly greater in the venlafaxine ER group (44 percent) than in the placebo group (30 percent; $p=0.018$). Remission rates were also significantly higher in the active treatment group (20 percent) than the placebo group (seven percent; $p<0.01$). Patients experienced no unexpected or serious adverse events.

In a multicenter study, 386 outpatients with SAD were randomized to venlafaxine ER 75 mg/day fixed dose, venlafaxine ER 150 to 225 mg/day flexible dose or placebo.[71] In this double-blind study, improvement on the LSAS, the primary outcome, was greater with either regimen of venlafaxine ER than placebo. This improvement was sustained throughout the six-month trial. Of patients receiving either dose of venlafaxine ER, 58 percent responded to treatment compared to 33 percent of those receiving placebo ($p<0.001$). Corresponding remission rates were 31 and 16 percent, respectively ($p<0.01$). There were no differences in outcome between the two venlafaxine ER dosage regimens.

venlafaxine ER (Effexor XR) and paroxetine

Four-hundred thirty-four adult outpatients with SAD were randomized to receive venlafaxine ER 75 to 225 mg/day, paroxetine 20 to 50 mg/day or placebo in a double-blind manner for 12 weeks.[72] Patients with other anxiety or depressive disorders were excluded from this trial. Treatment with venlafaxine ER or paroxetine was associated with significantly greater improvement in LSAS (primary efficacy variable), CGI-I and SPIN, than treatment with placebo ($p<0.05$ for all comparisons to placebo). No significant differences in any of the efficacy variables were observed between the venlafaxine ER and paroxetine groups. The week 12 response rates were similar for the venlafaxine ER (69 percent) and paroxetine (66 percent) groups and were significantly higher than the placebo group (36 percent; $p<0.05$). Both active treatments were generally well tolerated and were associated with a similar incidence of adverse events. The manufacturer of venlafaxine ER funded this study.

PANIC DISORDER

venlafaxine ER (Effexor XR) and placebo

In a double-blind trial, 361 adults with panic disorder were randomized to receive venlafaxine ER 75 to 225 mg/day or placebo for up to 10 weeks.[73] In this study, there was no difference between treatment groups in the proportion of patients free from full-symptom panic attacks, although there were fewer limited-symptom panic attacks in the venlafaxine ER group. Venlafaxine ER was also associated with a lower mean frequency of panic attacks, as well as higher response and remission rates and improvements in anticipatory anxiety, fear and avoidance.

NEUROPATHIC PAIN

duloxetine (Cymbalta) and placebo

In a 12-week, multicenter, double-blind study, 457 patients experiencing pain due to diabetic polyneuropathy were randomly assigned to treatment with duloxetine 20 mg once daily, 60 mg once daily, 60 mg twice daily (twice FDA approved dosage) or placebo.[74] The two higher doses of duloxetine demonstrated statistically significant greater improvement than placebo in the 24 hour mean VAS for pain, the primary efficacy measure, beginning one week after randomization and continuing throughout the 12-week trial. Significantly more patients in all three active-treatment groups achieved a 50 percent reduction in the 24-hour mean VAS for pain compared with placebo. Duloxetine treatment was considered to be safe and well tolerated with less than 20 percent discontinuation due to adverse events.

In a similar study, patients with diabetic peripheral neuropathic pain (DPNP) were randomized to treatment with duloxetine 60 mg or placebo once or twice daily for 12 weeks; the higher dose of duloxetine is twice the FDA-approved dosage.[75] Both doses of duloxetine were superior to placebo in reducing the 24-hour average pain severity score. Treatment with duloxetine also resulted in greater improvement in the secondary endpoints of CGI-S and PGI. This study was performed by the manufacturer of duloxetine.

venlafaxine ER (Effexor XR) and placebo

An eight-week, double-blind, randomized, placebo-controlled trial evaluated the effectiveness and safety of venlafaxine ER 75 and 150 mg on ongoing pain and quantitative sensory tests in 60 patients with neuropathic pain.[76] In the 55 patients who completed the study, VAS for pain decreased significantly in all three treatment groups. There was no difference regarding pain intensity and escape medication. While the degree of temporal summation to electrical and heat stimuli decreased significantly in both venlafaxine groups compared to placebo, the study showed no significant effect of venlafaxine on ongoing pain intensity.

Pediatrics

Although clinical trials with TCAs have failed to show efficacy in pediatric patients, this may be due to the faulty design of many early studies. The low rate of response to TCAs in children may also be due to a lack of effect of these predominantly noradrenergic drugs on the noradrenergic system that is not yet mature in children. Nonetheless, TCAs are indicated for the treatment of MDD in children 12 years and older.

Studies of SSRIs were the first to show antidepressant efficacy in children. As a result, these drugs are used most often in the treatment of children with MDD. The SSRIs are also first-line agents for the treatment of anxiety disorders in children. Non-SSRI antidepressants are most often used as first line therapy in children in the presence of comorbidities, such as attention-deficit/hyperactivity disorder (ADHD), where bupropion may be more effective than an SSRI.[77]

All of the antidepressants in this class have the following black box warning regarding suicidality in children and adolescents:

"Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of any antidepressant in a child or adolescent must balance this risk 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 of the need for close observation and communication with the prescriber. These drugs are not approved for use in pediatric patients. Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials."

Further labeling for these drugs states the following:
"All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits. Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers."

A FDA research team conducted a meta-analysis of 24 placebo-controlled studies of nearly 4,600 pediatric patients with MDD, OCD and GAD.[78] The drugs studied included bupropion, mirtazapine, nefazodone and venlafaxine, in addition to several SSRIs. There were 89 primary outcome events of suicidal behavior or ideation and 120 secondary outcome events of possible suicidal behavior or ideation. There were no completed suicides. The overall risk difference between active treatment and placebo was 0.01 for the primary outcome and 0.02 for the secondary outcome ($p<0.05$ for both outcomes).

<u>bupropion SR</u>

Of 11 adolescents with MDD enrolled in a study, eight completed an eight-week open-label trial of bupropion SR.[79] The SIGH-SAD, an expanded HAM-D, improved significantly. Improvement on the CGI-I was found in eight of 11 subjects. The mean daily dose of bupropion SR was 362 mg and was well tolerated; insomnia and weight loss were experienced by 55 percent of patients.

Investigators enrolled 24 adolescents (aged 11 to 16 years) with comorbid depression and ADHD.[80] Subjects received twice daily bupropion SR in a flexible dosing regimen up to 6 mg/kg/day; the mean final dose was 3.9 mg/kg/day. By CGI, clinicians rated 58 percent of the children as responders in both depression and ADHD, 29 percent as responders in depression only and four percent as responders in ADHD only. Parents' ($p<0.0005$) and children's ($p=0.16$) ratings of symptoms of depression improved significantly. Significant improvement in ADHD symptoms were noted by parents ($p<0.0005$), but not teachers ($p=0.08$). No subjects withdrew from the study because of side effects.

mirtazapine

An open-label study was performed to evaluate mirtazapine 30 to 45 mg daily in 24 adolescents (aged 12 to 18 years) with MDD.[81] The mean daily dose of mirtazapine at the conclusion of the 85 day study was 32.9 mg. Mirtazapine showed efficacy in HAM-D-17 and CGI and had a beneficial effect on sleep. There were no withdrawals due to adverse events, which were similar in type and incidence to those seen in adults.

Twenty-six subjects (aged three to 24 years) with pervasive developmental disorders (20 autistic, one Asperger's, one Rett's and four with unspecified) were treated with open-label mirtazapine 7.5 to 45 mg/day.[82] All but one of the subjects completed at least four weeks of treatment; the average duration of treatment was 150 days. Primary caregivers rated 35 percent of patients as CGI responders with improvement noted in the symptoms of aggression, self-injury, irritability, hyperactivity, anxiety, depression and insomnia. Mirtazapine did not improve core symptoms of social or communication impairment. Adverse effects were minimal and included increased appetite, irritability, and transient sedation.

nefazodone

Twenty-eight depressed children and adolescents (aged seven to 17 years) were enrolled in an open-label study in which they were given nefazodone for six weeks.[83] The drug was well tolerated and was associated with significant reductions in depressive symptoms ($p<0.001$). A similar study administered nefazodone at doses up to 400 mg to 10 adolescents with MDD for an eight-week period.[84] In LOCF analysis, significant improvement in both HAM-D and BDI was noted ($p=0.01$ for both analyses).

In another open-label study, seven treatment-refractory children (mean age 12.4 years), including four with bipolar depression, were given nefazodone at a mean daily dose 3.4 mg/kg for an average of 13 weeks.[85] A retrospective analysis showed that 56 percent of these subjects were CGI responders, including two of the patients with bipolar depression. Adverse events were reported in three subjects.

venlafaxine

A randomized trial of 40 children with MDD compared treatment regimens of psychotherapy with either venlafaxine or placebo.[86] In this six-week study, children in the venlafaxine treatment group were dosed based on age with children eight to 12 years getting 12.5 to 37.5 mg/day and children 13 to 17 years getting twice that dose. Patients in the venlafaxine and placebo groups showed significant improvement from baseline in HAM-D-17 and three pediatric-specific scales, the Children's Depression Inventory (CDI), Child Behavior Checklist (CBCL) and Children's

Depression Rating Scale (CDRS). There were no differences between venlafaxine and placebo in any of the outcome measures. There was a higher percentage of patients with adverse effects in the venlafaxine group at all time points.

Warnings / Contraindications

Pregnancy - For ethical reasons, double-blind randomized studies of antidepressant drug effects on the fetus and mother are unavailable. Based on animal data, the FDA has classified all of the drugs in this class in pregnancy category C.

Bupropion is contraindicated in patients with a seizure disorder, in patients with anorexia and/or bulimia and also in patients undergoing abrupt discontinuation of alcohol or sedatives.

Duloxetine should not be prescribed for patients with substantial alcohol use or evidence of chronic liver disease. Postmarketing reports indicated that elevated transaminases, bilirubin and alkaline phosphatase have occurred when duloxetine has been given to such patients.

Nefazodone has a black box warning for life-threatening liver failure (risk of one case resulting in death or transplant per 250,000 to 300,000 years of nefazodone treatment).

As a class, MAO-Is have been associated with hypertensive crises caused by the ingestion of foods containing high amounts of tyramine. Data for selegiline transdermal 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Patients receiving higher doses should follow the standard dietary modifications for patients taking MAO-Is.[87]

Drug Interactions

Inhibition potential at CYP450 enzyme systems at usual doses[88,89]

Drug	**1A2**	**2C9/19**	**2D6**	**3A4**
bupropion	low	low	low	low
duloxetine	--	--	moderate	--
mirtazapine	low	low	low	low
nefazodone	low	low	low	high
selegiline	--	--	--	--
venlafaxine	low	low	low	low

-- = no or negligible inhibition
Low = 20-50% inhibition
Moderate = 50-100% inhibition
High = 100-150% inhibition

Bupropion
- drugs metabolized by CYP2D6 – used concurrently with caution; use lower dose of concomitant medication
- levodopa, amantadine – higher incidence of adverse effects
- drugs that lower seizure threshold - increases the incidence of bupropion-related seizures
- other dopamine agonists and norepinephrine antagonists – potentiation and reduction in the effects of these drugs may occur when administered with bupropion

Duloxetine
- inhibitors of CYP2D6 – concomitant use increases duloxetine concentrations
- inhibitors of CYP1A2 – concomitant use increases duloxetine concentration
- drugs metabolized by CYP2D6 – duloxetine is a moderate inhibitor of CYP2D6 and increases the AUC and Cmax of drugs metabolized by this enzyme – use with caution
- drugs that raise the gastric pH - duloxetine is enteric coated and drugs that raise gastric pH may lead to early release of duloxetine
- drugs that are highly protein bound - duloxetine is highly protein bound and administration with another highly protein bound drug may increase free concentrations of the other drug

Nefazodone
- drugs that are metabolized by CYP3A4 - nefazodone inhibits the metabolism and increases the bioavailability of drugs metabolized by that enzyme; caution must be used when using nefazodone concurrently with these drugs.
- carbamazepine - the bioavailability of nefazodone is reduced by 95 percent when used concurrently with carbamazepine

Selegiline
- Contraindications – SSRIs, SNRIs, mirtazapine, TCAs, bupropion, meperidine, tramadol, methadone, propoxyphene, dextromethorphan, St. John's wort, cyclobenzaprine, carbamazepine, oxcarbazepine, sympathetic amines, general anesthesia

Trazodone
- CYP3A4 inhibitors – can inhibit the metabolism of trazodone
- CYP3A4 inducers – can induce the metabolism of trazodone
- Phenytoin – elevated levels of phenytoin have been reported with concurrent use

Venlafaxine
- haloperidol – the clearance of haloperidol in reduced and bioavailability increased
- ketoconazole – increased concentrations of venlafaxine and ODV

The non-MAO-I drugs in this class should not be used concomitantly within two weeks of stopping an MAO-I. Additionally, when converting from an MAO-I to one of these antidepressants, there must be a washout period of five to 14 days.

Adverse Drug Reactions

Drug	Wt Loss	Wt Gain	Dry Mouth	Nausea	Headache	Agitation	Insomnia	Somnolence	Withdrawals due to AE
bupropion IR[90]	23-28 (14-23)	9-14 (23)	28 (10-18)	23 (19)	26 (22)	32 (22)	19-29 (16)	---	10 (<10)
bupropion SR[91,92,93,94,95]	14-19 (6)	2-3 (4)	16-24 (7-12)	13-18 (8)	25-26 (23)	3-9 (2)	11-29 (4-6)	2-3 (2-6)	3-11 (0-4)
bupropion XL (Wellbutrin XL)[96,97]	15	---	13-26 (6-15)	13 (8)	34 (26)	2 (1)	7-20 (1-13)	---	3-10 (2-5)
duloxetine (Cymbalta)[98,99,100,101,102,103,104,105,106]	2-7 (1)	---	3-28 (2-7)	14-22 (7-9)	2-13 (2-10)	---	3-20 (6-14)	2-15 (0-5)	3-17 (2-7)
mirtazapine[107,108,109]	---	8-16 (0-2)	14-25 (15)	---	---	---	---	35-54 (18)	4-16 (7)
nefazodone[110,111,112,113]	---	---	25 (13)	---	---	---	11 (9)	15-25 (5-14)	5-19 (5-14)
selegiline[114,115]	5 (3)	2 (2)	8-9 (6-7)	4 (7)	18-23 (17-22)	---	7-12 (7)	7 (5)	7 (4)
trazodone[116]	6 (3)	5 (2)	34 (20)	13 (10)	20 (16)	---	6 (12)	up to 40	---
venlafaxine IR (Effexor)[117,118,119,120,121,122]	1-6 (0-1)	---	15-22 (11)	33-38 (11-14)	25 (24)	1-2 (0)	18-23 (10)	17-23 (4-9)	7-21
venlafaxine ER (Effexor XR)[123,124,125,126,127,128,129,130]	3-7 (0-2)	---	12-17 (4-6)	7-35 (5-14)	10-34 (5-33)	3-4 (1)	6-23 (5-11)	12-17 (6-11)	6-20 (5-14)

Adverse effects reported as a percentage. The incidence of adverse events in corresponding placebo groups in controlled trials is in parentheses.
--- unreported, rare or infrequent occurrence

Because these data are from clinical trials with different study designs, these data may not necessarily reflect the actual rate of these adverse effects in clinical practice or the actual differences between these various drugs.

bupropion: There is a dose-related risk of seizures with the use of bupropion. Seizures occur in roughly 0.1 percent of patients receiving bupropion SR up to 300 mg/day and 0.5 percent of patients receiving bupropion IR up to 450 mg/day. The incidence of seizures raises disproportionately at bupropion IR dosages above 450 mg/day.[131] In patients receiving bupropion IR 600 mg/day, the risk of seizures was estimated to be 10 times that of patients receiving the maximum daily recommended dose of 450 mg. According to the manufacturer, the incidence of seizures in patients taking bupropion ER as a single dose of 450 mg is 0.4 percent. Data from a computerized general practice database in the UK revealed a relative incidence of seizures during the first four weeks of bupropion of 3.62, which is equivalent to one additional seizure per 6,219 first time bupropion users.[132]

duloxetine (Cymbalta): Duloxetine increases the risk of elevation of serum transaminase levels. In clinical trials, one percent of patients treated with duloxetine had a >3X ULN elevation of ALT compared to 0.2 percent of patients receiving placebo. As a result, duloxetine is not recommended for use in patients with hepatic insufficiency or who use substantial amounts of alcohol.

mirtazapine: In premarketing trials, two out of 2,796 patients developed agranulocytosis and a third patient developed severe neutropenia. All three patients recovered upon discontinuation of mirtazapine. These cases yield a crude incidence of severe neutropenia of approximately 1.1 per 1,000 patients (95% CI 0.2-3.1 cases per 1,000). In clinical trials, nonfasting cholesterol increases to 20 percent ULN were observed for 15 percent of patients treated with mirtazapine compared to seven percent of patients treated with placebo. Nonfasting triglyceride increases to 500 mg/dL were observed in six percent of patients treated with mirtazapine, compared to three percent of patient receiving placebo. ALT elevations to 3X ULN were observed in two percent of patients exposed to mirtazapine compared to 0.3 percent of placebo patients.

selegiline: Application site reactions have been reported in 24 to 36 percent of patients receiving selegiline transdermal patches, compared to 12 to 17 percent of patients receiving placebo patches; rash occurred in four and two percent of patients, respectively.[133,134,135]

trazodone: Trazodone is associated with the occurrence of priapism. Permanent impairment of erectile function or impotence has been reported.

venlafaxine ER (Effexor XR): Clinically relevant increases in serum cholesterol were recorded in 5.3 percent of venlafaxine-treated patients and no placebo-treated patients for at least three months.

There have been spontaneous reports of adverse events occurring upon discontinuation (particularly when abrupt) of the SNRIs venlafaxine and duloxetine. Adverse events include dysphoria, irritability, agitation, dizziness, sensory disturbances, confusion, headache, lethargy, insomnia, hypomania, tinnitus and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms reported. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible.

Dosages - Adult

Drug	Starting Dose	Maintenance Dose	Maximum Dose	Hepatic Impairment	Renal Impairment	Dosage Forms
bupropion IR	100 mg twice daily	100 mg three times daily	150 mg three times daily	?	?	Tablets: 75, 100 mg
bupropion SR	150 mg every AM	150 mg twice daily	200 mg twice daily	?	?	Tablets: 100, 150, 200 mg
bupropion ER (Wellbutrin XL)	150 mg every AM	300 mg every AM	450 mg every AM	?	?	Tablets: 150, 300 mg
duloxetine (Cymbalta)	20 mg twice daily	60 mg/day in one or two doses	60 mg/day in one or two doses	drug not recommended	?	Capsules: 20, 30, 60 mg
mirtazapine	15 mg every evening	15 to 45 mg every evening	45 mg every evening	?	?	Tablets (oral and rapidly dissolving): 15, 30, 45 mg
nefazodone	100 mg twice daily	150 to 300 mg twice daily	300 mg twice daily	?	?	Tablets: 50, 100, 150, 200, 250 mg
selegiline (Emsam)	6 mg patch daily	6 mg patch daily	12 mg patch daily	--	--	Patches: 6, 9, 12 mg/24 hours
trazodone	150 mg/day in divided doses	150 to 400 mg/day in divided doses	400 mg/day in divided doses	?	?	Tablets: 50, 100, 150, 300 mg
venlafaxine IR (Effexor)	75 mg/day in two or three doses	150 mg/day in two or three doses	375 mg/day in three doses	?	?	Tablets: 25, 37.5, 50, 75, 100 mg
venlafaxine ER (Effexor XR)	37.5 to 75 mg once daily	75 to 225 mg once daily	225 mg once daily	?	?	Capsules: 37.5, 75, 150 mg

Doses are FDA-approved doses for outpatients.
-- = no dosage change required
? = consideration should be given to reducing the dose and/or dosage frequency

Bupropion - To minimize the risk of seizures, dose increases should not exceed 100 mg/day in a three day period and the maximum daily dosage of 450 mg should not be exceeded. Increases

above 300 mg/day should only be done in patients with no clinical effects after several weeks of treatment at 300 mg/day. The time between doses should be at least four hours for 100 mg IR doses, six hours for 150 mg IR doses and eight hours for SR doses. Cautious dose titration can also minimize agitation, motor restlessness and insomnia.

Venlafaxine has an ascending dose-response curve.[136] At the starting dosage of 75 mg/day, venlafaxine produces approximately the same number of responders as do the SSRIs. The percentage of responders increases with higher doses in a manner consistent with the drug's dual mechanism of inhibiting the uptake of serotonin initially and then norepinephrine at higher doses. Consistent with its pharmacology, higher doses of venlafaxine can also cause a higher incidence of serotonin- and norepinephrine-mediated adverse effects, including the potential to increase blood pressure.

Conclusion

While all second-generation antidepressants are effective at reducing symptoms of depression, there are no significant differences in efficacy among these agents. This is borne out in data from individual clinical trials as well as from systematic reviews.

One systematic review indicated that, based on fair-to-good evidence, the second-generation antidepressants all have similar efficacy in treating MDD.[137] Of 46 RCTs directly comparing agents in this class, all but five reported no statistically significant difference in any outcome measure at the end of the study. Meta-analyses suggest a small, but statistically significant, additional treatment effect for sertraline and venlafaxine compared with fluoxetine.

In another systematic review, researchers analyzed the results of 81 clinical trials involving more than 10,000 adults with MDD that compared newer antidepressants with placebo.[138] Mirtazapine, venlafaxine, nefazodone and bupropion were among the drugs included in this review, as were several SSRIs. As a group, the newer antidepressants were significantly (60 percent) more effective than placebo. The efficacy of different antidepressant classes was similar, as were the individual agents in each class. A comparison of older antidepressants with newer agents found no significant difference in efficacy with the exception of three studies showing a 20 percent greater effect for an SNRI than for trazodone (p=0.05).

A more recent systematic review of 39 placebo-controlled RCTs of duloxetine, venlafaxine and the SSRI, fluoxetine, used meta-regression analysis to compare the relative treatment effect of duloxetine with venlafaxine and fluoxetine in patients with MDD.[139] This analysis found no significant difference in treatment effect, as measured by HAM-D, between duloxetine and fluoxetine. It did, however, identify significantly better efficacy of venlafaxine compared to duloxetine with an OR of 2.0 for the number of responders.

Each of the groups of drugs in this class has a potential role in the treatment of MDD, primarily as a result of their heterogeneous spectrums of activity. As with many psychotropic drugs, patients failing to respond to one type of antidepressant may respond to a switch to, or augmentation with, an antidepressant with another mechanism of action.

The majority of the data regarding the use of the non-SSRI second-generation antidepressants for indications other than MDD involves the SNRIs, duloxetine and venlafaxine. For SAD and panic disorder, the ICGDA (International Consensus Group on Depression and Anxiety) expert panel guidelines recommends SSRIs as first-line therapy with the SNRIs as second-line therapy.

For GAD, the ICGDA recommends SSRIs, SNRIs, TCAs and CBT (Cognitive-Behavioral Therapy) as first line treatments.[140]

The role of the non-SSRI antidepressants in the treatment of neuropathic pain is still being defined, although the SNRIs have shown efficacy. Duloxetine is the only agent in this group with the treatment of neuropathic pain as an approved indication. Consensus guidelines from the Mayo Clinic recommend duloxetine, as well with oxycodone CR, pregabilin and TCAs as first-tier agents for the treatment of DPNP. Duloxetine is not recommended for patients with hepatic insufficiency or where drug interactions or cost are a factor. Venlafaxine ER, along with tramadol and the antiepileptic drugs carbamazepine, gabapentin and lamotrigine, are identified as second-tier agents. These guidelines were supported by a grant from the manufacturer of duloxetine.[141]

With the similarity in efficacy and overall incidence of adverse events between antidepressants, rates of adherence and discontinuation of the various medications are also generally equivalent. Specific agents, however, have different side effect profiles. Venlafaxine is associated with higher rates of nausea and vomiting than fluoxetine. Venlafaxine is also associated with a higher rate of discontinuation syndrome than the second-generation antidepressants. Bupropion appears to have the lowest risk of sexual adverse effects, although reports are variable. Mirtazapine is most associated with weight gain while bupropion results in a net loss of body weight. Nefazodone and trazodone are more likely to cause sedation, but this may be of benefit in patients with depression-related insomnia. Selegiline transdermal is associated with relatively few systemic effects, but it is associated with a high rate of skin reactions.

There have been reports of adverse liver toxicities with nefazodone. This drug has been removed from the European market based on deaths due to liver failure. Petitions have also been sent to the FDA asking for removal of this product from the US market. The FDA is currently reviewing the petitions. The manufacturer of Serzone brand nefazodone discontinued the manufacturing and sales of Serzone in 2004; generic nefazodone remains available.

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