Antidepressants, Other Review

04/14/2009

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Comments and suggestions may be sent to Editor@providersynergies.com.

Antidepressants, Other Review

FDA-Approved Indications

Drug	Mfr	Major Depressive Disorder (MDD)	Generalized Anxiety Disorder (GAD)	Social Anxiety Disorder (SAD)	Panic Disorder	Other Indications
bupropion hydrochloride IR	generic	X				
bupropion hydrochloride SR	generic	X				
bupropion hydrochloride ER (Wellbutrin® XL)	generic	X				prevention of major depressive episodes associated with seasonal affective disorder
bupropion hydrobromide ER (Aplenzin)	Biovail	X				
desvenlafaxine (Pristiq™)	Wyeth	X				
duloxetine (Cymbalta®)	Lilly	X	X			diabetic peripheral neuropathic pain; fibromyalgia
isocarboxazid (Marplan®)	Validus	X 2nd line therapy				
mirtazapine	generic	X				
nefazodone	generic	X				
phenelzine (Nardil®)	Pfizer	X 2nd line therapy				
selegiline (Emsam®)	BMS	X				
tranylcypromine (Parnate®)	GSK	X 2nd line therapy				
trazodone	generic	X				
venlafaxine IR	generic	X				
venlafaxine ER (Effexor® XR)	Wyeth	X	X	X	X	
venlafaxine ER	Upstate Pharma	X		X		

IR = immediate release

SR = sustained release
ER = extended release

Overview

Depression

As many as one-half of all patients with MDD do not experience sufficient symptom improvement despite several adequate trials of antidepressant drugs, with most patients taking a selective serotonin reuptake inhibitors (SSRI) as initial treatment. Among patients who remit, residual symptoms are common and associated with impaired psychosocial functioning and increased relapse rates. Until recently, known differences among antidepressant drugs were generally limited to safety and tolerability issues. However, over the past few years, a number of studies have emerged to evaluate possible differences among antidepressant classes in their ability to resolve specific symptoms of depression. 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.

While effectiveness is generally comparable among 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 depression. 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.

Oral monoamine oxidase inhibitors (MAO-Is), phenelzine (Nardil) and tranylcypromine (Parnate), are older agents with significant drug and food interactions which have limited their clinical utility in the management of depression. More recently, selegiline (Emsam), a transdermal formulation of a MAO-I, has become available. This different route of administration results in a different pharmacodynamic and safety profile than the older oral MAO-Is.

The 2001 algorithm for improved recognition and treatment of depression and anxiety by the ICGDA (International Consensus Group on Depression and Anxiety) recommend SSRIs as first line therapy for the treatment of depression and anxiety.[1]

The majority of the data regarding the use of the non-SSRI second-generation antidepressants for indications other than MDD involves the SNRIs, duloxetine (Cymbalta) and venlafaxine. For SAD and panic disorder, the ICGDA (International Consensus Group on Depression and Anxiety) expert panel guidelines recommend 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.[2]

Generalized Anxiety Disorder (GAD)[3,4]

GAD affects about 6.8 million adult Americans and about twice as many women as men. The disorder develops gradually and can begin across the life cycle, though the risk is highest between childhood and middle age. GAD is diagnosed when a person worries excessively about a variety of everyday problems for at least six months.[5] People with GAD can't seem to get rid of their concerns, even though they usually realize that their anxiety is more intense than the situation warrants. Patients can't relax, startle easily, and have difficulty concentrating. Often they have trouble falling asleep or staying asleep. Physical symptoms that often accompany the anxiety include fatigue, headaches, muscle tension, muscle aches, difficulty swallowing, trembling, twitching, irritability, sweating, nausea, lightheadedness, having to go to the bathroom frequently, feeling out of breath, and hot flashes.

Panic Disorder

Panic disorder is a severe, chronic anxiety disorder characterized by recurrent episodes of panic and the development of fear or anxiety regarding the possibility of future panic attacks. Estimates for the incidence of panic disorder range between three to six million people per year with two-thirds of those affected being female. Recent epidemiologic studies suggest that up to 15 percent of the general population experience isolated panic attacks, whereas up to 3.5 percent develop full panic disorder during their lifetime.

Social Anxiety Disorder (SAD)[6,7]

In the United States, SAD is the most common anxiety disorder affecting approximately 5.3 million people per year. It is the third most common psychiatric disorder after depression and alcohol abuse. This disorder is characterized by a marked and persistent fear of social or performance situations in which embarrassment may occur. Women and men are equally likely to develop the disorder, which usually begins in childhood or early adolescence. There is some evidence that genetic factors are involved. Social anxiety disorder is often accompanied by other anxiety disorders or depression, and substance abuse may develop if people try to self-medicate their anxiety.

Seasonal Affective Disorder[8]

Seasonal affective disorder is characterized by seasonal changes during the year with recurrent episodes of depression usually in the late fall and winter. The depressive episodes alternate with periods of normal or high mood the rest of the year. Seasonal Affective Disorder is more commonly diagnosed in women, beginning in their twenties, although men also report Seasonal Affective Disorder of similar severity. Many people with Seasonal Affective Disorder report at least one close relative with a psychiatric condition, most frequently a severe depressive disorder (55 percent) or alcohol abuse (34 percent).

Bright white fluorescent light therapy is now considered the first-line treatment intervention, and if properly dosed can produce relief within days. Antidepressants may also help, and if necessary can be used in conjunction with light.

Fibromyalgia[9,10,11,12,13]

Fibromyalgia is a chronic disorder characterized by pain, fatigue, and sleep disturbances. It predominantly affects women and is difficult to treat. A multidisciplinary approach should be utilized. Diagnostic criteria for fibromyalgia are based on the American College of Rheumatology (ACR) criteria, characterized by widespread musculoskeletal pain and excess tenderness in at least 11 of 18 predefined anatomic sites, referred to as trigger points. Pain is considered widespread when all of the following are present: pain in the left and right side of the body, pain above and below the waist, and axial skeletal pain (cervical spine, anterior chest, thoracic spine, or low back). Digital palpation should be performed with an approximate force of four kg. For a tender point to be considered "positive" the subject must state that the palpation was painful. "Tender" is not to be considered "painful." For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least three months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia. Lab tests for thyroid stimulating hormone (TSH) and erythrocyte sedimentation rate (ESR) are recommended to rule out hypothyroidism and polymyalgia rheumatica, respectively, as they have similar symptomatology.

The choice of agents used for fibromyalgia is often dependent on the drug's safety profile. Tricyclic antidepressants (TCAs), an unapproved class of drugs for the treatment of fibromyalgia, are associated with a number of side effects including anticholinergic effects (e.g. dry mouth and urinary retention), orthostatic hypotension, and cardiac dysfunction. They are not an optimal choice in the elderly (patients > 65 years old). Gabapentin, also unapproved for the treatment of fibromyalgia, has low bioavailability and is not rapidly absorbed; therefore, it requires a dosage regimen of three to four times daily. FDA-approved drugs for the treatment of fibromyalgia include duloxetine (Cymbalta) and pregabalin (Lyrica®). There is no evidence to support the superiority of pregabalin or duloxetine (Cymbalta) to each other in fibromyalgia. Pregabalin and duloxetine are treatment alternatives in patients with fibromyalgia. No trials comparing either duloxetine or pregabalin with other drugs such as TCAs or gabapentin have been completed. Safety and efficacy of pregabalin or duloxetine have not been established in pediatric patients.

Diabetic Peripheral Neuropathic Pain[14,15,16,17,18]

Diabetic peripheral neuropathy (DPN) is a common complication of diabetes mellitus. The etiology, though not completely understood, is thought to be multifactorial. The most common symptoms associated with DPN are pain or loss of feeling in the toes, feet, legs, and arms. DPN can affect many aspects of life and severely limit the patient's daily functions. Loss of sensation in the periphery may lead to muscle weakness and loss of reflexes, especially in the ankles, which can lead to gait disturbances. Patients with DPN may be unaware of pressure or injury, leading to blisters or sores appearing on numb areas of the foot or leg. These areas may go unnoticed for extended periods of time, increasing the risk for infection and possibly amputation.

Diagnosis of DPN is based on the presence of symptoms and a physical exam. A comprehensive foot exam is performed to assess skin appearance and integrity, muscles, bones, circulation, and sensation of the feet. Pin prick sensation, vibration perception, 10-g monofilament pressure sensation, and assessment of ankle reflexes are commonly performed tests used to screen, diagnose, and assess DPN. General treatment measures include glycemic control, foot care, and the treatment of pain.

Duloxetine (Cymbalta) 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 (Cymbalta), as well as oxycodone CR (Oxycontin®), pregabalin (Lyrica) and TCAs as first-tier agents for the treatment of DPN. Duloxetine (Cymbalta) is not recommended for patients with hepatic insufficiency or where drug interactions are a factor. Venlafaxine ER (Effexor XR), 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 (Cymbalta).[19]

Traditional and Second-Generation Antidepressants for Other Conditions

The 2008 World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive, and posttraumatic stress disorders state that SSRIs, serotonin-noradrenaline reuptake inhibitors (SNRIs) and the calcium channel modulator, pregabalin, are used as first-line therapies for several of the non-depression related conditions.[20.21] Tricyclic antidepressants (TCAs) are equally effective for some disorders, but many are less well tolerated than the SSRIs and SNRIs. In treatment-resistant cases, benzodiazepines may be used when the patient does not have a history of substance abuse disorders. Although these guidelines focus on medications, non-pharmacological interventions were also considered. Cognitive behavioral therapy (CBT) and other variants of behavior therapy have been sufficiently investigated in controlled studies in patients with anxiety disorders, obsessive-compulsive disorder, and post traumatic stress disorder (PTSD) to support them being recommended either alone or in combination with the above medications.

In November 2008, the American College of Physicians released guidelines on the use of second generation antidepressants in the pharmacologic management of the acute, continuation, and maintenance phases of MDD, dysthymia, subsyndromal depression, and accompanying symptoms including anxiety, insomnia, and neurovegetative symptoms.[22] Four strong recommendations were made by the American College of Physicians. The first recommendation is for clinicians to choose pharmacologic therapy for treatment of patients with acute major depression based on adverse effect profiles, cost, and patient preferences. Clinicians should assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis beginning within one to two weeks of initiation of therapy. The American College of Physicians recommends that clinicians modify treatment if the patient does not have an adequate response to pharmacotherapy within six to eight weeks of the initiation of therapy for major depressive disorder. Lastly, the American College of Physicians recommends that clinicians continue treatment for four to nine months after a satisfactory response in patients with a first episode of MDD. For patients who have had two or more episodes of depression, an even longer duration of therapy may be beneficial.

Pharmacology[23,24,25,26,27,28,29,30,31,3233]

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

Mechanism of Action	TCAs	SSRIs	MAO-Is isocarboxazid phenelzine selegiline tranylcypromine	NDRIs bupropion	Norepinephrine-Serotonin modulators mirtazapine	Serotonin modulators nefazodone trazodone	SNRIs duloxetine venlafaxine desvenlafaxine	Clinical and Physiological Effects
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

Pharmacokinetics

Drug	Protein Binding (%)	Half-Life (hr)	Active Metabolites
bupropion HCl (Wellbutrin, Wellbutrin SR, Wellbutrin XL)[34,35,36]	84	21	erythrohydrobupropion, hydroxybupropion, threohydrobupropion (half-lives 20-37 hours)
bupropion HBr (Aplenzin)[37]	84	21.3	erythrohydrobupion, hydroxybupropion, threohydrobupropion
desvenlafaxine (Pristiq)[38]	30	11	N-desmethyl-venlafaxine (19 percent) and N,O-didesmethylvenlafaxine (<5 percent)
duloxetine (Cymbalta)[39]	>90	12	none
isocarboxazid (Marplan)[40]	--	--	--
mirtazapine[41,42]	85	20 - 40	desmethyl metabolite
nefazodone[43]	>99	11 - 24	hydroxynefazodone, mCPP
phenelzine (Nardil)[44]	--	11.6	none
selegiline (Emsam)[45]	90	18-25	none
tranylcypromine (Parnate)[46]	--	--	--
trazodone[47]	--	5 - 9	chlorophenylpiperazine, mCPP
venlafaxine (Effexor, Effexor XR)[48,49]	27	5	O-desmethyl-venlafaxine (ODV) (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.[50] 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 (Wellbutrin XL).[51] Bupropion hydrobromide extended-release (Aplenzin) is an alcohol-resistant formulation.

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.[52]

selegiline (Emsam): 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.[53]

venlafaxine: 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.[54]

Contraindications/Warnings[55,56,57,58,59,60,61,62,63,64]

Black box warning

Antidepressants have a black box warning regarding the risk of suicide. Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of any antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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.

Class warnings

Screening patients for bipolar disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed, although not established in controlled trials, that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history including a family history of suicide, bipolar disorder, and depression. The antidepressants in this review are not approved for use in treating bipolar depression.

The development of a potentially life-threatening serotonin syndrome may occur with SNRI or SSRI treatment, particularly with concomitant use of serotonergic drugs, including triptans, and with drugs which impair metabolism of serotonin, including MAO-Is. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Concomitant use of these agents with an anti-migraine triptan agent requires careful observation of the patient particularly during treatment initiation and dosage increases. Concomitant use of these agents with serotonergic or anti-dopaminergic agents, including antipsychotics, should be discontinued immediately if signs of serotonin syndrome and/or neuroleptic malignant syndrome (NMS) emerge. These symptoms may include mental status changes, autonomic instability, neuromuscular aberrations, and/or gastrointestinal symptoms. Supportive symptomatic treatment should be initiated immediately.

SSRIs and SNRIs may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of any SSRI or SNRI and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

A gradual reduction in the dose of SNRIs rather than abrupt cessation is recommended whenever possible.

Concomitant use of these agents with serotonin precursors (e.g. tryptophan) is not recommended.

bupropion

Bupropion hydrochloride and bupropion hydrobromide are 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. In addition, bupropion is also contraindicated in patients using other bupropion products regardless of the indication (e.g. depression, smoking cessation, etc.). Also, discontinuation of an MAOI of at least two weeks is required prior to initiating use of bupropion.

desvenlafaxine (Pristiq)

Desvenlafaxine (Pristiq) is contraindicated for use in patients with hypersensitivity to desvenlafaxine, venlafaxine (Effexor, Effexor XR) or any excipients in its formulation.

The concomitant use of desvenlafaxine with an MAO-I is contraindicated. Do not use with an MAO-I or within 14 days of stopping an MAO-I. Allow seven days after stopping desvenlafaxine before starting an MAO-I.

Mydriasis has been reported in association with desvenlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma should be monitored.

Drugs containing desvenlafaxine or venlafaxine should not be used concomitantly with desvenlafaxine.

duloxetine (Cymbalta)

Duloxetine is contraindicated in patients with uncontrolled narrow-angle glaucoma. Concomitant use of duloxetine with MAO-Is is contraindicated.

Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine, especially during the first week of therapy or after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension or are potent CYP1A2 inhibitors and in patients taking duloxetine at doses above 60 mg daily. Consider discontinuation of duloxetine in patients with symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

Duloxetine treatment relative to placebo has been associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. In clinical trials, there was no significant difference in the frequency of sustained (three consecutive visits) elevated blood pressure. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment.

Duloxetine (Cymbalta) 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. There have been reports of hepatic failure, sometimes fatal, in patients treated with duloxetine.

Duloxetine has been known to affect urethral resistance. If symptoms of urinary hesitation develop with duloxetine, consideration should be given to the possibility that it might be drug-related.

Duloxetine was associated with a small increase in mean fasting blood glucose as compared to placebo in a study of up to 52 weeks of therapy. The mean fasting blood glucose increased by 12 mg/dL in the duloxetine group and decreased by 11.5 mg/dL in the routine care group. HbA1c changes were +0.5 percent with duloxetine and +0.2 percent with the routine care group.

nefazodone

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).

MAO-Is – isocarboxazid (Marplan), phenelzine (Nardil) and tranylcypromine (Parnate)[65, 66,67]

Isocarboxazid should not be used in patients who are hypersensitive to the drug or its ingredients, with a confirmed or suspected cerebrovascular defect, cardiovascular disease, hypertension, pheochromocytoma, history of liver disease or abnormal liver function tests, or severely impaired renal function.

Phenelzine should not be used in patients who are hypersensitive to the drug or its ingredients, with pheochromocytoma, congestive heart failure, severe renal impairment or renal disease, a history of liver disease, or abnormal liver function tests.

Tranylcypromine should not be administered to any patient with a confirmed or suspected cerebrovascular defect or to any patient with cardiovascular disease, hypertension, pheochromocytoma, or history of headache. Tranylcypromine should not be used in patients with a history of liver disease or in those patients with abnormal liver function tests.

Patients taking tranylcypromine or phenelzine should not undergo elective surgery requiring general anesthesia or receive cocaine or local anesthesia containing sympathomimetic vasoconstrictors. The possible combined hypotensive effects of MAO-Is and spinal anesthesia should be kept in mind. MAO-I therapy should be discontinued at least 10 days prior to elective surgery.

Phenelzine and tranylcypromine should not be administered in combination with MAO-Is [including procarbazine (Matulane®)] or dibenzazepine derivatives. Dibenzazepine derivatives include the tricyclic antidepressants (nortriptyline, amitriptyline, clomipramine, desipramine, imipramine, doxepin, trimipramine, and protriptyline), carbamazepine, cyclobenzaprine, perphenazine, amoxapine, maprotiline, and mirtazapine. MAO-Is should not be administered together or in rapid succession with other MAO-Is or with dibenzazepine-related entities. Hypertensive crises or severe convulsive seizures may occur in patients receiving such combinations. In patients being transferred to phenelzine or tranylcypromine from another MAO-I or from a dibenzazepine-related entity, allow a medication-free interval of at least seven days (tranylcypromine) to 10 days (phenelzine). MAO-Is are contraindicated in patients receiving guanethidine.

MAO-Is are contraindicated with bupropion products (Aplenzin, Wellbutrin products, Zyban®), buspirone, meperidine, and dextromethorphan. At least 14 days should elapse between discontinuation of an MAO-I and initiation of treatment with the contraindicated drugs.

MAO-Is should not be administered in combination with any SSRI. There have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic

instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma in patients receiving fluoxetine in combination with a MAO-I, and in patients who have recently discontinued fluoxetine and are then started on an MAO-I. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, fluoxetine and other SSRIs should not be used in combination with an MAO-I, or within 14 days of discontinuing therapy with an MAO-I. Since fluoxetine and its major metabolite have very long elimination half-lives, at least five weeks should be allowed after stopping fluoxetine before starting an MAO-I.

At least 14 days should elapse between discontinuation of a MAO-I and initiation of therapy with duloxetine (Cymbalta), desvenlafaxine (Pristiq), venlafaxine IR, or venlafaxine ER (Effexor, Effexor XR). In addition, at least five days should be allowed after stopping duloxetine, desvenlafaxine, venlafaxine/venlafaxine ER (Effexor, Effexor XR) before starting an MAO-I. Concomitant use in patients taking MAO-Is is contraindicated with duloxetine and venlafaxine products due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs.

MAO-Is should not be administered in combination with sympathomimetics, including amphetamines, cocaine, methylphenidate, dopamine, epinephrine, and norepinephrine or related compounds (including methyldopa, L-dopa, L-tryptophan, L-tyrosine, and phenylalanine) and over-the-counter drugs such as cold, hay fever, or weight-reducing preparations that contain vasoconstrictors.

The most important reaction associated with MAO-Is administration is the occurrence of hypertensive crises, which have sometimes been fatal. These crises are characterized by some or all of the following symptoms: occipital headache which may radiate frontally, palpitation, neck stiffness or soreness, nausea, vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin), dilated pupils, and photophobia. Either tachycardia or bradycardia may be present and can be associated with constricting chest pain. Blood pressure should be monitored. Therapy should be discontinued immediately upon the occurrence of palpitation or frequent headaches during therapy.

Hypertensive crises have sometimes occurred during therapy with MAO-Is after ingestion of foods with a high tyramine content. In general, the patient should avoid protein foods in which aging or protein breakdown is used to increase flavor. In particular, patients should be instructed not to take foods such as cheese (particularly strong or aged varieties), sour cream, Chianti wine, sherry, beer (including nonalcoholic beer), liqueurs, pickled herring, anchovies, caviar, liver, canned figs, dried fruits (raisins, prunes, etc.), bananas, raspberries, avocados, overripe fruit, chocolate, soy sauce, sauerkraut, dry sausage (including Genoa salami, hard salami, pepperoni and Lebanon bologna), the pods of broad beans (fava beans), yeast extracts, yogurt, meat extracts, or meat prepared with tenderizers. Excessive amounts of caffeine should be avoided.

Patients on MAO-Is should avoid many over-the-counter products including cold and cough preparations (including those containing dextromethorphan), nasal decongestants (tablets, drops, or spray), hay fever medications, sinus medications, asthma inhalant medications, anti-appetite medicines, weight-reducing preparations, and L-tryptophan containing preparations.

selegiline (Emsam)

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 (Emsam) 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.[68] MAO-Is, including selegiline transdermal, are contraindicated in patients with pheochromocytoma.

venlafaxine and venlafaxine ER (Effexor, Effexor XR)

Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma should be monitored.

Venlafaxine therapy is associated with sustained hypertension which is defined as supine diastolic blood pressure ≥ 90 mm Hg and ≥ 10 mm Hg above baseline on three consecutive visits. Venlafaxine IR studies revealed a dose-dependent increase (placebo: two percent; venlafaxine IR doses <100 mg daily: three percent; >100 to ≤200 mg daily: five percent; >200 to ≤300 mg daily: seven percent; and doses exceeding 300 mg daily: 13 percent). In premarketing studies with venlafaxine ER (Effexor XR) in MDD, 0.7 percent of patients discontinued treated because of elevated blood pressure. Pre-existing hypertension should be controlled before treatment with venlafaxine. Blood pressure should be monitored on a regular basis.

Drug Interactions

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 seven to 14 days. A more extensive discussion is located in the Contraindications/Warnings section.

Inhibition potential at CYP450 enzyme systems at usual doses[69,70]

Drug	1A2	2C9/19	2B6	2D6	3A4
bupropion HCl (Wellbutrin/ Wellbutrin SR / Wellbutrin XL)[71]	--	low	low	low	low
bupropion HBr (Aplenzin)[72]	--	--	low	low	--
desvenlafaxine (Pristiq)[73]	--	--	--	low	low
duloxetine (Cymbalta)[74]	--	--	--	moderate	--
isocarboxazid (Marplan)[75]	--	--	--	--	--
mirtazapine[76]	low	low	--	low	low
nefazodone[77]	low	low	--	low	high
phenelzine (Nardil)[78]	--	--	--	--	--
selegiline (Emsam)[79]	--	--	--	--	--
tranylcypromine (Parnate)[80]	--	--	--	--	--
venlafaxine (Effexor, Effexor XR)[81,82]	low	low	--	low	low

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

bupropion (Aplenzin/Wellbutrin SR / Wellbutrin XL)
- drugs metabolized by CYP2D6 – use 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

desvenlafaxine (Pristiq)
- drugs metabolized by CYP2D6 – concomitant use of drugs metabolized by CYP2D6 may result in higher concentrations of that drug
- drugs metabolized by CYP3A4 – concomitant use of drugs metabolized by CYP3A4 may result in lower concentrations of that drug and alternatively higher concentrations of desvenlafaxine

duloxetine (Cymbalta)
- inhibitors of CYP2D6 – concomitant use increases duloxetine concentration
- 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

isocarboxazid (Marplan)
- disulfiram (Antabuse) coadministration - cautious administration and monitoring suggested
- combination therapy with other psychotropics – generally not recommended and ten day wash-out interval suggested to avoid concomitant use

nefazodone
- drugs that are metabolized by CYP3A4 - nefazodone inhibit the metabolism and increase 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 (Emsam)
- Contraindications – SSRIs, SNRIs, mirtazapine, TCAs, bupropion, meperidine, tramadol, methadone, propoxyphene, dextromethorphan, St. John's wort, cyclobenzaprine, carbamazepine, oxcarbazepine, sympathomimetic 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 is reduced and bioavailability increased
- ketoconazole – increased concentrations of venlafaxine and O-desmethyl venlafaxine (ODV)

Adverse Effects

Drug	Wt Loss	Wt Gain	Dry Mouth	Nausea	Headache	Agitation	Insomnia	Somnolence	Withdrawals due to AE
bupropion HCl IR[83]	23-28 (14-23)	9-14 (23)	28 (10-18)	23 (19)	26 (22)	32 (22)	19-29 (16)	nr	10 (<10)
bupropion HCl SR[84]	14-19 (6)	2-3 (4)	17-24 (7)	13-18 (8)	25-26 (23)	3-9 (2)	11-16 (6)	2-3 (2)	0-2.4 (0.3)
bupropion HCl XL[85]	23 (11)	11 (21)	26 (15)	13 (8)	34 (26)	2 (<1)	20 (13)	nr	9 (5)
bupropion HBr ER (Aplenzin)[86] *	nr	nr	≥5	≥5	nr	≥5	≥5	nr	nr
desvenlafaxine (Pristiq)[87]	1-2 (1)	nr	11-25 (9)	22-41 (10)	20-29 (23)	<1-2 (1)	9-15 (6)	4-12 (4)	4.1-12 (3-3.8)
duloxetine (Cymbalta)[88] n=4,843	reported	nr	14 (6)	25 (9)	16 (15)	reported	11 (7)	11 (3))	9-19.5 (4-11.8)
isocarboxazid (Marplan)	nr	nr	6-9 (4)	4-6 (2)	6-15 (13)	nr	4-6 (4)	0-4 (0)	2-12 (5)
mirtazapine[89]	nr	12 (2)	25 (15)	nr	nr	nr	nr	54 (18)	1.5-16 (0-7)
nefazodone[90]	nr	nr	25 (13)	22 (12)	36 (33)	nr	11 (9)	25 (14)	16 (nr)
phenelzine (Nardil)[91]	nr	reported	reported	nr	reported	nr	reported	nr	nr
selegiline (Emsam)[92]	nr	nr	8 (6)	nr	18 (17)	nr	12 (7)	nr	7.1 (3.6)
tranylcypromine (Parnate)[93]	nr	nr	reported	reported	reported	reported	reported	nr	nr
trazodone[94]	6 (3)	5 (2)	34 (20)	13 (10)	20 (16)	nr	6 (12)	up to 40	nr
venlafaxine IR (Effexor)[95]	1	reported	22 (11)	37 (11)	25 (24)	2	18 (10)	23 (9)	nr
venlafaxine ER (Effexor XR)[96] n=357	3	> 1	12 (6)	31 (12)	>2	3 (1)	17 (11)	17 (8)	7-18 5-12

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.

* The most common adverse reactions associated with Aplenzin are twice the placebo rate or more.

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.[97] 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 (Wellbutrin XL) 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.[98]

desvenlafaxine (Pristiq): Cautious use in patients with bipolar disorder, cardiovascular/cerebrovascular disease, and lipid metabolism disorders is recommended.

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 upper limit of normal (ULN) elevation of alanine aminotransferase (ALT) compared to 0.2 percent of patients receiving placebo. Duloxetine is not recommended for use in patients with hepatic insufficiency or who use substantial amounts of alcohol.

isocarboxazid (Marplan): Isolated cases of akathisia, ataxia, black tongue, coma, dysuria, euphoria, hematologic changes, incontinence, neuritis, photosensitivity, sexual disturbances, spider telangiectases, and urinary retention have been reported. These adverse effects may necessitate discontinuation of therapy. In rare instances, hallucinations have been reported with high doses, but they have disappeared upon dose reduction or discontinuation of therapy.

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 elevations 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 elevations 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.

nefazodone: There have been reports of adverse liver toxicities with nefazodone. Nefazodone 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.

selegiline (Emsam): 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.[99,100,101]

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 none of the 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 (Effexor XR), desvenlafaxine (Pristiq), and duloxetine (Cymbalta). 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.

Special Populations[102,103,104,105,106,107,108,109]

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, SSRIs 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.[110]

All of the antidepressants in this class have a black box warning regarding suicidality in children, adolescents, and young adults:

“Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of any antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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.”

Further labeling for these drugs states the following:

“All 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.”

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and non-psychiatric, 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.[111] 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).

A meta-analysis of randomized controlled trials assessed the efficacy and risk of reported suicidal ideation/suicide attempt of antidepressants for treatment of pediatric MDD, OCD, and non-OCD anxiety disorders.[112] Data sources included PubMed 1988 to July 2006, relevant US and British regulatory agency reports, published abstracts of important scientific meetings (1998-2006), clinical trial registries, and information from authors. Studies were published and unpublished randomized, placebo-controlled, parallel-group trials of second-generation antidepressants (SSRIs, nefazodone, venlafaxine, and mirtazapine) in participants younger than 19 years of age with MDD, OCD, or non-OCD anxiety disorders. Selection included 27 trials of pediatric MDD (n=15), OCD (n=six) and non-OCD anxiety disorders (n=six), and risk differences for response and for suicidal ideation/suicide attempt were estimated by random-effects methods. Pooled risk differences in rates of primary study-defined measures of responder status significantly favored antidepressants for MDD (11 percent; [95% CI, 7.1 to 14.9 percent]), OCD (19.8 percent [95% CI, 13 to 26.6 percent]), and non-OCD anxiety disorders (37.1 percent [95% CI, 22.5 to 51.7 percent]), corresponding to a number needed to treat (NNT) of ten (95% CI, 7 to 15), 6 (95% CI, 4 to 8) and 3 (95% CI, 2 to 5), respectively. While there was increased risk difference of suicidal ideation/suicide attempt across all trials and indications for drug versus placebo, the pooled risk differences within each indication were not statistically significant. There were no completed suicides. Age-stratified analyses showed that for children younger than 12 years of age with MDD, only fluoxetine showed benefit over placebo. In MDD trials, efficacy was moderated by age, duration of depression, and number of sites in the treatment trial. Relative to placebo, antidepressants are efficacious for pediatric MDD, OCD, and non-OCD anxiety disorders, although the effects are strongest in non-OCD anxiety disorders, intermediate in OCD, and more modest in MDD. Benefits of antidepressants appear to be much greater than risks from suicidal ideation/suicide attempt across indications, although comparison of benefit to risk varies as a function of indication, age, chronicity, and study conditions.

Safety and effectiveness in the pediatric population have not been established for products in this class. Although no studies have been designed to primarily assess venlafaxine's impact on the growth, development, and maturation of children and adolescents, the studies that have been done suggest that venlafaxine may adversely affect weight and height.

The TORDIA (Treatment of Resistant Depression in Adolescents) study was a National Institute of Mental Health (NIMH) sponsored, twelve-week, double-blind, randomized, controlled trial of 334 patients aged 12 to 18 years with a primary diagnosis of MDD that had not responded to a

two month initial treatment with an SSRI.[113] The results were intended to assist in providing guidance for the care and management of adolescent depression that persists despite treatment with an SSRI. The patients were randomized to one of four groups: (1) switching to a second, different SSRI (paroxetine, citalopram, or fluoxetine, 20-40 mg), (2) switching to venlafaxine ER (150-225 mg), (3) switching to an alternative SSRI and receiving cognitive behavioral therapy (CBT), or (4) switching to venlafaxine ER and receiving CBT. The primary outcome measures were Clinical Global Impressions-Improvement score of 2 or less (much or very much improved); a decrease of at least 50 percent in the Children's Depression Rating Scale-Revised (CDRS-R); and change in CDRS-R over time. Cognitive behavioral therapy plus a switch to either medication regimen showed a higher response rate (54.8 percent; 95% CI, 47-62 percent) than a medication switch alone (40.5 percent; 95% CI, 33-48 percent; p=0.009), but there was no difference in response rate between venlafaxine and a second SSRI (48.2 percent; 95% CI, 41-56 percent versus 47.0 percent; 95% CI, 40-55 percent; p=0.83). There were no differential treatment effects on change in the CDRS-R, self-rated depressive symptoms, suicidal ideation, or on the rate of harm-related or any other adverse events. There was a greater increase in diastolic blood pressure and pulse and more frequent occurrence of skin problems during venlafaxine than SSRI treatment. For adolescents with depression not responding to an adequate initial treatment with an SSRI, the combination of cognitive behavioral therapy and a switch to another antidepressant resulted in a higher rate of clinical response than did a medication switch alone. However, a switch to another SSRI was just as efficacious as a switch to venlafaxine and resulted in fewer adverse effects.

Pregnancy

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. Safety of phenelzine (Nardil) and tranylcypromine (Parnate) for use by pregnant women has not been established.[114,115] Isocarboxazid (Marplan) should be given to a pregnant woman only if clearly needed.[116]

Neonates exposed to SNRIs or SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. When treating pregnant women with SNRIs or SSRIs, the physician should carefully consider the potential risks and benefits of treatment. Consider tapering therapy during the third trimester.

Renal Impairment

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. It should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered.

Desvenlafaxine (Pristiq) requires a dose adjustment to 50 mg every other day in patients with severe renal impairment or ESRD (End Stage Renal Disease).

Duloxetine (Cymbalta) is not recommended for patients with ESRD or severe renal impairment (estimated creatinine clearance < 30 mL/min).

Isocarboxazid (Marplan) should not be used in patients with severe renal impairment.

Caution is indicated in administering mirtazapine to patients with compromised renal function since its elimination is correlated with creatinine clearance.

Hepatic Impairment

Bupropion should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients, a reduced dose and frequency is required. Bupropion should be used with caution in patients with hepatic impairment, including mild to moderate hepatic cirrhosis, and a reduced frequency and/or dose should be considered. All patients with hepatic impairment should be closely monitored for possible adverse effects.

Desvenlafaxine (Pristiq) does not require a dosage adjustment in starting dosage for patients with hepatic disease.

Duloxetine (Cymbalta) should not be administered to patients with hepatic insufficiency as it increases the risk of elevation of serum transaminase levels. Duloxetine should also not ordinarily be administered to patients with substantial alcohol use.

Isocarboxazid (Marplan) should not be used in patients with a history of liver disease or in those with abnormal liver function tests.

Caution is indicated in administering mirtazapine to patients with compromised hepatic function.

Cases of life-threatening hepatic failure have been reported in patients treated with nefazodone. The physician may consider the value of liver function testing for patients treated with nefazodone and patients should be advised to be alert for signs and symptoms of liver dysfunction such as jaundice, anorexia, gastrointestinal complaints, and malaise and to report them to their doctor immediately should they occur. Nefazodone should be discontinued if clinical signs or symptoms suggest liver failure. Nefazodone should be withdrawn if evidence of hepatocellular injury such as increased serum AST or ALT levels ≥3X ULN develops and these patients should be presumed to be at increased risk for liver injury if the drug is reinitiated; therefore, these patients should not be considered for re-treatment.

Dosage adjustment for venlafaxine is necessary in hepatically impaired patients as it is well absorbed and extensively metabolized by the liver.

Dosages

For Adults

Drug	Starting Dose	Maintenance Dose	Maximum Dose	Hepatic Impairment	Renal Impairment	Dosage Forms
bupropion HCl IR	100 mg twice daily	100 mg three times daily	150 mg three times daily	↓	↓	Tablets: 75, 100 mg
bupropion HCl SR	150 mg every morning	150 mg twice daily	200 mg twice daily	↓	↓	Extended Release Tablets: 100, 150, 200 mg
bupropion HCl ER	150 mg every morning	300 mg every morning	450 mg every AM	↓	↓	Extended Release Tablets: 150, 300 mg
bupropion HBr ER (Aplenzin)	174 mg every morning (equivalent to 150 mg bupropion HCl)	Periodic assessment for maintenance dose determination	522 mg once daily (equivalent to 450 mg bupropion HCl)	↓	↓	Extended Release Tablets: 174, 348, 522 mg
desvenlafaxine (Pristiq)	50 mg daily	Ongoing assessment required	400 mg daily	--	↓	Extended Release Tablets: 50, 100 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
isocarboxazid (Marplan)	10 mg twice daily	Periodic assessment with incremental dose increases up to 20 mg/week	60 mg/day in two to four doses	drug not recommended	drug not recommended	Tablets: 10 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
phenelzine (Nardil)	15 mg three times daily	15 – 60 mg per day	90 mg per day in divided doses	nr	nr	15 mg tablet

Drug	Starting Dose	Maintenance Dose	Maximum Dose	Hepatic Impairment	Renal Impairment	Dosage Forms
selegiline (Emsam)	6 mg patch daily	6 mg patch daily	12 mg patch daily	--	--	Patches: 6, 9, 12 mg/24 hours
tranylcypromine (Parnate)	30 mg daily in divided doses	30 mg daily in divided doses	60 mg daily in divided doses	nr	nr	10 mg tablet
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	↓	↓	Extended Release Capsules: 37.5, 75, 150 mg
venlafaxine ER	37.5 to 75 mg once daily	75 to 225 mg once daily	225 mg once daily	↓	↓	Extended Release Tablets: 37.5, 75, 150, 225 mg

Doses are FDA-approved doses for outpatients. -- = no dosage change required ↓ = consideration should be given to reducing the dose and/or dosage frequency. nr = not reported

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 (522 mg of bupropion HBr) should not be exceeded. Increases above 300 mg/day (348 mg/day of bupropion HBr) should only be used 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. Bupropion HBr ER should be administered once daily as a single dose.

Venlafaxine has an ascending dose-response curve.[117] 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.

Clinical Trials

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity 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 psychotropic studies during follow-up, trials with more than 30 percent loss were still considered for inclusion in this review. 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.

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 (FDA) 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.[118] 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.[119]

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.[120] 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.[121]

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'.[122]

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.[123,124,125] 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).[126]

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.[127,128]

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.[129]

Sheehan Disability Scale (SDS) - A self-rated, three-item rating scale used to measure the degree of disease-related disability in the domains of work, family and social relationships. The limitation of this disability rating scale is that some patients may not accurately recognize their degree of disability until after successful treatment.[130]

Panic and Anticipatory Anxiety Scale (PAAS) - A rating scale for treatment efficacy assessment obtained from a daily diary maintained by the study participant and used to measure the number of panic attacks experienced, the number of episodes of anticipatory anxiety, and the percentage of time in each 24-hours spent worrying about having a panic attack (anticipatory anxiety).[131]

Children's Depression Rating Scale-Revised (CDRS-R) - Modeled after the Hamilton Rating Scale for Depression, the CDRS-R is a clinical interview tool designed for assessing six to 12 year-olds, and it has also been used successfully for adolescents. The CDRS-R helps clinicians rate 17 symptom areas: impaired schoolwork, difficulty having fun, social withdrawal, appetite disturbance, sleep disturbance, excessive fatigue, physical complaints, irritability, excessive guilt, low self-esteem, depressed feelings, morbid ideas, suicidal ideas, excessive weeping, depressed facial affect, listless speech, and hypoactivity. It is used to diagnose depression and can be repeated to measure response to treatments.[132]

MAJOR DEPRESSIVE DISORDER (MDD)

bupropion IR and fluoxetine (Prozac®)

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.[133] 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 were no significant differences 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.[134] 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 bupropion-treated patients and 46 percent of trazodone-treated patients were CGI responders. This is equivalent to an odds ratio (OR) for bupropion versus 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.[135] Anorexia and anxiety were reported significantly more often for the bupropion group. Somnolence, appetite increase, and edema were reported significantly more often in the trazodone group.

bupropion XL (Wellbutrin XL) and escitalopram (Lexapro®)

In two identical, double-blind, controlled-trials, 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.[136] Pooled data showed a significant difference between escitalopram and placebo, but not bupropion XL and placebo, in HAM-D-17 total scores. There were no significant differences among 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.

bupropion and sertraline, paroxetine or escitalopram (Lexapro)

Six double-blind, randomized clinical trials comparing bupropion (n=662) with an SSRI (n=655) for the treatment of MDD were pooled to examine whether the treatment of MDD with bupropion results in a greater resolution of sleepiness and fatigue than with the SSRIs: sertraline, paroxetine, or escitalopram.[137] Among the six studies pooled, three studies used sertraline, one used paroxetine and two used escitalopram as the SSRI comparator. Hypersomnia scores were defined as the sum of scores of the Hamilton Depression Rating Scale (HDRS) items #22, 23, and 24. Fatigue scores were defined as the score of HDRS item #13. There was a greater improvement in hypersomnia scores among bupropion-treated than SSRI-treated ($p<0.0001$) or placebo-treated patients ($p=0.0008$). There was also a greater improvement in fatigue scores among bupropion-treated ($p<0.0001$) and SSRI-treated ($p=0.0005$) than placebo-treated patients as well as a greater improvement in fatigue scores among bupropion-treated than SSRI-treated patients ($p=0.0078$). Fewer bupropion-remitters than SSRI-remitters experienced residual hypersomnia (20.5 percent versus 32.1 percent; $p=0.0014$) or residual fatigue (19.5 percent versus 30.2 percent; $p=0.0020$). The manufacturer of bupropion ER sponsored the study.

desvenlafaxine (Pristiq) and placebo

The efficacy of desvenlafaxine as a treatment for depression was established in four eight-week, randomized, double-blind, placebo-controlled, fixed-dose studies (at doses ranging 50 mg/day to 400 mg/day) in adult outpatients who met DSM-IV criteria for MDD.[138] With the first study, patients received 100 mg (n=114), 200 mg (n=116), or 400 mg (n=113) of desvenlafaxine once daily, or placebo (n=118). In a second study, patients either received 200 mg (n=121) or 400 mg (n=124) of desvenlafaxine once daily, or placebo (n=124). In two other studies, patients received 50 mg (n=150 and n=164) or 100 mg (n=147 and n=158) of desvenlafaxine once daily, or placebo (n=150 and n=161). Studies directly comparing 50 mg/day and 100 mg/day showed there was no additional benefit with the higher dose. In general, while discontinuation and adverse events were more frequent at higher doses, no severe toxicity was observed.

duloxetine (Cymbalta) and escitalopram (Lexapro)

A randomized, double-blind, placebo- and active comparator-controlled study, in which patients 18 years of age and older meeting DSM-IV criteria for MDD received duloxetine 60 mg once daily (n=273), escitalopram 10 mg once daily (n=274) or placebo (n=137).[139] The eight-week study was conducted to compare the speed of onset of antidepressant efficacy for duloxetine and escitalopram and to test whether duloxetine was at least as effective as escitalopram. Onset of efficacy was defined as a 20 percent decrease from baseline on the HAM-D-17 Maier subscale at week two that was maintained or exceeded at all subsequent visits. In this study, both duloxetine and escitalopram showed significantly greater improvement on the primary efficacy measure than placebo over the eight-week acute treatment period, while no differences were observed between drugs or between drugs and placebo on response and remission rates at eight weeks. Escitalopram at a starting dose of 10 mg daily was better tolerated than duloxetine at a starting dose of 60 mg daily as noted by more frequent occurrence of nausea, dry mouth, vomiting, yawning, and irritability for duloxetine-treated patients. This study's pre-defined primary objective was met and showed that duloxetine is not inferior to escitalopram in terms of onset of efficacy.

duloxetine (Cymbalta) and paroxetine

In a randomized, double-blind trial of eight weeks of active treatment, patients with non-psychotic MDD were randomized to duloxetine 60 mg (n=238) or paroxetine (n=240) once daily.[140] Efficacy was primarily measured on change in the HAM-D-17 using a non-inferiority test with a margin of 2.2. Secondary efficacy measures included the HAM-D-17 subscales, HAM-A, CGI-S, PGI-I, Somatic Symptoms Inventory and VAS for pain. Safety measures included treatment-emergent adverse events, vital signs, weight, laboratory analyses, and electrocardiograms. Non-inferiority of duloxetine to paroxetine was demonstrated because the upper bound of the confidence interval for mean difference in HAM-D-17 change (0.71) was less than the non-inferiority margin. Secondary efficacy endpoints did not differ significantly between treatments with the exception of VAS back pain, where the pooled mean was lower in the duloxetine group (17.1) compared with the paroxetine group (20.3, p=0.048). No significant differences were observed in the number of early discontinuations and overall adverse effects; however, a significantly greater proportion of duloxetine-treated patients experienced nausea and palpitations. No clinically relevant changes in other secondary efficacy endpoints were observed with either treatment. This study verifies the utility of duloxetine as an efficacious and safe treatment for both emotional and physical symptoms of MDD in this predominantly Asian patient sample.

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.[141] 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.[142] 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 ($p\leq0.01$). 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.[143] 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).

phenelzine (Nardil) and tranylcypromine (Parnate)

Phenelzine and tranylcypromine were compared in a double-blind, flexible dose study with 77 severely depressed patients with treatment resistant depression.[144] Patients had previously been treated with tricyclic antidepressants or fluvoxamine. A total of 87 percent of patients completed the trial with 52 percent of patients responding to therapy. Response was defined as a ≥50 percent reduction in HAM-D scores. No significant differences in response between both drugs were observed. Seventeen (44 percent) of 39 patients responded to tranylcypromine, and 18 (47 percent) of 38 responded to phenelzine. The mean reduction in HAM-D score was 10.4 +/- 8.3 for the tranylcypromine sample versus 8.3 +/- 8.4 for the phenelzine-treated patients. Only ten percent of patients used concomitant psychotropic medication. The most common adverse effects were dizziness, agitation, and insomnia; the incidence was the same in both groups (21 percent).

selegiline (Emsam) 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.[145] 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 were no significant differences 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.[146] 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.[147] 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≤0.05 for both comparisons endpoints).

In a 52-week, double-blind, placebo-substitution, parallel-group clinical trial, safety and efficacy of initial and continuation selegiline in patients with MDD was assessed.[148] After ten weeks of treatment with selegiline transdermal 6 mg/24 hr, 322 patients who responded with a HAM-D-17 score of ten or less were randomly assigned to double-blind treatment with selegiline transdermal 6 mg/24 hr or placebo for 52 weeks. Relapse was defined as meeting the following criteria on two consecutive visits: a score of 14 or more on the HAM-D-17 and a score of three or more with a two-point increase from double-blind baseline on the CGI-S with a MDD diagnosis. At study week 52, significantly fewer selegiline patients experienced relapse of MDD episode (25/149 [16.8 percent]) compared with placebo (50/163 [30.7 percent]) (p=0.0025). Additionally, patients receiving selegiline transdermal experienced a significantly longer time to relapse compared with those receiving placebo (p=0.0048). The safety profile of selegiline transdermal was similar to placebo, with the exception of application-site reactions. No cases of hypertensive crisis were reported despite the lack of requirement for dietary tyramine restrictions.

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.[149] 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≤0.05), and more trazodone-treated patients reported somnolence and dizziness (p≤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≤0.05). More combined events suggesting sedation (somnolence, asthenia) were reported with trazodone (42.6 percent) than with fluoxetine (21.5 percent, p≤0.05). Discontinuation rates for activation and sedation did not differ between treatments. The manufacturers of fluoxetine conducted the 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.[150] 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 the 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.[151] 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 versus 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.[152] 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 ≤6 rather than the more usual ≤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.[153] 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 IR group (83 percent) than in the sertraline group (68 percent; $p=0.05$). Similarly, HAM-D-21 remission rates were higher in the venlafaxine IR group than in the sertraline group (68 and 45 percent, respectively; $p=0.008$); this difference was more pronounced in patients who increased the dose. There were no significant differences observed between treatment groups for adverse events. The manufacturer of venlafaxine IR funded the 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.[154] 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 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.[155] 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 ER 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 ER group. More venlafaxine ER-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 ER-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.[156] 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 ER 75 to 225 mg/day, fluoxetine 20 to 60 mg/day or placebo; doses could be increased after two weeks.[157] 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 ER improved MADRS and CGI compared to placebo. Venlafaxine ER patients experienced significantly more dizziness and nausea than fluoxetine or placebo patients (p<0.05). The manufacturer of venlafaxine ER funded the 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.[158] 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. The 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 ER patients and 3.8 percent of sertraline patients. The manufacturer of sertraline funded this study.

FIBROMYALGIA

duloxetine (Cymbalta) and placebo

Efficacy and safety of duloxetine in reducing pain severity in 520 fibromyalgia patients with or without current MDD were evaluated in a six-month, multicenter, randomized, double-blind,

placebo-controlled study.[159] Patients were randomized to duloxetine 20 mg, 60 mg, or 120 mg per day or placebo. The duloxetine 20 mg per day group was titrated to 60 mg per day after three months. The primary outcome measures were the Brief Pain Inventory (BPI) average pain severity score and Patient Global Impressions of Improvement (PGI-I) score. The duloxetine 120 mg group improved significantly more than the placebo group on the primary outcome measures at three months (change in BPI score [-2.31 versus -1.39, p<0.001] and PGI-I [2.89 versus 3.39, p=0.004]) and at six months (change in BPI [-2.26 versus -1.43, p=0.003] and PGI-I [2.93 versus 3.37, p=0.012]). Compared with placebo, treatment with duloxetine 60 mg/day also significantly improved the co-primary measures at three months and BPI at six months. Duloxetine was well tolerated.

GENERALIZED ANXIETY DISORDER (GAD)

duloxetine (Cymbalta) and placebo

Three independent clinical studies were randomized, double-blind, placebo-controlled multicenter studies which were conducted in adult outpatients with DSM-IV-defined GAD. The studies examined the efficacy of duloxetine treatment for improving functional outcomes for patients with GAD.[160] One study compared nine-week, fixed-dose treatment with duloxetine 60 or 120 mg (n=168 and n=170, respectively) with placebo (n=175). The other two studies compared ten-week, flexible-dose treatment with duloxetine 60-120 mg (study two, n=168; study three, n=162) with placebo (study two, n=159; study three, n=161). The main functional outcome measure for each study was the Sheehan Disability Scale (SDS). Additional measures were the Q-LES-Q Short Form and the European Quality of Life 5 Dimensions. Duloxetine-treated patients improved significantly more than placebo-treated patients on SDS global functioning (study one, p≤0.001; studies two and three, p≤0.01) and SDS work, social life and family/home responsibilities scores (p values range from ≤ 0.05 to ≤0.001). At treatment endpoint, a greater percentage of duloxetine-treated patients had obtained SDS global functioning scores in the normative range than placebo-treated patients (p values range from ≤0.05 to ≤0.001). Duloxetine-treated patients also reported greater increases in quality of life, well-being, and health compared with the placebo group on the other functional measures (p values range from ≤0.05 to ≤0.001).

In a 10-week, double-blind, flexible-dose trial, 327 adult outpatients with GAD were randomized to duloxetine 60 to 120 mg (n=168) or placebo (n=159) treatment for the evaluation of efficacy, safety, and tolerability of duloxetine in the treatment of GAD.[161] The primary efficacy parameter was mean change from baseline to endpoint HAM-A total score. Secondary outcome measures included response rate (HAM-A total score reduction ≥50 percent from baseline), CGI-I scores, and Sheehan Disability Scale (SDS) scores. Patients who received duloxetine demonstrated significantly greater improvement in HAM-A total scores (p=0.02); a higher response rate (p=0.03), and greater improvement (p=0.04) than patients who received placebo. Duloxetine-treated patients were also significantly more improved than placebo-treated patients on SDS global functional (p<0.01) and work, social, and family/home impairment scores (p<0.05). Discontinuation rate for adverse effects was higher for the duloxetine group compared with the placebo group (p=0.002). The most common adverse effects with duloxetine were nausea, dizziness, and somnolence.

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.[162] The dosage of

venlafaxine ER (75, 150 or 225 mg/day) was based on symptom response. During weeks six through 28, response rates in the venlafaxine ER 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 ER 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.[163] Three trials were eight weeks in duration; two trials had a duration of 24 weeks. For 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 ER 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.[164] After two weeks, the dose could be doubled if the physician considered the response poor. At 24 weeks, the HAM-A showed improvement in the venlafaxine ER group (p=0.05 compared to placebo). Remission rates measured at 24 weeks were 28 percent for the venlafaxine ER 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.[165] A total of 272 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.

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.[166] In the 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.[167] Patients with other anxiety or depressive disorders were excluded from the 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 the 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.[168] In the 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.

venlafaxine ER (Effexor XR) or paroxetine

A total of 664 non-depressed adult outpatients who met DSM-IV criteria for panic disorder (with or without agoraphobia) were randomly assigned to 12 weeks of treatment with placebo or fixed-dose venlafaxine ER 75 mg/day or 150 mg/day, or paroxetine 40 mg/day in a double-blind study in the treatment of panic disorder.[169] The primary measure was the percentage of patients free from full-symptom panic attacks, assessed with the Panic and Anticipatory Anxiety Scale (PAAS). Secondary measures included the Panic Disorder Severity Scale, CGI-S and CGI-I scales; response (CGI-I rating of very much improved or much improved), remission (CGI-S rating of not at all ill or borderline ill and no PAAS full-symptom panic attacks); and measures of depression, anxiety, phobic fear and avoidance, anticipatory anxiety, functioning, and quality of life. Intent to treat, last observation carried forward analysis showed that mean improvement on most measures was greater with venlafaxine ER or paroxetine than with placebo. No significant differences were observed between active treatment groups. Panic-free rates at end point with active treatment ranged from 54 to 61 percent, compared with 35 percent for placebo. Approximately 75 percent of patients given active treatment were responders, and nearly 45 percent achieved remission. The placebo response rate was slightly above 55 percent, with remission near 25 percent. Adverse events were similar for active treatment groups and mild to moderate.

DIABETIC PERIPHERAL 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, or placebo.[170] 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.[171] 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. The study was performed by the manufacturer of duloxetine.

Meta-analyses

One systematic review indicated that, based on fair-to-good evidence, the second-generation antidepressants all have similar efficacy in treating MDD.[172] 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.[173] 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.[174] 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.

Summary

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. Several products have additional indications beyond MDD and anxiety disorders. Cymbalta has additional indications for use in diabetic peripheral neuropathic pain (DPNP) and fibromyalgia.

With the similarity in efficacy and overall incidence of adverse events among antidepressants, rates of adherence and discontinuation of the various medications are also generally equivalent. Specific agents, however, have different adverse 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 (Emsam) is associated with relatively few systemic effects, but it is associated with a high rate of skin reactions. In placebo-controlled trials, discontinuation of Cymbalta has occurred as a result of higher rates of nausea, vomiting, dizziness, somnolence, and fatigue.

All of the antidepressants in this class have a black box warning regarding suicidality in children, adolescents, and young adults through the age of 24 years. Related risks as compared to benefits of therapy in this population continue to be evaluated but appear to indicate greater benefit than risk as long as providers, families and caregivers are aware of the risks. Use caution in prescribing these agents and observe patients for signs of these possible adverse effects.

References

[1] Ballenger JC, Davidson JR, Lecrubier Y, et al. A proposed algorithm for improved recognition and treatment of the depression/anxiety spectrum in primary care. Primary Care Companion J Clin Psychiatry. 2001; 3:44-52.

[2] Bandelow B, Zohar J, Hollander E, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders. World J Biol Psychiatry. 2008; 9(4):248-312.

[3] Available at: http://www.nimh.nih.gov/health/publications/anxiety-disorders/generalized-anxiety-disorder-gad.shtml. Accessed April 6, 2009.

[4] Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of twelve month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). Archives of General Psychiatry. 2005; 62(6):617–627.

[5] Kendler KS, Neale MC, Kessler RC, et al. Generalized anxiety disorder in women. A population- based twin study. Archives of General Psychiatry.
1992; 49(4):267–272.

[6] Available at: http://www.nimh.nih.gov/health/publications/anxiety-disorders/social-phobia-social-anxiety-disorder.shtml. Accessed April 6, 2009.

[7] Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of twelve month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). Archives of General Psychiatry. 2005; 62(6):617–627.

[8] Available at: http://www.nami.org/Content/ContentGroups/Helpline1/Seasonal_Affective_Disorder_(SAD).htm. Accessed April 6, 2009.

[9] Goldenberg DL, Burckhardt C, Crofford L, et al. Management of fibromyalgia syndrome. JAMA. 2004; 292(19):2388-2395.

[10] Burckhardt CS, Goldenberg D, Crofford L, et al. Guideline for the management of fibromyalgia syndrome pain in adults and children. American Pain Society; 2005.. Available at: http://www.ampainsoc.org/press/2005/101005.htm. Accessed April 6, 2009.

[11] Clauw DJ. Fibromyalgia: update on mechanisms and management. Journal of Clinical Rheumatology. 2007; 13(2):102-109.

[12] Perahia DG, Pritchett YL, Desaiah D, et al. Efficacy of duloxetine in painful symptoms: an analgesic or antidepressant effect? Int Clin Psychopharmacol. 2006; 21(6):311-317.

[13] Rooks DS. Fibromyalgia treatment update. Curr Opin Rheumatol. 2007; 19(2):111-117.

[14] Diabetic Neuropathies: The Nerve Damage of Diabetes. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH. http://diabetes.niddk.nih.gov/dm/pubs/neuropathies/. Accessed April 6, 2009.

[15] American Diabetes Association. Standards of medical care in diabetes-2009. Diabetes Care 2009; 32(S1):S13-S61.

[16] Lyrica [package insert]. Vega Baja, PR; Pfizer; June 2007.

[17] Huizinga MM, Peltier A. Painful diabetic neuropathy: a management-centered review. Clinical Diabetes 2007; 25(1):6-15.

[18] Ziegler D. Treatment of diabetic neuropathy and neuropathic pain: how far have we come? Diabetes Care. 2008; 31(2):S255-S261.

[19] Consensus Guidelines: Assessment, Diagnosis, and Treatment of Diabetic Peripheral Neuropathic Pain. Mayo Clinic Proceedings. 2006; 81:S1-32.

[20] Bandelow B, Zohar J, Hollander E, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders. World J Biol Psychiatry. 2008; 9(4):248-312.

[21] Ballenger JC, Davidson JR, Lebrubier Y, et al. Consensus statement on generalized anxiety disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 2001;62(S11): 53-58.
[22] Qaseem A, Snow V, Denberg T, et al. Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008; 149(10):725-33.
[23] Bolden-Watson C, Richelson E. Blockade by newly developed antidepressants of biologic amine uptake into rat brain synaptosomes. Life Sci. 1993; 52:1023-9.
[24] Cusack B, Nelson A, Richelson E. Binding of antidepressants to human brain. Psychopharmacology (Berl). 1994; 114:559-65.
[25] de Boer T, Maura G, Raiteri M, et al. Neurochemical and autonomic pharmacological profiles of the 6-aza-analogue of mianserin, ORG 3770 and its enantiomers. Neuropharmacology. 1988; 27:399-408.
[26] de Boer T, Ruigt G, Berendsen H. The alpha2-selective adrenoceptor antagonist Org 3770 (mirtazapine remeron) enhances noradrenergic and serotonergic transmission. Hum Psychopharmacol. 1995; 10:107S-18S.
[27] Frazer A. Antidepressants. J Clin Psychiatry. 1997; 58(suppl 6):9-25.
[28] Preskorn SH. Clinical Pharmacology of Selective Serotonin Reuptake Inhibitors. Caddo, Okla: Professional Communications, Inc; 1996; 48-9.
[29] Golden RN, Dawkins K, Nicholas L, et al. (1998). Trazodone, nefazodone, bupropion, and mirtazapine. In A.F. Schatzberg, & C.B. Nemeroff (Eds.), Textbook of psychopharmacology (2nd ed., pp. 549–588). Washington, DC: American Psychiatric Press, Inc.
[30] Kelsey, J.E. Mood disorders. In R.E. Rakel & E.T. Bope (Eds.), Conn's current therapy, 2001, (pp. 1147–1154). Philadelphia: WB Saunders Company.
[31] Fontaine R, Ontiveros A, Elie R, et al. A double-blind comparison of nefazodone, imipramine, and placebo in major depression. J Clin Psychiatry. 1994; 55:234-41.
[32] Eison AS, Eison MS, Torrente JR, et al. Nefazodone: preclinical pharmacology of a new antidepressant. Psychopharmacol Bull. 1990; 26:311-5.
[33] Marplan [package insert]. Parsippany, NJ; Validus; August 2007.
[34] Wellbutrin [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2007.
[35] Wellbutrin SR [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2007.
[36] Wellbutrin XL [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2007.
[37] Aplenzin [package insert]. Dorado, PR; Biovail Labs International; April 2008.
[38] Pristiq [package insert]. Philadelphia, PA; Wyeth Pharmaceuticals; February 2009.
[39] Cymbalta [package insert]. Indianapolis, IN; Eli Lilly; February 2009.
[40] Marplan [package insert]. Parsippany, NJ; Validus; August 2007.
[41] Remeron [package insert]. West Orange, NJ; Organon; July 2007.
[42] Remeron SolTab [package insert]. West Orange, NJ; Organon; July 2007.
[43] Serzone [package insert]. Princeton, NJ; Bristol Myers Squibb; January 2005.
[44] Nardil [package insert]. New York, NY; Pfizer; May 2007.
[45] Emsam [package insert]. Princeton, NJ; Bristol-Myers Squibb; February 2008.
[46] Parnate [package insert]. Research Triangle Park, NC; GlaxoSmithKline; May 2007.
[47] Trazodone [package insert]. Corona, CA; Watson; August 2007.
[48] Effexor XR [package insert]. Philadelphia, PA; Wyeth-Ayerst; February 2009.
[49] Effexor [package insert]. Philadelphia, PA; Wyeth-Ayerst; February 2009.
[50] Wellbutrin SR [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2007.
[51] Wellbutrin XL [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2007.
[52] Serzone [package insert]. Princeton, NJ; Bristol Myers Squibb; January 2005.
[53] Emsam [package insert]. Princeton, NJ; Bristol-Myers Squibb; February 2008.
[54] Effexor [package insert]. Philadelphia, PA; Wyeth-Ayerst; February 2009.
[55] Bolden-Watson C, Richelson E. Blockade by newly developed antidepressants of biologic amine uptake into rat brain synaptosomes. Life Sci. 1993; 52:1023-9.
[56] Cusack B, Nelson A, Richelson E. Binding of antidepressants to human brain. Psychopharmacology (Berl). 1994; 114:559-65.
[57] de Boer T, Maura G, Raiteri M, et al. Neurochemical and autonomic pharmacological profiles of the 6-aza-analogue of mianserin, ORG 3770 and its enantiomers. Neuropharmacology. 1988; 27:399-408.
[58] de Boer T, Ruigt G, Berendsen H. The alpha2-selective adrenoceptor antagonist Org 3770 (mirtazapine remeron) enhances noradrenergic and serotonergic transmission. Hum Psychopharmacol. 1995; 10:107S-18S.
[59] Frazer A. Antidepressants. J Clin Psychiatry. 1997; 58(suppl 6):9-25.
[60] Preskorn SH. Clinical Pharmacology of Selective Serotonin Reuptake Inhibitors. Caddo, Okla: Professional Communications, Inc; 1996; 48-9.
[61] Golden RN, Dawkins K, Nicholas L, et al. (1998). Trazodone, nefazodone, bupropion, and mirtazapine. In A.F. Schatzberg, & C.B. Nemeroff (Eds.), Textbook of psychopharmacology (2nd ed., pp. 549–588). Washington, DC: American Psychiatric Press, Inc.
[62] Kelsey, J.E. Mood disorders. In R.E. Rakel & E.T. Bope (Eds.), Conn's current therapy, 2001, (pp. 1147–1154). Philadelphia: WB Saunders Company.
[63] Fontaine R, Ontiveros A, Elie R, et al. A double-blind comparison of nefazodone, imipramine, and placebo in major depression. J Clin Psychiatry. 1994; 55:234-41.
[64] Eison AS, Eison MS, Torrente JR, et al. Nefazodone: preclinical pharmacology of a new antidepressant. Psychopharmacol Bull. 1990; 26:311-5.
[65] Nardil [package insert]. New York, NY; Pfizer; May 2007.
[66] Parnate [package insert]. Research Triangle Park, NC; GlaxoSmithKline; May 2007.
[67] Marplan [package insert]. Parsippany, NJ; Validus; August 2007.
[68] Emsam [package insert]. Princeton, NJ; Bristol-Myers Squibb; February 2008.
[69] Harvey A, Preskorn SH. Cytochrome P450 enzymes: interpretation of their interactions with selective serotonin reuptake inhibitors. Part II. J Clin Psychopharmacol. 1996; 16:344-55.

[70] Shad MU, Preskorn SH. In: Levy R, et al, eds. Philadelphia, Pa: Lippincott, Williams & Wilkins; 2000:563-77.
[71] Wellbutrin [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2007.
[72] Aplenzin [package insert]. Dorado, PR; Biovail Labs International; April 2008.
[73] Pristiq [package insert]. Philadelphia, PA; Wyeth Pharmaceuticals; February 2009.
[74] Cymbalta [package insert]. Indianapolis, IN; Eli Lilly; February 2009.
[75] Marplan [package insert]. Parsippany, NJ; Validus; August 2007.
[76] Remeron [package insert]. West Orange, NJ; Organon; July 2007.
[77] Serzone [package insert]. Princeton, NJ; Bristol Myers Squibb; January 2005.
[78] Nardil [package insert]. New York, NY; Pfizer; May 2007.
[79] Emsam [package insert]. Princeton, NJ; Bristol-Myers Squibb; February 2008.
[80] Parnate [package insert]. Research Triangle Park, NC; GlaxoSmithKline; May 2007.
[81] Effexor [package insert]. Philadelphia, PA; Wyeth-Ayerst; February 2009.
[82] Effexor XR [package insert]. Philadelphia, PA; Wyeth-Ayerst; February 2009.
[83] Wellbutrin [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2007.
[84] Wellbutrin SR [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2007.
[85] Wellbutrin XL [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2007.
[86] Aplenzin [package insert]. Dorado, PR; Biovail Labs International; April 2008.
[87] Pristiq [package insert]. Philadelphia, PA; Wyeth Pharmaceuticals; February 2009.
[88] Cymbalta [package insert]. Indianapolis, IN; Eli Lilly; February 2009.
[89] Remeron [package insert]. West Orange, NJ; Organon; July 2007.
[90] Serzone [package insert]. Princeton, NJ; Bristol Myers Squibb; January 2005.
[91] Nardil [package insert]. New York, NY; Pfizer; May 2007.
[92] Emsam [package insert]. Princeton, NJ; Bristol-Myers Squibb; February 2008.
[93] Parnate [package insert]. Research Triangle Park, NC; GlaxoSmithKline; May 2007.
[94] Trazodone [package insert]. Corona, CA; Watson; August 2007.
[95] Effexor [package insert]. Philadelphia, PA; Wyeth-Ayerst; February 2008.
[96] Effexor XR [package insert]. Philadelphia, PA; Wyeth-Ayerst; February 2009.
[97] Skowron DM, Stimmel GL. Antidepressants and the risk of seizures. Pharmacotherapy. 1992; 12:18-22.
[98] R Hubbard, S Lewis, J West, et al. Bupropion and the risk of sudden death: a self-controlled case-series analysis using The Health Improvement Network. Thorax. 2005; 60:848-50.
[99] Amsterdam JD. A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. J Clin Psychiatry. 2003; 64:208-14.
[100] Emsam [package insert]. Princeton, NJ; Bristol-Myers Squibb; February 2008.
[101] Bodkin JA, Amsterdam JD. Transdermal selegiline in major depression: a double-blind, placebo-controlled, parallel-group study in outpatients. Am J Psychiatry. 2002; 159:1869-75.
[102] Wellbutrin [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2007.
[103] Cymbalta [package insert]. Indianapolis, IN; Eli Lilly; February 2009.
[104] Remeron [package insert]. West Orange, NJ; Organon; July 2007.
[105] Serzone [package insert]. Princeton, NJ; Bristol Myers Squibb; January 2005.
[106] Emsam [package insert]. Princeton, NJ; Bristol-Myers Squibb; February 2008.
[107] Trazodone [package insert]. Corona, CA; Watson; August 2007.
[108] Effexor [package insert]. Philadelphia, PA; Wyeth-Ayerst; February 2009.
[109] Pristiq [package insert]. Philadelphia, PA; Wyeth Pharmaceuticals; February 2009.
[110] American Academy of Child and Adolescent Psychiatry Official Action. Practice parameters for the assessment and treatment of children, adolescents and adults with depressive disorders. J Am Acad Child Adolesc Psychiatry. 1998; 37(10 Suppl):63S.
[111] Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry. 2006; 63:332-9.
[112] Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA. 2007; 297(15):1683-96.
[113] Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without CBT for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. JAMA. 2008; 299(8):901-13.
[114] Nardil [package insert]. New York, NY; Pfizer; May 2007.
[115] Parnate [package insert]. Research Triangle Park, NC; GlaxoSmithKline; May 2007.
[116] Marplan [package insert]. Parsippany, NJ; Validus; August 2007.
[117] Preskorn SH. Recent dose-effect studies regarding antidepressants. In: Balant LP, Benitez J, Dahl SG, et al., eds. European Cooperation in the Field of Scientific and Technical Research. Belguim: European Commission; 1998:45-61.
[118] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960; 23:56-62.
[119] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to changes. Br J Psychiatry. 1979; 134:382-9.
[120] Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959; 32:50-5.
[121] Leucht S, Engel RR. The Relative Sensitivity of the Clinical Global Impressions Scale and the Brief Psychiatric Rating Scale in Antipsychotic Drug Trials. Neuropsychopharmacology. 2006; 31:406-12.
[122] Leucht S, Engel RR. The Relative Sensitivity of the Clinical Global Impressions Scale and the Brief Psychiatric Rating Scale in Antipsychotic Drug Trials. Neuropsychopharmacology. 2006; 31:406-12.
[123] Duggleby W, Lander J. Cognitive status and postoperative pain: Older adults. J Pain Symptom Manage. 1994; 9:19-27.
[124] Williams J, Holleman D, Simel D. Measuring shoulder pain with the shoulder pain and disability index. J Rheumatol. 1995; 22:727-32.
[125] Valvano M, Leffler S. Comparison of bupivacaine and lidocaine/bupivacaine for local anesthesia/digital nerve block. Ann Emerg Med. 1996; 27:490-2.

[126] Connor KM, Davidson JRT, Churchill LE, et al. Psychometric properties of the Social Phobia Inventory (SPIN). Br J Psychiatry. 2000; 176:379-86.
[127] Hunt SM, McKenna SP. The QLDS, a scale for the measurement of quality of life in depression. Health Policy. 1992; 22:307-19.
[128] McKenna SP, Doward LC, Kohlmann T, et al. International development of the Quality of Life in Depression Scale (QLDS). J Affect Disord. 2001; 63:189-99.
[129] Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol Bull. 1993; 29:321-6.
[130] Available at: http://www.cqaimh.org/pdf/tool_lof_sds.pdf. Accessed April 7, 2009.
[131] Nardi AE, Nascimento I, Valenca AM, et al. Respiratory panic disorder subtype: acute and long-term response to nortriptyline, a noradrenergic tricyclic antidepressant. Psychiatry Research. 2003; 120:283-293.
[132] Available at: http://www2.massgeneral.org/schoolpsychiatry/screening_depression.asp. Accessed April 6, 2009.
[133] Feighner JP, Gardner EA, Johnston JA, et al. Double-blind comparison of bupropion and fluoxetine in depressed outpatients. J Clin Psychiatry. 1991; 52:329-35.
[134] Weisler RH, Johnston JA, Lineberry CG, et al. Comparison of bupropion and trazodone for the treatment of major depression. J Clin Psychopharmacol. 1994; 14:170-9.
[135] Lam RW, Kennedy SH. Using Meta-analysis to Evaluate Evidence: Practical Tips and Traps. Can J Psychiatry. 2005; 50:167–74.
[136] Clayton AH, Croft HA, Horrigan JP, et al. Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies. J Clin Psychiatry. 2006; 67:736-46.
[137] Papakostas GI, Nutt DJ, Hallett LA, et al. Resolution of sleepiness and fatigue in major depressive disorder: a comparison of bupropion and the selective serotonin reuptake inhibitors. Biol Psychiatry. 2006; 15; 60(12):1350-5.
[138] Pristiq [package insert]. Philadelphia, PA; Wyeth Pharmaceuticals; February 2009.
[139] Nierenberg AA, Greist JH, Mallinckrodt CH, et al. Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. Curr Med Res Opin. 2007; 23(2):401-16.
[140] Lee P, Shu L, Xu X, et al. Once-daily duloxetine 60 mg in the treatment of major depressive disorder: multicenter, double-blind, randomized, paroxetine-controlled, non-inferiority trial in China, Korea, Taiwan and Brazil. Psychiatry Clin Neurosci. 2007; 61(3):295-307.
[141] Wade A, Crawford GM, Angus M, et al. A randomized, double-blind, 24-week study comparing the efficacy and tolerability of mirtazapine and paroxetine in depressed patients in primary care. Int Clin Psychopharmacol. 2003; 18:133-41.
[142] Behnke K, Sogaard J, Martin S, et al. Mirtazapine orally disintegrating tablet versus sertraline: a prospective onset of action study. J Clin Psychopharmacol. 2003; 23:358-64.
[143] Gelenberg AJ, Trivedi MH, Rush AJ, et al. Randomized, placebo-controlled trial of nefazodone maintenance treatment in preventing recurrence in chronic depression. Biol Psychiatry. 2003; 54:806-17.
[144] Birkenhäger TK, van den Broek WW, Mulder PG, et al. Efficacy and tolerability of tranylcypromine versus phenelzine: a double-blind study in antidepressant-refractory depressed inpatients. J Clin Psychiatry. 2004; 65(11):1505-10.
[145] Bodkin JA, Amsterdam JD. Transdermal selegiline in major depression: a double-blind, placebo-controlled, parallel-group study in outpatients. Am J Psychiatry. 2002; 159:1869-75.
[146] Amsterdam JD. A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. J Clin Psychiatry. 2003; 64:208-14.
[147] Feiger AD, Rickels K, Rynn MA, et al. Selegiline transdermal system for the treatment of major depressive disorder: an 8-week, double-blind, placebo-controlled, flexible-dose titration trial. J Clin Psychiatry. 2006; 67:1354-61.
[148] Amsterdam JD, Bodkin JA. Selegiline transdermal system in the prevention of relapse of major depressive disorder: a 52-week, double-blind, placebo-substitution, parallel-group clinical trial. J Clin Psychopharmacol. 2006; 26(6):579-86.
[149] Beasley CM Jr, Dornseif BE, Pultz JA, et al. Fluoxetine versus trazodone: efficacy and activating-sedating effects. J Clin Psychiatry. 1991; 52:294-9.
[150] Costa e Silva J. Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. J Clin Psychiatry. 1998; 59:352-7.
[151] Dierick M, Ravizza L, Realini R, et al. A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. Prog Neuropsychopharmacol Biol Psychiatry. 1996; 20:57-71.
[152] Tylee A, Beaumont G, Bowden MW, et al. A double-blind, randomized, 12-week comparison study of the safety and efficacy of venlafaxine and fluoxetine in moderate to severe depression in general practice. Primary Care Psychiatry. 1997; 3:51-8.
[153] Mehtonen OP, Sogaard J, Roponen P, et al. Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder. Venlafaxine 631 Study Group. J Clin Psychiatry. 2000; 61:95-100.
[154] Cunningham LA. Once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. Venlafaxine XR 208 Study Group. Ann Clin Psychiatry. 1997; 9:157-64.
[155] Montgomery SA, Huusom AK, Bothmer J. A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. Neuropsychobiology. 2004; 50:57-64.
[156] Bielski RJ, Ventura D, Chang CC. A double-blind comparison of escitalopram and venlafaxine extended release in the treatment of major depressive disorder. J Clin Psychiatry. 2004; 65:1190-6.
[157] Rudolph RL, Feiger AD. A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. J Affect Disord. 1999; 56:171-81.
[158] Sir A, D'Souza RF, Uguz S, et al. Randomized Trial of Sertraline Versus Venlafaxine XR in Major Depression: Efficacy and Discontinuation Symptoms. J Clin Psychiatry. 2005; 66:1312-20.
[159] Russell IJ, Mease PJ, Smith TR, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. Pain. 2008; 136(3):432-44.
[160] Endicott J, Russell JM, Raskin J, et al. Duloxetine treatment for role functioning improvement in generalized anxiety disorder: three independent studies. J Clin Psychiatry. 2007; 68(4):518-24.

[161] Rynn M, Russell J, Erickson J, et al. Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. Depress Anxiety. 2008; 25(3):182-9.
[162] Gelenberg AJ, Lydiard RB, Rudolph RL, et al. Efficacy of venlafaxine extended-release capsules in no depressed outpatients with generalized anxiety disorder: A 6-month randomized controlled trial. JAMA. 2000; 283:3082-8.
[163] Katz IR, Reynolds CF, Alexopoulos GS, et al. Venlafaxine ER as a treatment for generalized anxiety disorder in older adults: pooled analysis of five randomized placebo-controlled clinical trials. J Am Geriatr Soc. 2002; 50:18-25.
[164] Lenox-Smith AJ, Reynolds A. A double-blind, randomized, placebo controlled study of venlafaxine XL in patients with generalized anxiety disorder in primary care. Br J Gen Pract. 2003; 53:772-7.
[165] Rickels K, Mangano R, Khan A. A double-blind, placebo-controlled study of a flexible dose of venlafaxine ER in adult outpatients with generalized social anxiety disorder. J Clin Psychopharmacol. 2004; 24:488-96.
[166] Stein MB, Pollack MH, Bystritsky A, et al. Efficacy of low and higher dose extended-release venlafaxine in generalized social anxiety disorder: a 6-month randomized controlled trial. Psychopharmacology (Berl). 2005; 177:280-8.
[167] Allgulander C, Mangano R, Zhang J, et al. Efficacy of Venlafaxine ER in patients with social anxiety disorder: a double-blind, placebo-controlled, parallel-group comparison with paroxetine. Hum Psychopharmacol. 2004; 19:387-96.
[168] Bradwejn J, Ahokas A, Stein DJ, et al. Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. Br J Psychiatry. 2005; 187:352-9.
[169] Pollack MH, Lepola U, Koponen H, et al. A double-blind study of the efficacy of venlafaxine extended-release, paroxetine, and placebo in the treatment of panic disorder. Depress Anxiety. 2007; 24(1):1-14.
[170] Goldstein DJ, Lu Y, Detke MJ, et al. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain. 2005; 116:109-18.
[171] Wernicke JF, Pritchett YL, D'Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology. 2006; 67:1411-20.
[172] Hansen RA, Gartlehner G, Lohr KN, et al. Efficacy and Safety of Second-Generation Antidepressants in the Treatment of Major Depressive Disorder. Ann Intern Med. 2005; 143:415-26.
[173] Williams JW, Mulrow CD, Chiquette E, et al. A Systematic Review of Newer Pharmacotherapies for Depression in Adults: Evidence Report Summary. Ann Intern Med. 2000; 132:743-56.
[174] Eckert L, Lancon C. Duloxetine compared with fluoxetine and venlafaxine: use of meta-regression analysis for indirect comparisons. BMC Psychiatry. 2006; 6:30.