

Clinical Pharmacology and Therapeutics of Antidepressants

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Introduction

An understanding of the clinical pharmacology of antidepressant agents is essential to optimal prescribing. The following chapter outlines general principles that influence prescribing, and then discusses specific subgroups of antidepressants. There is no generally accepted classification scheme for antidepressants, and current groupings reflect marketing, the history of development, and pharmacologic effects. We use the following terminology in our discussion: selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), cyclic antidepressants, mixed action agents, selective norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and alternative (non-traditional) antidepressants. Readers should keep in mind that there is no classification scheme that accurately reflects the actions of all the drug classes, and we have chosen a compromise classification system that is based on terms commonly used in clinical settings.

General Principles

Pharmacokinetics and Pharmacodynamics

There are several concepts that clinicians must be familiar with to understand the importance of different pharmacological characteristics among various antidepressants. These are broadly divided into pharmacokinetic and pharmacodynamic properties. Pharmacokinetics refers to drug absorption, distribution, and elimination. Pharmacodynamics refers to actions at the receptor and the cascade of events that follow.

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Some examples of the important clinical pharmacokinetic considerations in prescribing involve the presence of active metabolites, how long it takes for a drug to reach steady state, or how quickly it is eliminated. Drugs that are slowly eliminated, or have long-acting metabolites, may present less of a problem if a patient misses a dose and are less likely to be associated with a discontinuation syndrome. On the other hand, if toxicity or drug–drug interactions develop with such drugs, symptoms will persist after drug administration has ceased.

The clinical importance of pharmacodynamics is illustrated by receptor actions that influence therapeutic response and adverse effect profile. Clinicians should be cautious about using in vitro binding studies to make inferences about clinical effects; however, in many cases, there is a good correlation between binding and adverse effects. The relative potencies at the receptors that mediate antidepressant response provide a rationale for choosing medications, especially when faced with a poor response to initial therapy. Table 1 presents receptor binding data of commonly used antidepressants.

Table 1 Relative potencies at transporters

	Relative potencies		
	Serotonin transporters	Norepinephrine transporters	Dopamine transporters
Nefazodone	++	++	–
<i>Hydroxynefazodone</i>	+	+	–
<i>Triazole-dione</i>	–	–	–
<i>mCPP</i>	++	+	–
Trazodone	++	–	–
Amitriptyline	+++	++	–
Desipramine	++	++++	–
Paroxetine	++++	++	–
Sertraline	++++	+	±
Citalopram	++++	–	–
Fluoxetine	+++	+	–
Fluvoxamine	+++	+	–
Venlafaxine	++	+	±
<i>Desmethylvenlafaxine</i>	++	+	–
Chloroimipramine	ND	++++	–
Nortriptyline	++	+++	–
Imipramine	+++	++	–
<i>Norfluoxetine</i>	+++	+	–
<i>Desmethylsertraline</i>	++	+	–

Metabolites are italicized

– none; ± uncertain; +, ++, +++, +++++ weak, mild, moderate, strong;

ND not determined

Pharmacogenetics

Genetics influences both the metabolism and receptor effects of antidepressants. Genetic influences on metabolism are most important for antidepressants that have a low therapeutic index. Tricyclic antidepressants, for example, may cause toxic anticholinergic, cardiac, and CNS effects at plasma levels that are only two times therapeutic levels. Four different levels of CYP2D6 activity have been identified, and some leading laboratories now report seven levels from ultra rapid to poor (for a review see (1)). The clinical literature suggests that approximately 7–10% of Caucasians are slow metabolizers through CYP2D6 and toxic levels of imipramine, desipramine, and other agents metabolized via this pathway may result from standard therapeutic doses. Poor metabolizers of drugs that utilize the CYP2C19 may also develop adverse effects at standard doses. Although the SSRI have a large therapeutic index, so that most patients are able to tolerate wide fluctuations in plasma levels due to pharmacokinetic interactions, several are potent inhibitors of the CYP450 system (fluoxetine, fluvoxamine, paroxetine) and can affect toxicity of coadministered drugs that are metabolized via this system.

The activity level of specific cytochromes is determined both by genetics and by drug inhibition of their function. In the instance of genetic determinants, there is great variability in the allele frequencies among seemingly homogeneous populations with a history of migrations, isolation, and other factors. Although some centers advise genotyping all patients receiving antidepressants, we believe that if the usual dosing guidelines are followed, therapeutic levels can be achieved and toxicity avoided. Plasma levels are a reasonable, least costly alternative to genotyping at this time. On the other hand, genotyping may be appropriate for drugs that have a low therapeutic index, drugs that are associated with serious toxicity at levels close to therapeutic level, or high-risk patients, for whom high levels may be dangerous. For non-responders, it seems easier to examine plasma or serum levels to determine if adequate doses are being prescribed.

P-glycoprotein is a transmembrane transporter protein that has several functions, one of which is to transport xenobiotics out of the brain across the blood–brain barrier against a concentration gradient (2). Genetic variants of the gene encoding for P-glycoprotein (MDR1 or ABCB1 gene) may influence brain concentrations of several antidepressants, including citalopram, sertraline, venlafaxine, amitriptyline, nortriptyline, doxepin, and trimipramine, but not mirtazapine, fluoxetine, or bupropion. It is also located in intestinal epithelial cells, hepatocytes, and proximal tubular epithelial cells of the kidney. In most cases, pharmacogenetic testing is not required; however, in treatment-resistant depressions, these analyses may be helpful. Uhr et al. (3) reported that polymorphisms of ABCB1 were associated with outcome for citalopram, venlafaxine, and paroxetine. Drugs that are substrates of P-glycoprotein have higher rates of antidepressant response with these polymorphisms, suggesting that there is decreased efficiency of the transporter that removes drugs from the brain. One research group has suggested that antidepressants that inhibit P-glycoprotein increase cortisol in the brain, resulting in increased glucocorticoid-mediated negative

feedback on the HPA axis, and normalization of the glucocorticoid receptor resistance associated with major depression (4, 5).

Pharmacodynamic genetic studies have focused on hypothesis-driven approaches to genes encoding for receptors thought to be the target of antidepressants or altered in major depressive disorders. The most extensively studied gene is SLC6A4, which encodes for the serotonin transporter. Most studies have focused on a functional polymorphism in the 5' promoter region (5-HTTLPR). This polymorphism produces a short (S) allele and a long (L) allele (although rare long and extra long alleles have been reported in Asians and African Americans). There are a number of other variants reported, but for the purposes of drug response, we can focus on the S and L alleles, which have been linked to basal activity of the transporter and response to antidepressants. Although findings differ, the majority of studies show a poor response to SSRI in individuals with the S allele compared to LL subjects. The STAR*D study was able to replicate this finding only in a White, non-Hispanic subgroup. Other studies have found that the LL group responds better to placebo and sleep deprivation compared to the S allele group. At this time, genetic subtyping of the SLC6A4 gene is not clinically useful.

As described in chapter "Biological Theories of Depression and Implications for Current and New Treatments," substantial evidence suggests that overactivity of the HPA axis is a key neuropathological finding underlying unipolar major depression. Many authorities in the field believe that the core action of antidepressants is to normalize the HPA axis by reversing impaired activity of the glucocorticoid receptor. The genetic focus has been on FKBP5 which decreases binding affinity of the glucocorticoid receptor for cortisol. On the other hand, when FKBP4 replaces FKBP5, the receptor complex has high affinity for cortisol. Three polymorphisms in FKBP5 (rs 1360780, rs 4713916, and rs 3800373) have been associated with response to antidepressants (6). Homozygotes for the rare allele had a more rapid response to antidepressants (10 days earlier) than the other two genotypes. Perhaps most importantly, it was not limited to treatment with any specific antidepressant (2). Some support for these findings comes from the STAR*D study (7, 8), in which weak associations were found between rs 4713916 and response in a subgroup of the population identified as White, non-Hispanic. Other studies have found weaker associations than the original report (9) and the GENDEP study (10) with a cohort of 760 did not replicate the finding, nor did smaller Spanish and Korean studies (11, 12). The same alleles associated with a rapid antidepressant response are risk alleles for major depression, bipolar disorder, and PTSD. As explained by Horstmann and Binder (2), these alleles result in glucocorticoid receptor insensitivity by inducing FKBP5 mRNA and increased FKBP5, which in turn leads to prolonged elevated cortisol in response to stress (6, 13).

Given the central role of serotonin in the action of antidepressants, many studies have focused on genes coding for serotonin receptors. Promising findings come from studies of the HTR2A gene that codes for the 5-HT_{2A} receptor. The initial studies focused on two SNPs: (1) 102T/C, rs 6313 in exon 1 and (2) 1438 A/G, rs 6311 in the promoter region. While many have found an association between these SNPs and antidepressant response, many other larger studies could not replicate

the finding. Other variants of this gene have been associated with positive antidepressant response. STAR*D found that rs 7997012 was the only SNP associated with citalopram response (14, 15). When combined with a SNP located within the glutamate receptor inotropic kainite 4 (GRIK4) gene, namely rs 1954787, encoding for a high affinity kainite receptor improves prediction of response. Homozygotes for both GRIK4 and HTR2A alleles were 23% less likely to be non-responders compared to subjects not carrying these alleles. Similar other studies have found that a single SNP accounts for less than 3% of the variance, but when the investigators combined their three strongest predictors: 5HTR2A, GRIK4, and FKBP5 SNPs, thirteen percent of the variance was explained (16). Still other variants of the 5HTR2A gene may be associated with antidepressant response (10, 17). Using a genomewide association pharmacogenomic approach to antidepressant response, Ising et al. (18) did not find any single SNP predicted response. However, when individuals were characterized by the binary variable of high versus low number of response alleles, the model predicted antidepressant response. Patients with comorbid anxiety and a low number of response alleles had the worst outcomes. Research on pharmacogenetics is advancing rapidly; however, at the present time, routine use in clinical practice is premature.

Practical Aspects of Treatment

Prior to initiation of antidepressant treatment, clinicians should be confident that a medical condition, medication therapy, or substance use disorder is not the primary cause of depressed mood (see Tables 2 and 3). Some medical conditions, such as hypothyroidism, are so common that patients should be routinely screened. Others, such as diabetes, anemia, and vitamin deficiencies (folate, B12), are less common, but easily tested, and also should be ruled out. Some medical illnesses are common but more difficult to diagnose, such as autoimmune disorders, fibromyalgia, and chronic pain syndromes; fortunately, mood symptoms associated with these disorders often respond to antidepressants. Cushing's syndrome and polycystic ovary disease are commonly associated with mood disorders. Neurological conditions associated with depression include Parkinsonism, epilepsy, multiple sclerosis, cerebrovascular disease and stroke, dementia, and Huntington's disease. An association of depression and infectious disease is found with HIV and perhaps other viral illnesses. The association between depression and carcinoma is controversial, but if depression is the presenting complaint, there are usually symptoms that provide clues to the etiology (e.g., weight loss, pallor, fatigue that is worse in evening). In cases of depression associated with medical illness, treatment of the underlying disease is paramount, but antidepressants are often necessary. Superior efficacy for a particular antidepressant has not been established, so a reasonable approach is to use a medication that is unlikely to interact with drugs prescribed for the primary illness.

A meta-analysis found that mirtazapine, escitalopram, venlafaxine, and sertraline were more efficacious for MDD than duloxetine, fluvoxamine, paroxetine, and

Table 2 Medical illness with prominent psychiatric symptoms

Vitamin B deficiencies	Serum folate may be low in presence of normal tissue levels. RBC folate less subject to dietary changes. Clinically significant folate deficiency is associated with macrocytosis and megaloblastic anemia. Depressive symptoms associated with folate deficiency	Etiology is decreased dietary intake, alcoholism, pregnancy. Less common are malignancy, liver disease, hemolytic disorders	Testing requires levels of folate, B12. Also, in folate deficiency, homocysteine levels are elevated and methylmalonic acid levels normal. In B12 deficiency, both homocysteine and methylmalonic acid are elevated
Diabetes mellitus	Routine screening in depressed patients with risk factors is recommended. Fasting blood glucose over 120, hypertension, obesity, polycystic ovary disease, acute coronary syndrome, high triglycerides, low HDL-C. Classic symptoms of polyuria, polydipsia, polyphagia, weight loss, paresthesias, yeast infections, blurred vision	Genetic predisposition, high caloric intake, low energy expenditure. Secondary causes are ingestion of glucocorticoids, atypical antipsychotics, diseases that decrease insulin sensitivity (Cushing's, pheochromocytoma, acromegaly)	Fasting plasma glucose of 126 mg/dl or greater on two occasions. Random glucose greater than 200 mg/dl with symptoms of diabetes, HbA1c of 6.5% or higher
Thyroid disease	Hypothyroidism: weakness, fatigue, lethargy, cold intolerance, dry skin, decreased sweating, headache, edema, impaired cognition, depression, weight gain, paresthesias, arthralgias, muscle cramps, constipation	Hashimoto's thyroiditis, iodine deficiency, pituitary damage, irradiation, drugs (lithium, glucocorticoids, L-dopa, dopamine, iodide, sulfonylureas, phenylbutazone, phenytoin, salicylates, propylthiouracil, propranolol, amiodarone)	Measure free T3 and free T4 in serum (decreased in hypothyroidism). TSH increased in hypothyroidism. TSH-immunometric assay distinguishes between normal and reduced levels of TSH. Persistent high TSH after treatment may indicate pituitary adenoma. Consider Hashimoto's thyroiditis and Grave's disease (thyroid microsomal antibodies present in both 95 and 55%, respectively). Thyroglobulin antibodies with 60% of Hashimoto patients. Graves disease has antibodies against TSH receptor

Fibromyalgia	Chronic diffuse pain in muscles and joints, multifocal and migratory, stiffness, poor sleep, daytime lethargy, cognitive dysfunction, depression, anxiety, dizziness	Genetic contribution, altered serotonin function, toxins, HPA axis hyperactivity, more common in women	Labs to rule out other disorders (hypothyroidism, rheumatoid arthritis, systemic lupus erythematosus, etc)
Cushing's syndrome	Typical pattern of weight gain, purple stretch marks, skin thinning, easy bruising, proximal muscle weakness, in women menstrual irregularities, in men loss of libido and impotence, hypertension, diabetes mellitus, osteoporosis, depression, emotional lability, cognitive impairment	Exogenous steroid administration, pituitary adenoma, adrenal adenoma, oat cell or small cell carcinoma of lung. Carcinoid tumors	Urinary free cortisol, serum and salivary cortisol, dexamethasone-CRH test
Polycystic ovary disease	Depression, menstrual abnormalities, infertility, hyperandrogenism (excess hair in male pattern, acne, enlarged clitoris), obesity, acanthosis nigricans, diabetes mellitus, sleep apnea	Abnormalities in regulation of androgens and estrogens	Labs to rule out acromegaly, thyroid disease, Cushing's, and hyperprolactinemia
Pituitary adenomas	May produce a variety of psychiatric symptoms depending on hormones involved. If large may have mass effects. Symptoms may include those associated with thyroid disease, elevated prolactin levels, Cushing syndrome, somatotropin (acromegaly)	Diagnosed by hormone levels of LH, FSH, estradiol, adrenocorticotropin, cortisol, growth hormone, testosterone, prolactin, thyrotropin, thyroxine, insulin-like growth factor-I, and α subunit glycoprotein. Challenge tests are also used (e.g., TRH challenge and others)	Treatment usually surgical with adjunctive medication

(continued)

Table 2 (continued)

Multiple sclerosis	Multiple sclerosis May be relapsing and remitting or progressive. Weakness of limbs, optic neuritis, sensory defects, cognitive decline. T1 hypointensities, brain, spinal cord atrophy, fatigue cognitive slowing, depression, central vertigo, nystagmus, urinary incontinence, bipolar, dementia, high suicide rate	Diagnosis: elevated IgG in plasma cells and CSF. Elevated IgG index, T2 hyperintensities in white matter, inflammation and degeneration of gray matter and cortical atrophy-associated potentials, visual and somatosensory-evoked potentials, histology indicating perivascular infiltration of inflammatory cells, but other findings common. Expression of HLA, interferon γ , IL-12, B7 molecules increased early in disease	Treatment: β interferons and drug treatment of associated symptoms (e.g., for depression, spasticity, tremors, fatigue, etc)
Parkinson's disease	Early symptoms: daytime sleepiness, constipation, loss of smell. REM behavior disorder. Motor signs begin with asymmetrical resting tremor in upper extremity, progresses to clumsiness in hand, bradykinesia, rigidity, gait disturbance. Tremors may progress to lower extremities, tongue, lips. Dementia late	Diagnosis is clinical. No characteristic laboratory. PET scans show decrease of labeled dopa in putamen	Treatment includes selegiline, rasagiline (MAO-B inhibitors) are used early in disease. Dopamine produgs are primary agents (levodopa/carbidopa); other agents include dopamine agonists, anticholinergics, NMDA inhibitors, COMT inhibitors. Surgical intervention is deep brain stimulation
Dementia	All types may have prominent depressive symptoms and may be difficult to distinguish from severe depression with neurovegetative signs		
Epilepsy	Depression is common co-morbidity		

Porphyria	Porphyria, acute intermittent: abdominal pain, psychiatric symptoms—depression is common, motor neuropathies (can mimic Guillain-Barré syndrome)	Caused by genetic impaired functioning of porphobilinogen-deaminase and exposure to substances that increase heme synthesis (e.g., estrogens, barbiturates, sulfonamides, alcohol (see websiteU of Queensland) Diagnosed by urine porphyrin elevation (especially coporphobilinogen, some labs do not routinely include porphobilinogen and must be specifically ordered—this is the sine qua non of AIP; if porphobilinogen is not elevated AIP diagnosis is eliminated. During attack may have hyponatremia, SIADH	Other types of porphyria: (1) CHESTER: Genetic etiology with symptoms of AIP but reduction in activity of both porphobilinogen deaminase (as in AIP) and protoporphyrinogen. This subtype does not have cutaneous symptoms or photosensitivity. Labs indicate increased urine for porphyrins. May be confirmed by genetic testing. (2) Hereditary coproporphyria: Prominent psychiatric symptoms that mimic depression, mania, psychotic disorders, delirium seizures, peripheral neuropathy. Severe abdominal pain that is colicky in nature and lasts for several days, constipation, vomiting. Blisters develop in sun-exposed areas, and may lead to scarring. May have excessive hair growth in sun-exposed areas. Diagnosed by clinical features and elevated stool coproporphyrins 10–20 times above normal, urine levels may also be elevated. (3) ALA dehydratase deficiency
Huntington's disease	Usually choreiform movement are initial presentation, with dementia and psychiatric symptoms appearing late	Genetic etiology	
Systemic lupus erythematosus	Fatigue, fever, arthralgia, malar rash, discoid rash, photosensitivity, alopecia, renal disease (50% clinically significant)seizures, psychosis, delirium, depression, optic neuropathy, cognitive deficits	Diagnosed by clinical presentation and laboratory ENA panel, consisting of ANA titers, Anti-dsDNA, complement, Anti-Sm, Anti-SSA, Anti-SSB, Anti-ribosomal P, Anti-RNP, Anticardiolipin, Inflammatory markers, and others	

(continued)

Table 2 (continued)

Mixed connective tissue disease	Arthralgia, arthritis, edema of hands, Raynaud's phenomenon, myositis, esophageal hypomotility, rash, leucopenia, pulmonary hypertension, pleuritis, pericarditis. Depression and anxiety common	Laboratory shows high-titer speckled pattern fluorescent antinuclear antibody (FANA) may be present, not specific; High levels of anti-RNP antibodies and anti-U1-70 kd small nuclear ribonucleoprotein	NSAIDS, corticosteroids, plaquenil, cyclophosphamide, and symptomatic treatment
Fibromyalgia	Depression, anxiety, fatigue, and sleep disturbance present in most cases. Other symptoms include increased pain sensitivity, mainly in muscles, joints, but which include entire body. Pain is described as burning, of severe intensity, and may be migratory. The patient's complaint of having "pain all over" is often dismissed by inexperienced clinicians as hypochondriasis. Complaints of pain vary considerably and may include headache, pelvic pain, chest pain, dyspepsia, jaw pain, abdominal pain, and irritable bowel syndrome. Women often have urinary frequency and urgency. Syncope and shortness of breath may also be present. Cognitive function is impaired, especially memory	There is a genetic component to fibromyalgia, and studies have focused on SNP's of COMT, β -2-adrenergic receptor genes, and the serotonin transporter gene. HPA axis dysfunction and cytokine inflammatory factors have been implicated in the etiology of the illness	Antidepressants, such as duloxetine (Cymbalta), Milnacipram (Savella), and amitriptyline have been used with some success. Dosages required are not the same as antidepressant doses. Anticonvulsants, such as pregabalin (Lyrica) and gabapentin (Neurontin), are also helpful. Other agents include sedative hypnotics, muscle relaxants, and clonidine

Table 3 Drugs used for medical conditions that may induce depression

Medications	Comment
β -adrenergic blockers	In 1967, a letter to the British Medical Journal reported a case series of 89 patients treated with propranolol, of whom 30% developed depression. Two of these patients committed suicide (396). Subsequent pharmacoepidemiologic and meta-analyses studying patients on many different agents in the class have found no difference in depression compared to placebo (397). The likelihood of depression is highest for propranolol, which is lipophilic and readily enters the brain. Depression is most likely in individuals with a history of depression and occurred at dosage increases. Dose reduction or discontinuation results in resolution of depression (398). Lipophilic agents in this class may present greatest risk (propranolol, carvedilol, bucindolol)
ACE inhibitors	No direct evidence implicating ACE inhibitors in depression. Relationship based solely on a study that found antidepressant prescriptions higher in patients treated with ACE inhibitors than controls. Clinical experience does not support depression induced by this class of agents
Angiotensin II blockers	Case reports of depression, psychosis, and delirium associated with valsartan and losartan. There is insufficient evidence to establish this adverse reaction; however, clinicians should be aware of a potential psychiatric adverse effect
Calcium channel blockers	Case reports have implicated nifedipine, diltiazem, and verapamil in drug-induced depression. Larger studies did not confirm this (399), although one did report the risk of suicide was 1.1 suicides per 1,000 person-years, higher than other cardiovascular agents (400). We believe evidence supporting this adverse event is weak
Diuretics	Thiazides are not associated with depression, although neuropsychiatric symptoms may develop in the context of hypernatremia and hypercalcemia. Furosemide is not associated with new onset depression, but long-term use leads to thiamine deficiency and Wernicke's syndrome. Acetazolamide, a carbonic anhydrase inhibitor, can produce, fatigue, malaise, lethargy, and delirium most likely related to drug-induced acidosis
Corticosteroids	Clinical experience is extensive. There is substantial variability among patients, but depression, hypomania, mania, paranoia, psychosis. Risk factors unknown
Leukotriene inhibitors	Montelukast-induced depression recognized by WHO and FDA. May be associated with aggressive behavior, agitation. Abnormal dreams, hallucinations, insomnia, suicidal ideation, and suicide. Risk not known at present time
Interferons	α Interferons induce depression in about 30% of patients. β Interferons have a much lower likelihood of causing depression, but are not without risk
Varenicline	There is a substantial risk of new onset suicidal ideation and depression within days to 6 weeks of starting treatment (there are insufficient data to establish the true period of risk). Anxiety and abnormal dreams also possible
Levonorgestrel (norplant)	One of the most common reasons for discontinuation of drug is onset of depression. Major depression usually develops within 1–3 months of starting the drug and resolves 1–2 months after the implant is removed
Isotretinoin	There is an established relationship between the drug and new onset of depression and suicide. FDA warning
Finasteride	Men treated for alopecia may develop moderate to severe depression with an onset during the first few months of therapy. Mechanism may be reduction in neurosteroid allopregnanolone

reboxetine (19). Escitalopram and sertraline demonstrated the best acceptability, suggesting that these agents may be the best initial treatments for major depression, although interpretation of the results is confounded by the absence of data on dose, duration, patient adherence, and other methodological problems.

Once the diagnosis of a primary depression is established, it is important to consider the following subtypes: unipolar, bipolar, psychotic features, melancholia (some prefer the term “endogenous”), retarded, agitated, anxious, and atypical depressions. As will be described in various sections below, many (but certainly not all) studies indicate that these subtypes predict response to different antidepressants. Anxious depression, co-morbid substance abuse, and chronic severe depressions are less responsive to pharmacotherapy than first-episode depressions.

A controversial meta-analysis suggests that the greatest benefit from antidepressant treatment occurs in the most severe depressions (20), although other studies and clinical experience suggest that moderate depression also responds to antidepressants (21, 22). Therefore, in clinical practice, the decision to start an antidepressant depends not only on severity but also on chronicity and resistance to behavioral treatments. Despite the aforementioned meta-analysis, superior efficacy of a particular antidepressant has not been established, and the selection of an antidepressant for initial treatment is based on avoiding certain adverse effects and taking advantage of others. For example, in depressed patients with insomnia, a sedating antidepressant is helpful, but daytime administration should be avoided. Similarly, highly anticholinergic agents would be a poor first choice in an elderly patient because of the potential for urinary retention and memory problems. With the exceptions of citalopram, escitalopram, and sertraline, many of the SSRIs produce clinically significant inhibition of cytochrome P450 enzymes, and are usually not the first choice in patients who are taking other prescribed medications that are metabolized by this system. In the reality of clinical practice, the choice of a specific agent or combination of drugs is restricted by algorithms developed by formulary committees, decisions that are based primarily on comparative cost of agents with established efficacy.

Once an antidepressant is selected, a trial of adequate doses for at least 8–12 weeks is recommended (23). Many experienced psychopharmacologists believe that if a partial response is not achieved by 3 weeks, a change in drug should be instituted. The goal of treatment is a complete remission, although many patients will have only partial response of their symptoms. When a partial response is observed during this time period, dosage adjustments or augmentation with other agents is recommended. If the patient can tolerate an increase in dose, this is the most straightforward approach and is supported by clinical studies (24). An alternative strategy is to use another medication in combination with the antidepressant to achieve full remission. The usual strategies in partial or non-responders are to increase dose, augmentation with another medication, or switch to another agent. There is no evidence that establishes the superiority of any one of these approaches.

Although there was an intriguing finding in the STAR*D trial, suggesting that in non-responders augmentation response rates were higher than response rates to switching drugs, a valid comparison cannot be made because of bias inherent in the study design. The specific problem with the design was that a subject's decision to switch or augment after failure of citalopram treatment was not randomized. Several atypical antipsychotics, including olanzapine, aripiprazole, and quetiapine are FDA approved for augmentation of partial antidepressant response, and a combination product of olanzapine/fluoxetine (Symbyax) is marketed for treatment-resistant depression and depressive episodes associated with Bipolar I disorder.

Once full response is achieved, continuation therapy is based on the natural course of depression. On average, the course of an untreated depression is about 1 year, after which 40% of patients achieve spontaneous recovery, 40% stay depressed, and 20% have dysthymia (25). Some clinicians find it useful to describe three treatment phases, an acute phase of 6–12 weeks with the goal of full remission, a continuation phase that lasts up to a year, and a maintenance phase of 1 year or longer. For first episodes of unipolar major depression, treatment of the episode is continued for at least 1 year. In cases of recurrent depressions, severe single episodes, onset of the first episode before the age of 20 years, and a family history of serious depression, antidepressant therapy may continue indefinitely. Even with successful treatment, the risk of recurrence of major depression is substantial. It has been estimated at 50% after one episode, 70% after two episodes, and 90% after three episodes (25). Fifty percent of patients with a major depression will experience only one episode, while 30% become chronically depressed, and 20% have a recurrent episodic course.

There are two commonly used terms to describe improvement during antidepressant treatment: *response* and *remission*. Response is defined as a 50% or greater reduction from baseline score on a standardized depression scale (most commonly Hamilton Depression Scale (HDRS), the Montgomery Asberg Depression Rating Scale (MADRS), or the Quick Inventory of Depressive Symptomatology (QIDS)). Remission is defined as achieving a specific score on one of these scales. For example, commonly used scores indicating remission are a score of 7 or lower on the HDRS-17, a score of 10 or lower on the MADRS (7, 8), or a score of 5 or lower on the QIDS 16. The STAR*D study, which simulated typical clinical practice, reported a remission rate of about 30% with citalopram treatment. Approximately half of these remissions occurred within 6 weeks of beginning the drug (26). The response rate (50% reduction on the QIDS-SR16) was 47%. Predictors of poor response were mixed anxiety and depression, melancholic or atypical features, poor quality of life, lower socio-economic level, and minority status. Distinguishing response and remission has clinical implications. Patients who achieve full remission are less likely to relapse than responders. The responder group experiences longer periods of depression and greater impairment in social functioning over a 10-year follow-up period compared to patients who achieved full remission (27–29).

SSRIs

History

The first selective serotonin reuptake inhibitor (SSRI), fluoxetine, was introduced to the American market in 1988 (30). Other SSRIs, sertraline, paroxetine, and fluvoxamine, followed closely. Although widely used in Europe for some time, it was not until the late 1990s that another SSRI, citalopram, became available to American clinicians; and later, its enantiomer, escitalopram, was introduced. By the early 1990s, the SSRIs became first-line antidepressants in clinical practice and accounted for more than half of all antidepressant prescriptions. They enjoyed unprecedented marketing success (31), had great exposure in popular literature and news, and at first were thought to be orders of magnitude superior to already existing antidepressant drugs. Indeed, SSRI compounds have a more favorable side effect profile, simpler dosing strategies, better tolerability, and thus better adherence than older antidepressants. Their relative safety in overdose, minimal cardiovascular effects, and lower anticholinergic activity make them especially appealing as first-line agents.

As clinical experience with SSRIs has grown, it has become apparent that they have their own share of adverse effects. Also, the equivalence of SSRIs' efficacy to TCAs' has been challenged, and still remains a matter of some controversy. Even with these concerns, SSRIs are widely used and are effective in a wide range of psychiatric disorders other than depression, such as anxiety disorders, obsessive-compulsive disorder (OCD), panic disorder, bulimia nervosa, social phobia, post-traumatic stress disorder (PTSD), premenstrual dysphoric syndrome (PMDS), dysthymia, and seasonal affective disorder. SSRIs are the most widely prescribed antidepressants in America and worldwide (32).

Six SSRIs are available in the United States: *citalopram (Celexa)*, *escitalopram (Lexapro)*, *fluoxetine (Prozac)*, *fluvoxamine (Luvox)*, *paroxetine (Paxil)*, and *sertraline (Zoloft)*. All except fluvoxamine are approved by the U.S. Food and Drug Administration for use in depression; fluvoxamine is FDA approved for treatment of OCD but not depression (33). In Europe, however, fluvoxamine has been used as an antidepressant for many years (34). Table 4 lists the FDA-approved indications at the time of the writing of this chapter.

Pharmacokinetics

The pharmacokinetic properties and the cytochrome inhibiting properties of the SSRIs (with some comparison antidepressants) are shown in Tables 5 and 6. Of clinical importance is the fact that fluoxetine, paroxetine, and fluvoxamine do not exhibit linear kinetics or dose proportionality. That means that as the dose increases, there is not a proportional increase in plasma levels due to autoinduction of

Table 4 FDA-approved indications for commonly used antidepressants

Citalopram (Celexa)	MDD
Escitalopram (Lexapro)	MDD, GAD
Fluoxetine (Prozac)	MDD, OCD, bulimia nervosa, panic disorder with or without agoraphobia
Fluvoxamine (Luvox)	OCD
Paroxetine (Paxil CR)	MDD, OCD, panic disorder with or without AG, social anxiety disorder, GAD, PTSD
Sertraline (Zoloft)	MDD, acute and maintenance OCD. PD with or without agoraphobia PTSD. PMDD, social anxiety
VenlafaxineXR (Effexor XR)	MDD, GAD, social anxiety disorder, panic disorder with or without agoraphobia
Desvenlafaxine (Pristiq)	MDD
Mirtazapine (Remeron)	MDD
Bupropion (Wellbutrin)	MDD
Nefazodone	MDD
Trazodone	MDD with or without anxiety
Clomipramine (Anafranil)	OCD
Duloxetine (Cymbalta)	MDD, GAD, diabetic peripheral neuropathic pain, fibromyalgia
Milnacipram (Savella)	Fibromyalgia (not FDA approved for treatment of depression)
Selegiline (EMSAM)	MDD
Tranylcypromine (Parnate)	MDD without melancholia
Phenelzine (Nardil)	Depression characterized as atypical, nonendogenous, neurotic
Isocarboxazid (Marplan)	Major depression, especially with anxious mood, panic, and phobic symptoms

enzymes that metabolize these drugs. Citalopram, escitalopram, and sertraline differ in this regard, showing linear kinetics at the usual therapeutic doses.

Stereochemistry influences pharmacological activity and the pharmacokinetics of SSRIs. Fluoxetine and citalopram are racemic mixtures of the parent compound (30, 35). Although the S- and R-enantiomers of fluoxetine are approximately equivalent in their ability to inhibit serotonin reuptake, their metabolites, S- and R-norfluoxetine, respectively, are not. R-norfluoxetine is not active in terms of serotonin inhibition, while S-norfluoxetine is a more potent serotonin reuptake inhibitor than the parent drug (36). Furthermore, plasma levels of the S-enantiomer of norfluoxetine can be twice that of the R-enantiomer. S-norfluoxetine, but not R-norfluoxetine, is metabolized via cytochrome P450 2D6; therefore, individual variations in CYP 2D6 or drug interactions have the potential to affect clinical response. Paroxetine and sertraline are marketed as the most serotonergically potent forms of their two isomers. Citalopram's S-enantiomer, escitalopram, is the most active of citalopram's isomers and metabolites; it is a more potent and a more selective serotonin reuptake inhibitor than citalopram itself (37). These stereochemical differences may be one reason why it has been so difficult to establish therapeutic plasma concentrations for SSRIs, and could explain some interindividual differences in antidepressant response and adverse effects.

Another factor influencing the pharmacokinetics of antidepressants is the activity of membrane transport proteins. P-glycoprotein, a member of the ATP-binding

Table 5 Pharmacology of SSRIs

	Fluoxetine (Prozac®) (Sarafem®)	Fluvoxamine (Luvox®)	Paroxetine (Paxil CR®)	Sertraline (Zoloft®)	Citalopram (Celexa®)	Escitalopram (Lexapro®)
Time to peak plasma level after oral dose (h)	6–8	5	6–10	4.5–8.4	2–4	4–5
Protein binding (%)	94.5	77	93–95	98	50	56
Elimination half-life	Parent 1–3 days acute 4–6 days chronic metabolite 4–16 days (acute or chronic)	15 h	15–20 h	26 h (parent) 62–104 h (metabolite)	33 h	27–532 h (parent) 50–54 (metabolite)
Active metabolite	Norfluoxetine	No	No clinically important metabolites	Desmethyl-sertraline (limited activity)	Desmethyl -citalopram	S-desmethyl citalopram. Not clinically important

Adapted with permission from Ciraulo et al. (401)

Table 6 Inhibition of human cytochromes P450 by selected antidepressants

Cytochrome P450 inhibition							
	1A2	2C9	2C19	2D6	2E1	3A	2B6
Fluoxetine	+	++	+ to ++	+++	–	+	+
Norfluoxetine	+	++	+ to ++	+++	–	++	0
Sertraline	+	+	+ to ++	+	–	+	+
<i>Desmethyl-sertraline</i>	+	+	+ to ++	+	–	+	0
Paroxetine	+	+	+	+++	–	+	+++
Fluvoxamine	+++	++	+++	+	–	+	+
Citalopram	+	0	0	0	0	0	0
<i>Monodesmethyl-citalopram</i>	0	0	0	+	0	0	0
Escitalopram	0	0	0	+	0	0	0
Nefazodone	0	0	0	0	–	+++	0
<i>Triazole-dione</i>	0	0	0	0	–	+	0
<i>Hydroxy nefazodone</i>	0	0	0	0	–	+++	0
Duloxetine	0	0	0	++	0	0	0
Venlafaxine	0	0	0	0/+	–	0	0
Desmethyl-venlafaxine	0	0	0	+	–	0	0
Mirtazapine	0	0	0	0	0	0	0
Bupropion	0	0	0	++	0	0	+

Adapted with permission from Greenblatt et al. (402)
Metabolites are italicized
0 Minimal or zero inhibition; +, ++, +++ mild, moderate, or strong inhibition; Dash (–) indicates no data available

cassette family of membrane transport proteins, is an important functional component of the blood–brain barrier and the intestinal epithelial cells (38). Alterations in P-glycoprotein can thus affect drug entry into the brain as well as bioavailability. Some evidence indicates that paroxetine and venlafaxine may be P-glycoprotein substrates, while animal studies suggest that amitriptyline, fluoxetine, and norfluoxetine are not (39). With respect to inhibition of P-glycoprotein activity, sertraline and paroxetine have the potential to do so, but only at concentrations of 250–500-fold higher than found clinically. One study found citalopram brain concentrations higher in mice without P-glycoprotein activity (40). Nefazodone is an inhibitor of P-glycoprotein activity in clinically relevant doses (41). P-glycoprotein inhibition has been proposed as a possible therapeutic mechanism of antidepressants, not only allowing higher brain AD levels but also resulting in higher corticosteroid levels to counteract the insensitivity of the GR receptor.

Dosages (Table 7)

There is not a consensus on the optimal dosing of SSRIs. One authority has suggested that adequate trials of SSRIs would consist of at least 4-week treatment with sertraline, at least 100 mg daily, fluoxetine or paroxetine or citalopram, at least

Table 7 SSRI doses (33, 34)

SSRI	Dose range (mg/day)	Initial dose (333)	Usual range (333)	Available formulations
Citalopram	10–80	10–20	20–40	Tablets 20, 40 mg; oral solution 10 mg/5 ml
Escitalopram	10–20	10	10	Tablets 10, 20 mg
Fluoxetine	10–80	10–20	20–60	Capsules 10, 20, 40 mg ^a ; tablets 10 mg; oral solution 20 mg/5 ml
Fluvoxamine	50–300	25–50	150–200	Tablets 25, 50, 100 mg
Paroxetine	10–50	10–20	20–40	Tablets 10, 20, 30, 40 mg; oral suspension 10 mg/5 ml
Sertraline	50–200	25–50	100–200	Tablets 25, 50, 100 mg; oral concentrate 20 mg/ml

^aFluoxetine is also available as a “Prozac Weekly.” The formulation is a delayed release, enteric-coated capsule containing 90 mg; it was calculated to achieve a blood concentration equivalent to a standard daily dose of 10–20 mg. The formulation has been shown to be as effective an antidepressant as daily doses of 20 mg fluoxetine, with similar adverse effects and similar tolerability (403–405). Adherence to the dosing schedule for patients on Prozac Weekly is a bit higher than daily dosing: 87.5 and 79–85% patients on daily dosing, respectively, although the difference appears modest (403, 405, 406). Since fluoxetine and norfluoxetine have long elimination half-lives, occasional non-adherence or skipping a dose is rarely clinically significant with the standard formulation. Fluoxetine is also marketed as Sarafem for premenstrual dysphoric disorder. Administered daily or 14 days before menstruation and through first day of menses. Repeat each cycle

20 mg daily, or fluvoxamine, at least 100 mg daily (34). We would recommend higher doses and an 8-week trial although full remission may take 12 weeks or longer in some patients (42). In most patients, some improvement should occur after 2–3 weeks. If the depression severity remains unchanged by 4 weeks, it is unlikely that an additional 2–4 weeks of treatment with the same drug at the same dose will be successful. Unfortunately, plasma levels do not appear helpful in guiding dosage; therapeutic plasma levels have not been established for any SSRI.

Mechanism of Action

Prevailing theories on the mechanism of action of antidepressant agents center around their aminergic effects, despite recent data suggesting other mechanisms may be important (see chapter “Biological Theories of Depression and Implications for Current and New Treatments,” this volume). All SSRIs, although differ structurally, have the same mechanisms of action: as the name implies, these compounds selectively inhibit the serotonin transporter (43). While the degree of selectivity varies depending on the *in vitro* model used, all agents are potent inhibitors of the serotonin reuptake transporter. In addition, paroxetine may have relatively greater inhibitory potential at the norepinephrine transporter, and sertraline at the dopamine transporter, based on *in vitro* studies, and fluoxetine may be a 5-HT_{2C} agonist, although the clinical implications of these differences are not established (44). Further

complicating the matter is the presence of heteroreceptors, serotonin receptors that modulate activity via their location on non-serotonergic neurons, including GABA interneurons, and glutamate, dopamine, noradrenergic, and cholinergic neurons. Thus, there is great danger in assuming that *in vitro* binding studies will provide a reliable guide to clinical differences between SSRIs. As with other antidepressants, the onset of full antidepressant action of SSRI is usually delayed for weeks.

Acute administration of SSRIs inhibit the 5-HT reuptake pump (SERT) of the presynaptic serotonin neuron, resulting in an increased concentration of serotonin around the somatodendritic area of the neuron, and to a lesser degree in the synapse itself (45). Early effects on serotonin probably account for adverse effects, while therapeutic actions depend on subsequent neuronal events. It is only after some time of continuous SSRI administration (usually 2 or more weeks), the lasting high concentrations of 5-HT in the somatodendritic area of the neuron cause desensitization of the somatodendritic 5-HT_{1A} autoreceptors, which are responsible for inhibition of 5-HT release. The result is increased 5-HT in the synapse and desensitization of postsynaptic serotonin receptors. In addition, various SSRIs and other antidepressants have differing activities at serotonin receptor subtypes. The existence of serotonin receptor isoforms is also likely, further complicating our understanding of how these drugs exert their antidepressant effect. Downstream actions that affect signal transduction and gene expression are likely to be responsible for the actual therapeutic action and delayed onset, linking the aminergic changes to other mechanisms such as synthesis of brain-derived neurotrophic factor and other neuronal growth factors. In addition, the HPA axis and the serotonin system are functionally linked; serotonin stimulates CRH release which is mediated by 5-HT₂, 5-HT_{1A}, and 5-HT_{1C} receptors. As a result, the mechanism of action of SSRI may be to normalize activity of glucocorticoid receptors. Decreased function of glucocorticoid and/or mineralocorticoid receptors (GR, MR) has been linked to lower 5-HT_{2A} protein levels in the hippocampus, decreased 5-HT_{2A} receptor binding in frontal areas, and lower serotonergic innervations of frontal cortex in animal models. The role of serotonin receptor subtypes remains unclear, but activity of several subtypes is associated with neurogenesis in the limbic region. For example, agonists of the 5-HT_{1A} heteroreceptor increase neurogenesis in the sublentiform zone (SZ) and the subgranular zone of the dentate gyrus (SGL/DG), agonists of the 5-HT_{2A} are more selective, increasing growth only in the SGL/DG, while agonists of 5-HT_{2C} act on the SZ (46). Another study found that 5-HT_{1A} activation promotes the growth factor VEGF in the hippocampus, and that fluoxetine-induced neurogenesis can be blocked by 5-HT_{1A} antagonists (47).

A novel theory is that SSRIs increase brain levels of the neurosteroid, allopregnanolone, which enhances GABA function in the brain (48). Supporting this mechanism is the fact that depressed patients have low levels of CSF allopregnanolone, which normalize with treatment with fluoxetine and fluvoxamine and correlate with improvement assessed by the HDRS.

Some evidence suggests that a loss of SERT-binding sites occurs with long-term SSRI administration (49). This occurs only after 10–15 days of drug exposure, the

time frame of antidepressant response. Recent theories have extended the mechanism of antidepressant response to signal transduction pathways. Under one such model, antidepressants are believed to decrease the activity of protein kinase C (PKC) which catalyzes phosphorylation, whereby they may directly affect the SERT and/or serotonin receptors. Other studies support a role for activation of protein kinase A and calcium calmodulin-dependent protein kinase II (CaMKII). PKA-mediated phosphorylation results in changes in neurotransmission and gene expression. CaMKII, also through the process of phosphorylation, may facilitate neurotransmitter activity. Phosphorylation of CREB influences gene expression, such as those for BDNF and its receptor *trkB*. Since BDNF is able to promote neurogenesis, it may reverse the neuronal atrophy in the brain, believed by some to be the fundamental pathology of depression.

Although there is not universal consensus on the role of the presynaptic 5-HT_{1A} receptor (the autoreceptor), it is believed that after a week or two of SSRI administration desensitization of this receptor must occur to turn off the feedback inhibition of serotonin release. Attempts to hasten or augment SSRI antidepressant response have been examined in studies with pindolol. Pindolol, a β -adrenergic blocker that also antagonizes the 5-HT_{1A} autoreceptor, has been extensively studied as a possible SSRI augmenting strategy (50–55). It has been hypothesized that pindolol used concomitantly with SSRIs blocks the presynaptic somatodendritic 5-HT_{1A} autoreceptors in the dorsal raphe nucleus more rapidly than an SSRI alone.

Clinical studies are contradictory, complicated by the variability among SSRIs in the potency of 5-HT_{1A} blockade, low doses of pindolol and study design differences. Doses of pindolol that have been used do not produce complete blockade of the receptor (56). In addition, genetic polymorphism of the 5-HT_{1A} receptor (57, 58) and the mixed enantiomer formulations of pindolol complicate interpretation of existing studies (59). In some studies, pindolol augmented the antidepressant effect of concomitantly administered SSRIs and shortened the time necessary for achieving a full therapeutic response (50, 51, 53, 60, 61). These findings have encouraged the study of antagonists of other serotonin receptors such as 5-HT_{2A/C} that inhibit serotonin release. The ultimate goal would be to synthesize a compound that inhibited SERT and 5-HT_{2A/C}.

Attempts that have been made to link actions of SSRI on serotonin receptor subtype are interesting but in the early stages in clinical studies. Of importance is that we know that the antidepressants share some but not all of the actions at these receptor types. This could explain why switches within class of SSRI are often successful, and why there might be significant differences in clinical effects based on the postsynaptic receptor activity.

Receptor subtypes also contribute to adverse effects, e.g., 5-HT₃ to gastrointestinal discomfort, although the role of other subtypes remains uncertain. Generally, *in vitro* studies indicate that SSRIs have very low affinity for other neuroreceptors such as α , histaminic, and muscarinic receptors, which is consistent with their adverse effect profile (30, 43).

Paroxetine is the only SSRI antidepressant which has been shown to inhibit norepinephrine uptake. A study comparing norepinephrine and serotonin transporter function in human transporter transfected cells in serum from patients

assigned to either desipramine or paroxetine (44) found that both drugs acted as mixed serotonin/norepinephrine uptake inhibitors, especially at doses of 40 mg or higher of paroxetine. Sertraline is the only SSRI to show dopamine reuptake inhibition in in vitro models. These data also support the notion that SSRIs are not homogeneous in their mechanisms of action.

Drug Interactions/P450 Metabolism

SSRIs are predominantly metabolized by the hepatic cytochrome P450 system and may inhibit their own metabolism or that of other drugs (Table 6). Among SSRIs, sertraline, citalopram, and escitalopram possess minimal interactions within the P450 system; this quality makes them the antidepressants of choice in medically ill patients requiring coadministration of other medications.

The inhibitory action of SSRIs may give rise to multiple drug–drug interactions with other medications; these interactions when the drugs are coadministered may lead to no effect, intoxication, or even improving a drug’s therapeutic response via a rise in its plasma concentration. Generally, SSRIs that inhibit the CYP 450 systems will impair metabolism of other medications (P450 enzyme substrates), thus prolonging their elimination half-life and increasing their blood level. For example, the SSRI inhibition of cytochrome P450 activity may lead to elevated levels of concurrently administered TCAs which are metabolized by CYP 2D6 and 3A4 isoenzymes (62). This may lead to side effects, but it may also permit clinicians to use a low-dose TCA to augment or potentiate the SSRI. Citalopram does not alter TCA levels (62). On the other hand, fluvoxamine inhibits the CYP 1A2 isoenzyme and can produce toxic levels of medications that are usually metabolized by this isoenzyme, namely tacrine, warfarin, theophylline, propranolol, and many others.

Since SSRIs are also substrates for the hepatic cytochrome system, medications such as carbamazepine, rifampin, dexamethasone, which induce CYP 450 isoenzymes, accelerate SSRI metabolism if coadministered. Medications such as quinidine, cimetidine, and diltiazem inhibit CYP 450; they will delay SSRI clearance and may produce toxic levels of SSRI (34, 63, 64). Comprehensive lists of drug interactions with SSRI antidepressants can be accessed at <http://www.drugfactsand-comparisons.com>, *The Medical Letter: Adverse Drug Interactions Program*, or other computer databases (35, 63–67).

Adverse Effects

Overview

Although generally well tolerated, SSRIs may produce anxiety, sleep disturbances, and gastrointestinal discomfort, especially at the initiation of therapy. These can usually be managed by lowering the dose, slowing dose escalation, or temporarily

treating the target symptom (e.g., ondansetron for nausea, lorazepam for insomnia). More troublesome and persistent are sexual adverse effects, including anorgasmia, decreased libido, ejaculation disturbances, and erectile dysfunction. Transient adverse effects are likely the result of acute stimulation of postsynaptic serotonin receptors; however, efforts to link these symptoms to specific receptor subtypes are speculative. Table 8 lists common adverse effects associated with SSRIs, and options for clinical management.

Table 8 Common adverse effects associated with SSRIs

Symptom	Approximate incidence in clinical practice	Management
Headache	Common initially, especially with fluoxetine	Dosage reduction, slow/stop dose increases, NSAIDs, or change to another antidepressant
Nervousness	Common initially, highest with fluoxetine, sertraline, but can occur with others	Dosage reduction, slow/stop dose increases, lorazepam, or change to another antidepressant
Insomnia	Less common with paroxetine	Dosage reduction, slow/stop dose increases, add lorazepam, “Z” drug hypnotic, or sedative antidepressant, or change to another antidepressant
Drowsiness	More common with paroxetine	Dosage reduction, slow/stop dose increases; some clinicians recommend temporary stimulant (methylphenidate) addition
Nausea	Common for all agents generally at initiation of therapy	Antiemetic agents (5-HT ₃ blockers such as ondansetron are preferred by some clinicians) or mirtazapine
Sexual dysfunction	30–60%, paroxetine slightly higher than others, but difference probably not clinically significant	Dosage reduction, slow/stop dose increases, sildenafil (Viagra), or change to another antidepressant, bupropion
Anorexia	Only early in treatment	Time limited
Dizzy/lightheaded	5–10% fluoxetine at low end	Dosage reduction, slow/stop dose increases, or change to another antidepressant
Tremor	Common early in treatment for all agents	Dosage reduction, slow/stop dose increases, or change to another antidepressant
Diarrhea	More common with sertraline and less common with paroxetine	Dosage reduction, slow/stop dose increases, loperamide, add low dose of an anticholinergic antidepressant, or change to another antidepressant
Constipation	Most common with paroxetine	Dosage reduction, slow/stop dose increases, temporary laxatives/stool softener, or change antidepressant

Gastrointestinal

The most common gastrointestinal adverse effect experienced by patients is nausea, occurring in 15–35% of all patients on SSRIs (68, 69). Some patients may also experience vomiting and/or diarrhea (33). These tend to decrease over time, in most cases after a few weeks of treatment. For some patients, these symptoms may be quite troublesome and interfere with adherence. In these cases, if lowering the dose is unsuccessful, we recommend specific therapy. Ondansetron or other 5-HT₃ blockers (mirtazapine) are very effective for nausea; ranitidine may be helpful for dyspepsia; loperamide may be used to reduce diarrhea. Occasionally, a medication change is required. For example, if diarrhea is problematic, changing the medication to paroxetine may be helpful.

Very rare cases of hepatotoxicity in the form of either cholestatic or hepatocellular injury have been reported with fluoxetine, sertraline, and paroxetine (70–72). The incidence of such cases is quite low; sertraline, for example, has been associated with hepatotoxicity at a rate of 1.28 cases per 100,000 patient-years (72).

CNS

Both tension headaches and migraines have been reported to worsen when SSRIs are started (33), although improvement has also been noted. In some cases, headaches tend to increase in frequency over time (69). Sedation or activation with insomnia is known to occur, especially at the initiation of treatment, although this is somewhat variable depending on the SSRI. Some patients report increased dreaming, vivid dreams, and nightmares. Some authorities believe that fluoxetine has the highest incidence among SSRIs of insomnia, nervousness, restlessness, and anxiety (68). Decreasing the dose and titrating slowly and adding eszopiclone are usually effective management.

Tremors, increased anxiety, anger attacks, and akathisia have been observed with SSRI treatment in a small proportion of patients (73, 74). In general, the incidence of extrapyramidal side effects (EPS) such as Parkinsonism, dystonia, and akathisia is quite low but does occur (73, 75).

SSRIs may induce a switch to mania, with some experts estimating rates as high as 10–20% (34) but most others suggest rates of under 5% (76). Rates of manic switch in bipolar patients on placebo are 4%, and in patients taking TCAs it is estimated at 11% (76). The evidence for inducing mania or hypomania in unipolar depression is mostly anecdotal; the rate of manic switch in these patients is estimated at less than 1% (76). Some believe that antidepressant-induced manic episodes are generally milder and of shorter duration than spontaneous manic episodes experienced by bipolar patients (77).

Behavioral toxicity may also occur with SSRIs. The “apathy syndrome” may occur in patients who have been successfully treated for depression but develop loss of motivation, passivity, and lethargy, often described by patients as “flatness.” This condition can be differentiated from the patient’s depressive state as there is lack of prevailing sadness, tearfulness, decreased concentration, hopelessness/helplessness,

and suicidality. In these patients, decreasing the SSRI dose and/or adding a stimulant is recommended. Bupropion and mirtazapine have also been used in combination with SSRI-induced apathy. It is often necessary to switch to another antidepressant of a different class.

Suicidality

In the early 1990s, reports of treatment emergent suicidal ideation in patients treated with fluoxetine appeared (78). Subsequent studies, however, did not confirm greater risk of de novo suicidal ideation in patients on SSRI treatment. A study of more than 1,000 outpatients in Boston centers failed to find a relationship between increased suicidality and fluoxetine treatment (79). A meta-analysis of 17 double-blind studies comparing fluoxetine, tricyclics, and placebo, evaluating a total of 3,065 patients with major depression failed to detect any increased risk of emergence of suicidal ideation with fluoxetine when compared to either placebo controls or patients treated with tricyclic antidepressants; moreover, the suicidal ideation was found significantly less in patients on fluoxetine than in patients on placebo (80). Another concluded that even though a small percentage of patients experienced increased anxiety, anger attacks, and akathisia during SSRI treatment, there was no evidence of a direct link between SSRI use and violent or suicidal behavior (74). Case reports and litigation have claimed an association between suicidal ideation and paroxetine, especially in children and young adults. The FDA has issued a black box warning for all antidepressants. It states “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.”

Some clinicians remain convinced of an association even if extremely uncommon. According to some, the rare cases of suicidal ideation can be explained by the adverse somatic effects of the SSRI. One possibility is that the activating properties of SSRIs energize some patients to act on pre-existing suicidal plans (81). Also suggested by some is that SSRIs induce akathisia and severe insomnia, which is associated with self-destructive or aggressive impulses (81). Emergence of akathisia-like effects may activate suicidal thoughts or impulses in especially susceptible patients (82).

It has been noted that the association between SSRIs and suicidality, even if it truly exists, may be lost in larger epidemiologic studies (81). Similarly, most clinical trials exclude suicidal patients from participation, thus undermining the generalizability of pooled data analyses (81). In any event, the findings do not alter the usual clinical practice of close monitoring of all depressed patients for emergence of suicidal ideation, especially early in treatment. Frequent visits are necessary for children and young adults, who may have a greater risk than adults.

Serotonin Syndrome

Serotonin syndrome is a potentially fatal condition resulting from excessive serotonergic activity, usually the result of coadministration of similarly acting medications. It can occur when SSRIs are combined with MAOIs (83) or with other drugs that increase CNS serotonergic activity, such as other SSRIs, other antidepressants, especially clomipramine, but also nefazodone, venlafaxine, trazodone, amitriptyline, imipramine, and also other drugs such as tramadol, meperidine, amphetamine, cocaine, and tryptophan (84). Unfortunately, this syndrome often is not recognized in a timely manner due to varied, nonspecific symptoms (84). Diagnostic criteria for serotonin syndrome have been proposed by Sternbach (83). In general, patients with serotonin syndrome will present with cognitive changes such as confusion, disorientation, behavioral changes such as agitation or restlessness, neuromuscular problems of ataxia, hyperreflexia, myoclonus, and/or problems with autonomic nervous function such as fever, shivering, diaphoresis or diarrhea (83). Others have suggested more stringent criteria that require a triad of pyrexia, neuromuscular symptoms, and mental status changes (84), although the most important issue is that clinicians should always be alert for the development of the serotonin syndrome when prescribing SSRI. Fatalities have been associated with the syndrome (33, 83, 84). The therapy for serotonin syndrome is discontinuation of the offending agents and supportive patient care. Dantrolene and bromocriptine have been used with mixed results.

It should be noted that even reversible MAOIs such as moclobemide can produce the serotonin syndrome when given with an SSRI (e.g., citalopram) (85). It may also occur as a result of pharmacokinetic drug–drug interactions. Five suspected cases of serotonin syndrome were reported in HIV-infected patients taking fluoxetine concomitantly with their antiretroviral therapy (protease inhibitors and non-nucleoside reverse transcriptase inhibitors) (86). The symptoms were attributed to the antiretroviral drug inhibition of the P450 enzymes and elevation of SSRI levels, resulting in enhanced serotonergic tone. The patients recovered completely after SSRIs were either stopped or their doses adjusted.

Endocrine System

The endocrine effects of SSRIs are still not fully elucidated. The picture is complicated by neuroendocrine disturbances in depression. It has been postulated that the

hypothalamus–pituitary–adrenal (HPA) axis is activated in depressed patients, possibly in an attempt to normalize neuroendocrine function (87). Plasma ACTH was reduced but cortisol and vasopressin remained at the same levels during treatment of depressed patients with fluoxetine (88). A possible explanation is that SSRIs restore glucocorticoid negative feedback on ACTH levels and return the HPA axis to a normal state (88).

SSRIs, like all antidepressants, can cause the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (34). The risk of developing the syndrome seems to be related to older age, female sex, concomitant use of hyponatremia-inducing medications and increasing the SSRI doses (89). On geriatric psychiatry units, this is a common adverse effect that precipitates hospitalization. SSRIs have also been reported to produce galactorrhea and increase prolactin levels (33).

Weight loss may occur in patients with initiation of fluoxetine treatment (90, 91); but these effects are transient (an exception may be in some elderly patients). Fluoxetine as well as paroxetine and citalopram have actually been known to cause weight gain in patients on long-term treatment (91, 92). The rate of emergence of significant weight gain (defined as 7% increase from baseline patient weight) during long-term treatment has been estimated as 6.8% for fluoxetine and 4.2% for sertraline. Paroxetine may be associated with the greatest weight gain, estimated at 25.5% (92).

Hematologic

There have been some reports of serotonergically mediated platelet dysfunction and abnormal bleeding associated with SSRIs (93). This effect is more likely to occur with high doses of SSRI medications. Fluoxetine, paroxetine, sertraline are the SSRIs most commonly associated with bleeding and abnormal hematological tests (94). Hemostatic markers that may be abnormal in SSRI-treated patients include decreased platelet aggregation and prolongation of bleeding time, although changes in platelet count, PT, and PTT are less common. In addition to the three SSRI mentioned above, other antidepressants, such as fluvoxamine, venlafaxine, mirtazapine and the tricyclic agents, amitriptyline, and imipramine may affect hemostasis. There is substantial evidence that abnormal bleeding is causally related to antidepressant treatment, and that potent serotonergic reuptake inhibition is the mechanism involved. Gastrointestinal bleeds occur at twice the rate in SSRI-treated patients compared to patients taking other antidepressants. Blood transfusions during surgery were more common in patients taking SSRI than other antidepressants. The prescription of drugs that are associated with increased bleeding, such as NSAIDs or aspirin, should be avoided whenever possible (34).

Sexual

Among the sexual side effects most commonly associated with SSRIs are decreased or absent libido, difficulties with sexual arousal, erectile dysfunction, delayed

ejaculation, painful orgasm, and anorgasmia (95–99). These effects of SSRIs appear to be dose related (100). Most experts agree that SSRIs cause significantly more sexual dysfunction than either TCAs or MAOIs (96). Studies differ as to the incidence of these findings. For example, the percentage of patients developing anorgasmia is reported to be from 8.3 (101) to 75% (102) with fluoxetine. A review article concluded that 30–40% of patients on an SSRI will experience some degree of sexual dysfunction (103). A well-designed multicenter prospective study of 344 patients of both genders found that the frequency of adverse sexual effects was highest on paroxetine (65%), followed by fluvoxamine (59%), sertraline (56%), and fluoxetine (54%) (100). None of the patients in this study had sexual problems prior to initiation of SSRI antidepressant therapy; none had a medical illness or additional psychiatric disorders. The study used systematic inquiry of sexual dysfunction, performed by a physician, but was somewhat limited by lack of randomization of treatment and concurrent medications.

The frequency of SSRI-induced sexual dysfunction is still unknown; however, it is significantly higher than previously reported in pre-marketing studies and in product labeling of the SSRI (97, 98). A possible explanation for this underestimation of the incidence may be due to a lack of a structured assessment of sexual dysfunction (98) as well as to underreporting by patients (96).

SSRI-induced sexual dysfunction is a serious problem that often leads to drug discontinuation if not properly managed. There are several approaches to management: including dose reduction, waiting for tolerance to develop, switching to a different antidepressant, drug holiday, or addition of other medications (99). Medications that have been studied include α_2 -adrenergic antagonist yohimbine, nefazodone, serotonin antagonist cyproheptadine, granisetron, mirtazapine, amantadine and pramipexole, methylphenidate, bupropion, the herb ginkgo biloba, and sildenafil and related phosphodiesterase Type 5 inhibitors (96, 98, 99).

Sildenafil citrate has been an effective agent to treat SSRI-induced sexual dysfunction. A small open study of sildenafil showed improved erectile dysfunction in patients with antidepressant-induced sexual side effects (104). Another open-label trial of 10 female patients, who had developed sexual dysfunction as a result of ongoing antidepressant treatment, reported that all patients who took sildenafil as instructed experienced a “complete or very significant reversal” of their sexual dysfunction (105). And finally, a review of sildenafil’s efficacy in erectile dysfunction analyzed the results of 3 randomized, placebo-controlled trials and data from 10 earlier clinical trials (106). The authors concluded that sildenafil is an effective first-line treatment for either SSRI-induced or depression-related erectile dysfunction.

Another strategy is the addition or switch to bupropion (107). Some also recommend weekend drug holidays of 3-day duration (Thursday noon to Sunday noon), which was shown to improve sexual functioning in 30 outpatients who were maintained on an SSRI after recovering from a depressive episode and who had SSRI-induced sexual dysfunction (108). None of the patients experienced return of depressive symptoms, nor were there any significant increases in mean HAM-D

scores after SSRI holidays. Patients who were taking sertraline and paroxetine reported improvement; patients taking fluoxetine reported no change, which may relate to the long half-life of this drug and its metabolite (108). We recommend periodic use of sildenafil (Viagra®) 50–100 mg, vardenafil (Levitra®) 2.5–20 mg, or tadalafil (Cialis®) 5–20 mg, as needed to treat SSRI-induced sexual dysfunction.

SSRI Discontinuation/Withdrawal Syndrome

Serotonin withdrawal syndrome, also known as SSRI discontinuation syndrome, can develop when an SSRI drug is stopped abruptly after a long-term use. The symptoms are “flu-like”; patients describe nausea, diarrhea, general malaise, myalgias and paresthesias, dizziness, vertigo, headache, and insomnia (109, 110). Vivid dreams, anxiety, and irritability may also be present (33). The criteria proposed for the diagnosis of SSRI discontinuation syndrome require two or more of the following symptoms developing within 1–7 days of discontinuation or reduction in dosage of an SSRI after at least 1-month use and not accounted for by medical illness: dizziness, lightheadedness, vertigo, paresthesia, anxiety, diarrhea, fatigue, gait instability, headache, insomnia, irritability, nausea or emesis, tremors, and visual disturbances (110).

The syndrome was first noted with paroxetine (111); however, all antidepressants can lead to a discontinuation syndrome if they are not gradually tapered. Fluoxetine, with its active metabolite’s long half-life, was at first thought to be free of this effect due to presumed self-tapering of serum levels; however, the syndrome still may appear after long-term fluoxetine treatment. It had been reported that the withdrawal symptoms occur an average of 6.4 days after fluoxetine discontinuation as compared with 2–4 days after fluvoxamine, sertraline, or paroxetine discontinuation (30). In our experience, it is still much less common and not as severe with fluoxetine as with other SSRIs, such as paroxetine. The treatment for the SSRI discontinuation syndrome is drug reinstitution and then gradual tapering of the offending antidepressant (109), or a substitution of fluoxetine for shorter acting SSRI, followed by the taper of fluoxetine.

Safety

Safety in Overdose

SSRIs are perhaps the safest antidepressants on the market with respect to overdose risks, having a very high therapeutic index (32, 69). A study of SSRI overdoses analyzed published cases, data from the American Association of Poison Control Centers, and reports to the U.S. Food and Drug Administration adverse event database (112). This analysis concluded that SSRI antidepressants were far safer than the TCAs in overdose. There was also no difference among SSRIs with

respect to morbidity or mortality. In general, mild to moderate overdoses of up to 30 times the usual daily dose were asymptomatic or associated with mild symptoms, and patients recovered fully without sequelae. Larger overdoses, of up to 75 times the prescribed daily dose, were associated with drowsiness, tremor, nausea, and vomiting. More serious consequences were associated with the largest overdoses and included seizures and ECG changes. There have been fatalities with overdoses of more than 150 times the usual daily dose. Almost all fatalities occurred in patients who took SSRIs and other substances, usually alcohol, benzodiazepines, or other drugs (112).

Reporting of overdoses is sporadic, making it impossible to accurately calculate the true incidence of morbidity and mortality. There are more data available on fluoxetine and citalopram because they have been in clinical use for a longer time. Some evidence has suggested higher overdose toxicity of citalopram compared to other SSRIs. Six fatalities from a citalopram overdose have been reported (113). However, as was pointed out by Glassman (114), 5 of the reported deaths involved citalopram taken with either alcohol or sedative drugs and the amounts of drugs ingested were quite high. In the only reported case of overdose with citalopram taken alone, the patient had taken 4,000 mg of the drug, which at the usual daily dose of 20 mg, is a 6-month supply. On the other hand, the didesmethyl metabolite of citalopram, which has demonstrated cardiotoxicity in animals, may reach high enough levels in overdose to cause morbidity.

Safety in Pregnancy and Lactation (See Also Chapter “Diagnosis and Treatment of Depression During Pregnancy and Lactation”)

The treatment of depression during pregnancy and the postpartum period are discussed in detail in Chapter “Diagnosis and Treatment of Depression During Pregnancy and Lactation.” Briefly, untreated major depression during pregnancy poses a risk to both mother and fetus. Both psychosocial and pharmacologic treatments have been used to treat pregnant women. When psychotherapeutic interventions are unsuccessful, clinicians and patients are faced with difficult decision regarding the safety of antidepressant therapy. Even the most competent clinician can be overwhelmed by the conflicting safety data generated by many studies. The first practical point is that there are not sufficient data to ensure the safety of any antidepressant. For adverse effects that are as rare as teratogenicity, very large sample sizes are required to avoid a Type II error (not finding an effect that would be evident with larger samples). There are no studies large enough to differentiate the risk of specific antidepressants on the fetus. Paroxetine has been associated with cardiac malformations and resulted in a change in product labeling and an FDA advisory, although other studies have not replicated the finding. A prospective multicenter controlled cohort study to assess risk of SSRI teratogenicity studied infants of 267 women exposed to SSRIs (fluvoxamine, paroxetine, and sertraline) during pregnancy and the infants of 267 controls (115). Investigators did not find increased risk for major malformations or higher rates of miscarriage, stillbirth, or prematurity in

infants born to mothers treated with SSRIs during pregnancies. There were no detectable differences in infant birth weights or gestational ages at delivery among the groups, although the sample size was probably too small. An additional three studies were larger (116–118) and did not find cardiac abnormalities with paroxetine exposure. In the large studies, the malformations included ventricular and atrial septal defects, with one study reporting a 4% risk with paroxetine compared to a 2% risk with other antidepressants. The risks from other SSRIs are not known, but there is some evidence to suggest that the risk of teratogenicity for tricyclic antidepressants and bupropion appears lower than SSRI, with the exception of clomipramine.

The risk of spontaneous abortion may be increased with antidepressant use during pregnancy, although the rate in the general population is high and studies do not always support increased risk with antidepressant treatment. Studies have also found an increased rate of preterm birth in women who took SSRIs during pregnancy, although this finding is complicated by the failure to control for depression severity. One study found a six fold increase in persistent pulmonary hypertension in newborns of women who took SSRIs during the second half of the pregnancy (119), although the finding has not been consistently replicated.

Most studies have not found developmental delays in infants whose mothers took antidepressants during pregnancy although one study (118) found gross motor delays and delays in attention in children whose mothers had taken SSRIs in the second or third trimester compared to a control group of women who were depressed during pregnancy and not taking antidepressants. Scores remained within the normal range for the exposed group, and the clinical significance of these findings was uncertain. A withdrawal syndrome is sometimes seen in neonates whose mothers took antidepressants up to the time of delivery. Symptoms include jitteriness, poor muscle tone, weak or absent cry, respiratory distress, hypoglycemia, seizures, and low Apgar scores. It is possible to avoid this by a slow taper prior to delivery; however, the clinician should be cautious about recurrence of depression in the mother.

In summary, the clinician is faced with making decisions about antidepressant therapy in pregnancy without a consistent database to inform the discussion with the patient. Our approach is to discuss the rates of pregnancy complications with the patient and present the potential increased risk of antidepressant therapy based on our best evaluation of the data. If the rate of a specific anomaly in the general population is 2%, and the risk of a specific drug-induced anomaly is doubled, we present the information as percentages – 2 chances out of 100 compared to 4 out of 100. Even this approach overstates the chances, because it does not account for the severity of depression and associated hyperactivity of the HPA axis and other physiologic changes associated with depression alone that may contribute to adverse fetal effects.

Efficacy

As a class, SSRIs have been proven effective in a wide range of psychiatric disorders; mood disorders including dysthymia (120), obsessive-compulsive disorder (OCD)

(121, 122), panic disorder (123), social phobia (124–126), eating disorders (127), premenstrual dysphoric disorder (128), and GAD (129).

In his review article of available pharmacological treatments for PTSD, Davidson cites evidence from large long-term clinical trials of SSRI antidepressants' efficacy in patients with this disorder (130). In chronic PTSD, we have found that the combination of SSRIs and atypical antipsychotics produces the best effects (see also Chapter "Antidepressants in the Treatment of PTSD").

SSRI may be the preferred class of antidepressants in depression associated with medical illness. Fluoxetine proved significantly better than placebo in the treatment of depression in patients with HIV and AIDS, diabetes mellitus, or strokes (131). The long half-life of fluoxetine and norfluoxetine, as well as their potential for interactions with other medications via P450 isoenzymes are potential limitations for use in medically ill patients. Sertraline and escitalopram would appear to be better choices in the medically ill, due to a lower likelihood of pharmacokinetic interactions (132) (see Chapter "Treatment of Depression in the Medically Ill").

SSRIs are being studied as possible treatment for alcohol-induced depression and appear most effective when used in combination with naltrexone (see also Chapter "Substance Abuse and Depression") (133, 134). At present, there are no widely accepted typologies that predict SSRI response in alcohol-dependent subjects.

Equivalent efficacy between SSRIs and TCAs is a matter of some debate. A meta-analysis of approximately 300 double-blind randomized controlled clinical trials found that most antidepressants have similar efficacy, and that MAOIs, SSRIs, and TCAs all have response rate of 60–68%, as defined by 50% improvement in the HAM-D or the Montgomery Asberg Depression Rating Scale (MADRS) (135). This concurs with another study where SSRIs were deemed not more efficacious or faster acting than TCAs in MDD (68). In another study, fluoxetine appeared to be no better than imipramine for treatment of atypical depression (136). These results held true in many reviews of specific SSRIs and in other studies (69, 137). One study found that sertraline but not other SSRIs were as efficacious as TCAs in patients with melancholic depression (138), although this remains a controversial issue. A 1-year, double-blind study of suicidal behavior in patients with repeated suicide attempts found that paroxetine significantly reduced suicidal behavior (139), although the issue of suicidality remains controversial. Others have questioned the equivalency of SSRIs and TCAs (see TCA section).

SSRIs may lose their efficacy during maintenance treatment. A recent study found return of depressive symptoms in 9–57% of the patients during maintenance treatment; most of these patients were treated with an SSRI (140). Another double-blind study reported relapse in depression in 26 out of 77 patients on a maintenance dose of 20 mg daily of fluoxetine (141). In these cases, increasing the dose, switching to a different class of antidepressant, or adding an augmenting agent is recommended.

To summarize, the SSRI antidepressants remain the first-line treatment for major depression, dysthymia, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, social phobia, PTSD, and bulimia. They have a favorable side effect profile as compared to older antidepressants, better patient tolerability, ease

of administration, and well-proven safety in overdose. The drug interactions of some SSRIs may be significant and it is prudent to use the SSRI with least potential for drug–drug interactions (citalopram, escitalopram, sertraline) when treating patients with other medical or other psychiatric comorbidities. Information on interactions mediated by induction or inhibition of transporters, such as P-glycoprotein, is incomplete, but should be considered as potential confounders of clinical effects and toxicity.

Cyclic Antidepressants

History

Imipramine was the first tricyclic antidepressant (TCA) used in clinical practice. After unsuccessful trials as a potential antihistamine and antipsychotic (31), in 1957, Roland Kuhn in Switzerland reported its efficacy in the treatment of depression (142). Some years later, Klerman and Cole demonstrated superiority of imipramine to placebo in depressed patients by analyzing pooled data from 23 published studies; 65% of patients from those studies improved clinically on imipramine compared to only 31% improvement among placebo patients (143). For three decades, TCAs were the first-line agents for the treatment of depression.

Desipramine is the demethylated metabolite of imipramine, and like its parent drug, it has antidepressant action. Amitriptyline was also introduced in the 1960s, and later its secondary amine metabolite, nortriptyline, was marketed. The TCAs offer advantages over monoamine oxidase inhibitor (MAOI) antidepressants, having less risk of drug–drug interactions and requiring no food restrictions, but they have troublesome adverse effects in many patients. They also have a low therapeutic index, which can present problems in patients with suicidal risk. Heterocyclic and other types of antidepressants were introduced to the market over the past 20 years, but none have demonstrated superior efficacy to the TCAs.

Currently, the following tricyclic and heterocyclic compounds are FDA approved for treatment of depression in the United States: *amitriptyline* (Elavil, Vanatrip), *amoxapine* (Asendin), *clomipramine* (Anafranil), *desipramine* (Norpramin), *doxepin* (Sinequan, Zonalon), *imipramine* (Tofranil), *maprotiline* (Ludiomil), *nortriptyline* (Aventyl, Pamelor), *protriptyline* (Vivactil), and *trimipramine* (Surmontil). Among these, amoxapine and maprotiline are less commonly used.

Pharmacology

The basic tricyclic structure is similar to that of chlorpromazine and related phenothiazines, which have a 6-member central ring joining two benzene rings, resulting in a planar molecule. Most classifications of TCAs distinguish between tertiary and secondary amines. The tertiary amine tricyclics, such as imipramine and

amitriptyline, are made up of two benzene rings linked by a central imino ring. The 7-member central ring distorts the molecule and it becomes non-planar. Imipramine and amitriptyline are tertiary amines as three carbon substituents are located on the terminal nitrogen of their side chains. Desipramine is a demethylated metabolite of imipramine and thus a secondary amine; it has two carbons on the terminal nitrogen of the side chain. Similarly, nortriptyline is the demethylated metabolite of amitriptyline.

Doxepin, trimipramine, and protriptyline all have the three-ring structure of imipramine with some minor differences. Drugs in this family that were developed subsequently had a different molecular structure (tetracyclic, heterocyclic, or even structurally unrelated compounds). Amoxapine, a drug introduced in 1980, for example, has the three-ring structure of imipramine but has a fourth ring as a side structure. Maprotiline is a tetracyclic compound, with the central portion consisting of four rings. However, both amoxapine and maprotiline are often classified as TCA-like, because they share the same action, efficacy, and side effect profile (144). Thus, the term “TCA,” which is still commonly used in clinical practice and literature to denote all drugs in this family, is inaccurate, and terms such as “cyclic,” “atypical,” and “mixed action” are sometimes used. Other classification schemes use terms such as “nonselective serotonin and norepinephrine reuptake inhibitors (NSNRI)” and “selective norepinephrine reuptake inhibitors (SNRI)” to maintain consistency with the SSRI terminology. None of these approaches is entirely satisfactory or precise. As we approach the era of triple reuptake inhibitors and drugs that promote reuptake inhibition and also mixed receptor agonist/antagonist properties, we expect that the current nomenclature will be radically revised.

Pharmacokinetics

TCAs are highly lipophilic, well absorbed from the gastrointestinal tract with large volumes of distribution, and relatively long half-lives (145). TCAs are bound to α_1 -acid glycoprotein and albumin. Since they are highly protein bound, they are subject to drug interactions that are caused by displacement from protein binding sites and factors such as medical illnesses, which alter the amounts or activity of binding proteins may change the free fraction of active drug that enters the brain, at least transiently. Metabolism of TCAs occurs in the liver via demethylation and/or hydroxylation, followed by glucuronide conjugation (145). Metabolism may also occur within the brain. There is wide interindividual variation in the hepatic metabolism of TCAs. The presence of active metabolites complicates the interpretation of the therapeutic and adverse effects of these agents. Metabolites differ from the parent compound in their pharmacokinetic characteristics and effects on different neurotransmitter systems. Among tertiary amines, imipramine is demethylated to desipramine and hydroxylated to 2-hydroxyimipramine and 2-hydroxydesipramine. Imipramine is 86–93% protein bound and has an elimination half-life of 15–30 h. The metabolism of amitriptyline is complex, since its hydroxy metabolites, and those of its demethylated metabolite nortriptyline, exist as isomers. Amitriptyline is 95% protein bound with an elimination half-life of 9–25 h. Desipramine is

85–90% protein bound with an elimination half-life of 12–36 h. Nortriptyline is 92% protein bound with an elimination half-life of 18–33 h. During treatment with either amitriptyline or nortriptyline, the *E*-10-OH-nortriptyline reaches greater plasma and cerebrospinal fluid concentrations than the parent drug (145). In contrast, 2-OH-desipramine plasma levels are less than half that of the parent drug during desipramine administration (146). Hydroxy metabolites pass the blood–brain barrier and contribute to pharmacodynamic effects. Clinical doses of non-SSRIs and their cytochrome substrates are shown in Tables 9 and 10.

The pharmacokinetic properties of TCAs have several clinical implications: (1) Within the usual therapeutic range, increases in dose will produce proportional increases in plasma levels; (2) correlation between clinical outcome and plasma levels has been difficult to establish, in part due to a failure of some studies to consider metabolites, free concentration of drug, activity of transporter proteins, such as P-glycoprotein, and failure to assay for isomers; however, many clinicians believe that nortriptyline response is optimal in a therapeutic window of plasma levels between 50 and 150 ng/ml, while other TCAs such as desipramine require a minimal plasma concentration, exhibiting the classical sigmoidal response curve; (3) first-pass metabolism by the liver is genetically determined and is the major factor leading to large interindividual variability in plasma levels; (4) metabolites contribute to the therapeutic and toxic effects and may reach higher levels than the parent compound; (5) renal clearance is an important route of elimination for hydroxylated metabolites, and factors such as age and disease may impair excretion; (6) impaired elimination in the young and elderly is believed to be related to renal function; (7) gender differences in metabolism have not been consistently found; however, increased metabolism and plasma volume during pregnancy may require dosage adjustments.

Cyclic antidepressants are subject to pharmacokinetic drug–drug interactions as a consequence of metabolism via the hepatic cytochrome P450 system. Pharmacokinetic drug–drug interactions of TCAs can be anticipated with knowledge of the cytochromes that are involved in metabolism and familiarity with drugs that induce or inhibit these enzymes. The most commonly encountered clinical situations involve combined therapy of antidepressants with inhibitors or inducers of the cytochromes involved in antidepressant metabolism. It is also possible to encounter an interaction with other drugs that are substrates for the same cytochromes if the latter have higher affinity for binding sites. An example of this is the ability of some TCAs to compete for CYP2C19 and alter phenytoin metabolism. The discussion that follows focuses on the most common pharmacokinetic interactions of the TCA. It is meant to outline some of the principles of these interactions, not serve as an exhaustive list of all interactions.

Whereas *N*-demethylation of TCAs is catalyzed by CYP1A2, CYP2C19, and CYP3A4, the contribution of active hydroxy metabolites makes the hydroxylation step, mediated by CYP2D6, extremely important. Approximately 7–10% of Caucasians are poor CYP2D6 metabolizers (147), whereas less than 1% of Asians are PM. Several antipsychotics, SSRI antidepressants (see SSRI section), and moclobemide (an MAOI marketed outside of the United States) are the most common psychotropic agents to impair CYP2D6-mediated metabolism. Some other drugs that impair CYP2D6 are cimetidine, ranitidine, methadone, metoprolol, and

Table 9 Adult doses and formulations of antidepressants

Tertiary amines	Usual starting dose ^a	Maximal dose ^a	Formulation	Available dosages
Amitriptyline	25 mg t.i.d.	300 mg q.d.	Suspension, tablet	Suspensions: 10 mg/ml Tablets: 10, 25, 50, 75, 100, 150 mg
Imipramine	25 mg t.i.d.	300 mg q.d.	Tablet, capsule	Tablets: 10, 25, 50 mg Capsule: 75, 100, 125, 150 mg
Clomipramine	25 mg q.d.	250 mg q.d.	Capsule	25, 50, 75 mg
Trimipramine	75 mg q.d.	300 mg q.d.	Capsule	25, 50, 100 mg
Secondary amines				
Nortriptyline	25 mg q.d.	150 mg q.d. (monitor plasma levels)	Capsule, solution	Capsule: 10, 25, 50, 75 mg Solution: 2 mg/ml
Desipramine	25 mg b.i.d.	250–300 mg q.d.	Tablet	10, 25, 50, 75, 100, 150 mg
Protriptyline	15 mg q.d.	60 mg q.d.	Tablet	5, 10 mg
Amoxapine	50 mg b.i.d. or t.i.d.	120–300 mg q.d.	Tablet	25, 50, 100, 150 mg
Aminoketones				
Bupropion	100 mg b.i.d. (IR) 150 mg q.d. (SR)	150 mg t.i.d. (IR) 200 mg b.i.d. (SR)	Tablet, SR tablet	Tablet: 75, 100 mg SR Tablet: 100, 150 mg
Tetracyclics				
Mirtazapine	15 mg q.h.s.	45 mg q.d.	Tablets, dissolving tablets	15, 30, 45 mg
Maprotiline	75 mg q.d.	225 mg q.d.	Tablet	25, 50, 75 mg
Phenylethamine				
Venlafaxine XR	75 mg b.i.d.	375 mg q.d.	Tablet, SR capsule	Tablet: 25, 37.5, 50, 75, 100 mg SR Capsule: 37.5, 75, 150 mg
Desvenlafaxine	50 mg q.d.	+	XR tablet	50, 100 mg
Triazolopyridine				
Trazodone	50 mg t.i.d.	400–600 mg	Tablet	50, 100, 150, 300 mg
Phenylpiperazine				
Nefazodone	100 mg b.i.d.	600 mg q.d.	Tablet	50, 100, 150, 200, 250 mg
Thiophenpropylamine				
Duloxetine	40–60 mg	120 mg	Delayed release tablets	20, 30, 60 mg

Used in clinical trials

+ No additional benefit noted at doses higher than 50 mg daily, although doses up to 400 mg daily

^aLower doses should be used in the elderly

Table 10 Selected non-SSRI antidepressant metabolites

Tertiary amines	Metabolites	Cytochrome substrates
Amitriptyline	Nortriptyline 10-OH nortriptyline (cis, trans, +, -), 10-OH amitriptyline (cis, trans, +, -)	1A2, 2C19, 2C9, 2D6, 3A4
Imipramine	Desipramine 2-OH desipramine 2-OH imipramine	2C19, 2C9, 1A2, 3A4, 2D6
Clomipramine	Desmethylclomipramine 8-OH clomipramine 8-OH desmethylclomipramine	3A4, 2D6 (also inhibits 2D6), 2C19
Trimipramine	Desmethyltrimipramine Didesmethyltrimipramine 2-OH trimipramine 2-OH desmethyltrimipramine	2C19, 1A2, 3A4, 2D6
Doxepin	Desmethyldoxepin	2C19, 3A4, 1A2, 2C9
Secondary amines		
Nortriptyline	10-OH nortriptyline (cis, trans, +, -)	2D6
Desipramine	2-OH desipramine	2D6
Protriptyline	2-OH protriptyline desmethylprotriptyline <i>N</i> -acetylprotriptyline	?2D6
Aminoketones		
Bupropion	Hydroxybupropion Threohydrobupropion Erythrohydrobupropion	2B6 (also inhibits 2B6), 2D6 (also inhibits 2D6)
Tetracyclics		
Mirtazapine	Desmethylmirtazapine (8-OH mirtazapine) (mirtazapine <i>N</i> -oxide)	3A, 2D6, 1A2
Maprotiline	Desmethylmaprotiline	2D6, 1A2
Phenylethylamine		
Venlafaxine	<i>O</i> -desmethylvenlafaxine	2D6
Desvenlafaxine	None clinically significant	Conjugation (UGP), 3A4 minor
Triazolopyridine		
Trazodone	<i>m</i> -CPP	3A4
Phenylpiperazine		
Nefazodone	Hydroxynefazodone Meta-chlorophenylpiperazine (<i>m</i> -CPP) Triazole-dione	3A4 (also inhibits 3A4), 2D6
Thiophenepropylamine		
Duloxetine	4-hydroxy duloxetine glucuronide , 5-hydroxy, 6-methoxy, duloxetine sulfate (do not contribute to clinical actions)	CYP1A2, CYP2D6 Conjugation (UGP)

amiodarone, celecoxib, and ritonavir. Ritonavir and other antivirals (indinavir, nelfinavir, saquinavir, delaviridine), antifungals (ketoconazole, itraconazole), macrolide antibiotics (erythromycin, clarithromycin), ciprofloxacin, and the calcium channel blocker diltiazem inhibit CYP3A4. Fluoroquinolones inhibit CYP1A2. Enzyme inducers, such as modafinil (1A2), barbiturates (3A, 2B6, 2C9), rifampin

(2D6, 3A, 2C19, 2B6), carbamazepine (2C19, 3A), tamoxifen (3A), and chronic ethanol may all lower plasma levels of cyclic antidepressants. Some foods, such as grapefruit juice, may also reduce CYP3A4 and CYP1A2 activity.

Mechanism of Action

The antidepressant action of TCAs is thought to be due to their inhibition of norepinephrine (NE) and serotonin (5-HT) reuptake, thus leading to increased concentrations of these monoamines in the synaptic cleft. Down-regulation of postsynaptic receptors and subsequent changes in gene expression (see SSRI section and Chapter “Biological Theories of Depression and Implications for Current and New Treatments”) are ultimately responsible for the antidepressant action. TCAs inhibit NE and 5-HT in different proportions. In general, secondary amines such as desipramine and nortriptyline are much more selective and preferentially block NE reuptake. Thus, desipramine, nortriptyline, and also protriptyline, are primarily NE reuptake inhibitors, with only some 5-HT reuptake inhibition. Conversely, clomipramine inhibits 5-HT reuptake much more than it does NE reuptake. Imipramine, amitriptyline, doxepin, and trimipramine inhibit NE and 5-HT reuptake equally, although one must also take into consideration the effect of their metabolites, which together with the parent compound produce a mixed noradrenergic–serotonergic effect. Nortriptyline, amitriptyline, and clomipramine are also antagonists at the 5-HT_{2A} receptor, although the clinical significance of this effect is not known.

Adverse effects of TCAs are due to their actions as agonists at α_1 -adrenergic (orthostatic hypotension), H₁-histaminic (sedation, weight gain), and anticholinergic receptors (dry mouth, urinary retention, constipation, blurred vision, memory problems). All of the TCAs have clinically significant anticholinergic effects, although the two with the least among them are desipramine and nortriptyline. Nortriptyline has the lowest α_1 -adrenergic antagonism, with desipramine having somewhat more, but still less than the tertiary amines. Amitriptyline, doxepin, and trimipramine have the strongest histaminergic (H₁) antagonism among the group.

Adverse Effects

TCAs have strong anticholinergic (antimuscarinic) activity, which may cause constipation, dry mouth, urinary hesitancy/retention, blurred vision, dyspepsia, and confusion (32, 148). In elderly patients, more severe side effects, such as tachycardia, confusion, agitation, or even delirium may occur at therapeutic doses (149). Although rare, these severe complications may occur when a patient has been taking another anticholinergic drug concomitantly with a TCA; neuroleptics, anti-Parkinsonian agents, antihistamines, antispasmodics and over the counter sleeping pills are commonly involved.

Initial management of mild to moderate symptoms should include decreasing the TCA dose or slowing dosage escalation. In patients who still have troublesome

symptoms, oral bethanechol 25–50 mg 3 or 4 times per day may relieve peripheral cholinergic symptoms. Central nervous system symptoms may be reversed by intravenous physostigmine; however, this should be done by an experienced clinician, because it can be associated with tremors, vomiting, and seizures if given too rapidly or at too high a dose. Some clinicians recommend 4% pilocarpine eye drops for blurred vision and a 1% solution for dry mouth; however, we have found bethanechol as effective and more convenient for patients. If a patient cannot tolerate the anticholinergic effects, switching classes is the best approach.

Cardiovascular: Orthostatic Hypotension

Direct peripheral α -adrenergic receptor blockade causes orthostatic hypotension, dizziness, and drowsiness (150, 151). This effect does not directly correlate with the patient's age or dose of TCA, although the consequence can be disastrous in the elderly or cardiac impaired patient. Following the onset of orthostatic hypotension, further dosage increases do not produce greater declines in blood pressure (150). In many patients, the severity of orthostatic hypotension will prohibit TCA use; up to 10% of otherwise medically healthy patients and up to 25–50% of patients with pre-existing cardiac disease will require alteration of dose or discontinuation of the medication (152). Orthostatic hypotension is of special concern in the elderly, in whom falls may result in physical injuries such as fractures or significant lacerations. Injuries resulting from falls may occur at a rate of up to 4% of patients treated with imipramine (150). Nortriptyline may offer some advantages over other TCAs. Lack of postural effect was reported in a study of 32 patients, two-thirds of whom were taking nortriptyline (153). Nortriptyline was found to be significantly less likely to cause orthostatic hypotension than imipramine, desipramine, clomipramine, or amitriptyline. This property makes it the TCA of choice in the elderly population (153, 154).

Cardiovascular: Conduction Effects

One of the most serious adverse effects of TCAs is a consequence of their effects on cardiac conduction. ECG changes are well known and consist of T wave flattening, lengthening of the P-R interval, and the QRS complex (153). TCAs slow cardiac atrio-ventricular conduction, lengthen the QT interval, and are associated with arrhythmias, especially in overdose and in patients with pre-existing cardiac disease (155). TCAs are class 1A antiarrhythmics (similar to quinidine), which exert their clinical effect by slowing conduction through the His–Purkinje system and myocardium (155). This class of antiarrhythmics can actually produce arrhythmias after myocardial infarction. Cardiac mortality associated with TCA use is a matter of some controversy. Studies prior to the introduction of antidepressants indicated that there was higher mortality in severely depressed patients compared to the general population, with cardiovascular mortality 8 times more likely (156). Witchel and

associates (155) have proposed that TCA-induced prolongation of the QT_c interval (greater than 440 ms) may be responsible for proarrhythmic effects and sudden death. Drawing comparisons to genetic forms of long QT syndrome (LQTS), these investigators suggest that TCAs may induce QT prolongation by direct effects on ion channels within the myocardium fibers. Identification of genes encoding for these ion channels and defective functioning of these channels in LQTS led to the hypothesis that TCAs (and other drugs) may produce altered function, especially in individuals who have “silent mutations.” These authors also stress that the multiple additional effects of TCAs such as monoamine reuptake inhibition, anticholinergic activity, antihistamine effects, as well as blockade of Ca and K channels influence the risk of prolonged QT_c (155). In cases of TCA overdose, the TCA-induced QT interval prolongation has been linked to *torsades de pointes* (TdP), complete heart block, and sudden cardiac death. The risk of arrhythmia is especially high in patients with pre-existing cardiovascular disease or conduction abnormalities, those on high doses of TCA medications, and in overdose (see discussion below) (152).

Although cardiac toxicity in overdose was well known during early clinical use of TCAs (157), prevailing clinical opinion has been that there were a few cardiovascular side effects from TCA treatment if patients did not have pre-existing cardiovascular pathology (150). As noted above, in some cases, the TCAs proved to have antiarrhythmic properties, suppressing ectopic pacemakers and suppressing premature ventricular contractions (158). On the other hand, it was also recognized that these drugs should not be used in patients with a known cardiac illness, such as pre-existing conduction delays second-degree heart block, bifascicular heart block, sick sinus syndrome heart failure, or bundle branch disease (159). The risks of TCA-induced impairment of left ventricular function remain unresolved (160).

The Cardiac Arrhythmia Suppression Trial (CAST) evaluated the effect of antiarrhythmic therapy in patients with either mildly symptomatic or asymptomatic ventricular arrhythmias after myocardial infarction. The CAST study was stopped prematurely when a significantly higher death rate in the groups treated with either encainide or flecainide (and eventually moricizine) versus placebo group was found (161, 162). The results indicated that both class 1C and 1A antiarrhythmics, the latter of which includes TCAs, had a proarrhythmic effect post-MI. When cardiac tissue becomes anoxic or ischemic, the class 1 antiarrhythmics become pro-arrhythmic (151). Thus, SSRI are the preferred antidepressants for these patients. Most cyclic antidepressants are associated with arrhythmia risk, including amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, and nortriptyline. Doxepin, once thought to be safer in patients with cardiac disease, has cardiac risk comparable to other drugs of this class (163).

Sexual Dysfunction

Sexual dysfunction has not been well studied in TCAs, but it is generally believed that they are associated with decreased libido, erectile or ejaculatory dysfunction, delayed orgasm, anorgasmia, and less commonly, impotence (95–97). There are no

reliable data that indicate how often these occur, and many studies refer only to a “decrease or impaired sexual function.” Several studies have used clomipramine, a strong serotonergic TCA, as a comparator to SSRI and found equivalent rates of sexual dysfunction. Clomipramine was associated with anorgasmia in approximately 90% of patients in a study in patients with OCD (164). The most often quoted numbers for depressed patients who experience decreased sexual function and libido while being treated with clomipramine are 14% for females and 26% for males (97); however, women may be less likely to report sexual side effects (96). On the other hand, an increase in libido with imipramine and amoxapine has been known to occur (97). These disparate findings highlight the difficulty in separating sexual dysfunction associated with depression and that resulting from drug therapy.

Other Adverse Effects

Other common adverse effects include tremors, myoclonus, and perspiration. Maprotiline has been associated with seizures at high therapeutic doses. All TCAs lower the seizure threshold, but this is usually only a problem in patients with a seizure disorder or in overdose. Amoxapine has been associated with extrapyramidal symptoms.

Overdose

TCAs have a relatively low therapeutic index and serious consequences in overdose. For most TCAs, the therapeutic dose is about 3–4 mg/kg/day and a potentially lethal dose is 15–20 mg/kg/day. The potentially fatal dose is only a 5-day supply of medication. This creates an obvious problem in the treatment of depressed patients, many of whom have suicidal ideation. The epidemiological data from the 1970s to mid-1980s, prior to the SSRIs’ entry into the market, provide the richest data on TCA overdose. During that period, the annual incidence of TCA overdose in United States was estimated at 500,000 (144). Approximately 1,500–2,000 patients a year committed suicide with TCAs (150). TCAs became the most commonly ingested drugs among suicidal patients and the third most common cause of drug-related death, following closely deaths from alcohol–drug combinations and heroin overdoses (165). In 1983 and 1984, TCAs were the most common drug involved in overdose deaths, and 70% of patients taking TCAs in suicides died before reaching the hospital (144) and a substantial number died within 5–6 h of admission to a hospital (165). More recently, some have opined that the risk of overdose has been exaggerated. For example, it has been argued that only 5% of suicidal patients use their prescribed antidepressant medications for that purpose (81); however, most clinicians are unwilling to take any risk as long as safer alternatives are available.

The clinical presentation of TCA overdose is an extension of their pharmacodynamic actions. Frommer and associates (144) describe the initial symptoms as primarily anticholinergic, including mydriasis, blurred vision, urinary retention, dry mucous membranes, decreased peristalsis, tachycardia, general CNS excitation with increased reflexes, hyperactivity, and insomnia. CNS toxicity includes confusion, agitation, hallucinations, and seizures. CNS depression may begin as drowsiness or lethargy and progress rapidly to coma and respiratory arrest in the most severe cases (144). Cardiac abnormalities may include hypotension and arrhythmias, such as sinus tachycardia, supraventricular and ventricular tachycardia, prolongation of PR, QRS, and QT intervals, bundle branch or second- and third-degree blocks, or sudden death (32). Death is caused by intractable myocardial depression or cardiac arrhythmias such as ventricular tachycardia or fibrillation (144). Generalized seizures are associated with increased mortality and often occur immediately prior to cardiac arrest. The progression from mild symptoms to death can be extremely rapid, and often does not follow a predictable pattern.

In terms of individual differences among cyclic antidepressants, amoxapine has been associated with least cardiotoxicity in large overdoses (144, 166); however, it has significant CNS toxicity, and has been known to cause status epilepticus and coma with overdose (166, 167). Maprotiline, a tetracyclic compound, was reported to possess greater cardiac and CNS toxicity (seizures) than other agents (168).

Treatment of a TCA overdose includes administration of activated charcoal lavage, fluids, and supportive measures. Several authors have proposed specific therapies for hypotension, seizures, and arrhythmias; however, there are substantial variations in approach. Regardless of the specific approaches used, all patients should be hospitalized in a cardiac or intensive care unit. Some clinicians advise administration of physostigmine, but this may precipitate seizure and cardiac arrhythmias in some instances (168).

Clinical Use

A study published in 1993 analyzed data on antidepressant use from three National Ambulatory Medical Care Surveys for years 1980, 1985, and 1989 (169) and found that TCAs were the most widely prescribed type of antidepressant in an office-based practice throughout 1980s, and were still widely used at the time of that publication. TCAs have now become second-line agents in the United States, but in other countries, they remain first-line agents. This is especially true for European psychiatrists, many of whom believe in the superior efficacy of tertiary amines such as clomipramine and amitriptyline over other antidepressants (32). In the United States, however, newer antidepressants, such as SSRIs, have replaced the TCAs as first-line agents, primarily due to the belief of equivalent efficacy, greater safety, improved tolerability, and ease of dosing compared to TCAs.

Most clinicians believe that data support the equivalent efficacy of all the TCA, although some argue for the superior effectiveness of clomipramine. Estimates indicate that up to 80% of heterogeneous depressed patients will experience clinically significant improvements in depression when treated with adequate doses of TCAs (148).

There remains disagreement on the issue of superior efficacy of TCAs compared to SSRI. In a review of 186 randomized controlled trials that compared amitriptyline with other antidepressants, including SSRIs, heterocyclics, and other tricyclics, Barbui and Hotopf (170) concluded that amitriptyline was more efficacious in the treatment of depression than SSRIs, heterocyclics, or other TCAs. A small, but statistically significant, higher response rate was found with amitriptyline (170). Boyce and Judd (171) have argued that not only are the TCAs more effective in melancholic depression and inpatients with depression but also the tolerability and safety of SSRI have been overstated.

There is support for the position that TCAs should remain a first-line treatment for patients with severe depression (sometimes referred to as endogenous or melancholic depression). The Danish University Antidepressant Group found that clomipramine was superior in efficacy to citalopram, paroxetine, and moclobemide (172). In another study, nortriptyline was found superior to fluoxetine, for treating depression in hospitalized elderly patients, especially for those patients with a melancholic subtype of depression (173). In a review of 6 controlled trials, Perry (174) concluded that TCAs are more effective agents in the treatment of “endogenous depression or major depression with melancholic features” compared to SSRIs. On the other hand, clinicians should be aware that there are many studies that have found the two classes “equivalent,” although most of these have not differentiated melancholic subtypes of depression. Equivalency studies are notorious for Type II errors, i.e., having a sample size that is too small to detect significant group differences.

TCAs have a broad spectrum of efficacy. In addition to major depression and dysthymia, they are effective in panic disorder, social phobia, other anxiety disorders, bulimia nervosa, PTSD, ADHD, and, in young children, enuresis. Toxicity of TCAs in children has been the matter of some controversy. Some reports have linked desipramine to sudden death in children; however, a review by a leading authority in the area did not find an association (175). As a precaution, ECG should be monitored in children taking TCAs. Clomipramine is approved for treatment of obsessive-compulsive disorder. Adult as well as childhood ADHD responds well to treatment with TCAs, with most data available for imipramine and desipramine (176, 177). TCAs are sometimes used for chronic pain syndromes and migraine headaches, but more effective medications (duloxetine, milnacipram, gabapentin, pregabalin) have largely supplanted their use in these illnesses.

Gender differences in therapeutic response to TCAs have been studied but have produced inconsistent findings. A 12-week, double-blind, randomized prospective study found that depressed men were significantly more likely to show a favorable response to imipramine, a TCA, than to sertraline, a SSRI, while the reverse was true for women. This difference was most apparent in premenopausal women; postmenopausal women had equal rates of response to the two agents (178). In general,

women had a slower antidepressant response to imipramine and poor tolerability of the TCA. The reasons for the gender differences are unclear but may include the presence of SSRI-responsive subtypes of depression in women (e.g., atypical, premenstrual dysphoric disorder) and/or an interaction between antidepressants and female sex hormones. Complicating the interpretation of this study are high drop-out rates for women taking imipramine and for men taking sertraline (179).

A retrospective study analyzed data for 1,746 patients treated with TCAs (imipramine, desipramine), SSRIs (fluoxetine), MAOIs (phenelzine, tranylcypromine, *l*-deprenyl), or placebo over a 20-year period (180). The authors found no difference in response rates to TCAs and fluoxetine between male and female patients of all studied ages, but women had a statistically significant superiority in their response to MAOI antidepressants. The authors also failed to find a clinically relevant difference in treatment response of female patients in older age groups, suggesting a lack of influence by menopausal status.

Other Antidepressants

A number of antidepressants were introduced after SSRIs. *Venlafaxine* is a nonselective serotonin and norepinephrine reuptake inhibitor. *Desvenlafaxine*, the primary metabolite of venlafaxine, has a similar profile to its parent compound, but dosing may be easier. *Duloxetine* is also a nonselective serotonin and norepinephrine reuptake inhibitor, but has greater potency than venlafaxine (181). Neither compound has significant anticholinergic or antihistaminic effects. *Mirtazapine* is a noradrenergic α_2 antagonist at auto- and heteroreceptors, enhancing serotonin release and a 5-HT_{2A} and 5-HT₃ antagonist. *Nefazodone* and *trazodone* are phenylpiperazine derivatives. *Nefazodone* is a 5-HT_{2A} antagonist and serotonin reuptake inhibitor. *Bupropion* is an aminoketone that in vivo may block norepinephrine reuptake via its active metabolite hydroxybupropion and also increase dopamine activity by an unknown mechanism. *Reboxetine* is a selective norepinephrine reuptake inhibitor that is currently used to treat mood disorders in Canada and Europe but is not available in the United States. These newer antidepressants offer some advantages in tolerability over the older agents and perhaps more importantly have different mechanisms of action, which may provide alternatives for patients who do not respond to other antidepressants.

Bupropion

Bupropion is an aminoketone compound that was introduced in the United States in 1989 amid concerns about its seizure-inducing potential, a factor that delayed its marketing from the original FDA approval in 1985. A large study in the interim period established that the seizure risk from bupropion at usual therapeutic doses was similar to the cyclic antidepressants. Bupropion has three active metabolites: hydroxybupropion, threobupropion, and erythrobupropion. The relative contributions

of the metabolites to clinical or adverse effects are unclear; however, they reach higher plasma levels than the parent compound. Bupropion's plasma half-life after chronic dosing is about 20 h and it is 80% protein bound. The half-life of hydroxybupropion is longer, about 22 h, and it is a norepinephrine reuptake inhibitor (182).

Bupropion is believed to exert its antidepressant action by inhibiting norepinephrine reuptake and enhancing dopamine activity. It has no serotonergic, anticholinergic, or antihistaminergic effects, nor does it interact with monoamine oxidase (182). There is still some ambiguity concerning its mechanism of action which arises from differences in bupropion's actions in vivo and in vitro. Bupropion is a potent dopamine reuptake inhibitor as well as a moderate norepinephrine reuptake inhibitor in vitro. In vivo, the drug is twice as potent in its norepinephrine reuptake inhibition compared to its dopamine reuptake inhibition (183). Although bupropion has demonstrated dopamine uptake inhibition using in vitro models, the concentrations required may not have clinical relevance. In addition, even though homovanillic acid is increased during bupropion treatment (an indication of enhanced dopamine activity), these levels are not associated with a positive antidepressant response. Hydroxybupropion is associated with down-regulation of postsynaptic β -adrenergic receptors in animal models.

Bupropion IR (immediate release) carries a relatively higher risk of lowering seizure threshold compared to SSRIs. Bupropion IR has a risk of seizures of 0.4% at doses up to 450 mg/day, which is about 2–4 times higher than the incidence of seizures associated with SSRI treatment (0.1–0.2%) (184). Seizure risk is strongly related to dose and the rate of dosage escalation. Even with modest increases of the dose to 450–600 mg/day seizure risk increases tenfold. An extended release formulation has lowered the risk of seizures to a level comparable to other antidepressant classes. A seizure rate of 0.1% was associated with bupropion SR (sustained release) at doses of 300 mg/day and 0.4% at 400 mg/day (184). Clinicians should be aware that Wellbutrin® and Zyban® are both bupropion, and inadvertent overdoses have occurred when both have been prescribed for the same patient to treat depression and for smoking cessation.

Because of bupropion's dopaminergic and adrenergic actions, it can be activating and may cause overstimulation, agitation, nausea, nervousness, and insomnia as well as tremors and palpitations (182, 184, 185); however, in our experience, it is usually very well tolerated. It has the potential to induce mania in bipolar patients; however, bupropion-induced mania tends to be milder and have a shorter course than either spontaneous mania or mania elicited in patients by tricyclic or SSRI antidepressants (77). Bupropion has a favorable cardiovascular profile and does not cause orthostatic hypotension or conduction delay. Some patients may have elevated blood pressure with bupropion, but in our experience is not as frequent a problem as with venlafaxine.

Since bupropion does not interact with serotonergic receptors, it has an extremely low incidence of sexual side effects which are common with SSRIs and most other antidepressants (97, 184, 185). Bupropion is a reasonable alternative to SSRI when sexual adverse effects limit their use. Bupropion is not associated with weight gain.

Dermatologic adverse effects of bupropion are rare but may also include urticarial and pruritic rashes and very rarely extreme dermatologic reactions (186).

Because of its unique mechanism of action and good tolerability it has become one of the first choices for SSRI augmentation for many clinicians.

Venlafaxine

Venlafaxine is a bicyclic phenylethylamine derivative marketed as a racemic mixture of its R- and S-enantiomers; the R-enantiomer is more potent of the 2 (187). Venlafaxine is only 27% protein bound and has a half-life of 4–5 h. It undergoes first-pass metabolism to *O*-demethylvenlafaxine, ODV, which is active and just as potent as its parent compound, and has an elimination half-life 11 h. Clearance of both venlafaxine and ODV is decreased by 55% in patients with severe renal disease and by 33% in patients with cirrhosis (188). Venlafaxine XR (extended release) formulation has become the preferred agent, and the immediate release formulation is rarely used in the US. Pharmacologically, the XR it is quite similar to the original venlafaxine IR (immediate release); the differences are increased time to peak plasma concentration as well as lower plasma concentrations of the XR drug (189).

Venlafaxine acts on both serotonergic and norepinephrine reuptake at higher therapeutic doses (225 mg or higher), but at lower doses, it affects mainly serotonin, making it comparable to SSRI. However, as the dose is increased, it becomes a potent inhibitor of the synaptic reuptake of norepinephrine (182, 187, 188). At low doses, inhibition of serotonin reuptake is about three to fivefold higher than that of norepinephrine reuptake (32, 188). Venlafaxine also possesses weak affinity toward the dopamine receptor (188). It rapidly down-regulates β -adrenergic receptors, a property that some contend supports those studies that have found a more rapid onset of antidepressant effect with venlafaxine compared to other agents. It has minimal or no interaction with muscarinic, histaminic, or α -adrenergic receptors, which accounts for its low incidence of adverse effects (187). It is an effective antidepressant and antianxiety agent.

Most common adverse effects include those associated with SSRI, such as nausea, vomiting, sexual dysfunction, somnolence, and sweating (182, 185, 190). The incidence of sexual dysfunction is thought by some to be lower than SSRI (103, 185, 191).

Of most concern has been elevated blood pressure which occurs at higher doses of venlafaxine (between 101 and 300 mg daily) that returns to normal after drug discontinuation (69, 182). Blood pressure changes are dose related, with an incidence of about 5% at doses under 200 mg daily and 13% at doses greater than 300 mg daily. Pre-existing hypertension does not appear to be a risk factor for this effect. If the dose cannot be reduced, blood pressure should be treated pharmacologically, using standard drug algorithms.

Discontinuation syndromes upon abruptly stopping venlafaxine have been reported (192). The most common symptoms are dizziness or lightheadedness, excessive sweating, irritability, dysphoria, and insomnia, which is similar to the SSRI discontinuation syndrome (192). A slow taper of the medication usually

prevents the occurrence of this syndrome. On rare occasions, it may be necessary to reinstitute the medication or switch to a long-acting SSRI, such as fluoxetine.

Venlafaxine is one of the few antidepressants that has been studied in pregnancy. A recent prospective study of 150 pregnant women receiving venlafaxine found no significant differences between women taking venlafaxine during pregnancy and those taking either SSRI antidepressants or known non-teratogenic drugs (193). The rates of major neonatal malformations in all groups were the same as baseline rate for the general population of 1–3%. It should be noted that the sample size is too small to detect rare occurrences of adverse effects, such as teratogenic risk.

Desvenlafaxine is the major active metabolite of the SNRI antidepressant venlafaxine formulated as an extended-release tablet for once-daily, oral administration. It inhibits the neuronal reuptake of both serotonin and norepinephrine and, to a lesser degree, dopamine. It is approximately tenfold more potent at inhibiting serotonin uptake than norepinephrine uptake. Desvenlafaxine lacks monoamine oxidase inhibitory activity and shows no affinity for muscarinic cholinergic, H₁-histaminergic, or α_1 -adrenergic receptors in vitro.

Desvenlafaxine is well absorbed after oral administration (80% bioavailability) but somewhat slowly, with a T_{\max} of 7–8 h. It has a mean terminal half-life ($t_{1/2}$) of approximately 9–15 h. Metabolism is primarily through phase II glucuronidation and, to a minor extent, through CYP3A4. It has linear pharmacokinetics through supratherapeutic doses, with very small differences between subjects. It does not inhibit CYP2D6 to a clinically significant extent. Desvenlafaxine plasma binding is approximately 30% and independent of drug concentration. There are no active metabolites, and it is excreted by the kidney as unchanged desvenlafaxine and the glucuronide conjugate.

Several studies have established the efficacy of desvenlafaxine in major depression and it is FDA approved for that indication. Despite an active research program in the area, studies do not yet support the efficacy and safety of desvenlafaxine for vasomotor symptoms associated with menopause, such as hot flashes, night sweats, and associated sleep disruptions.

Similar to its parent compound, discontinuation symptoms are observed after cessation of desvenlafaxine treatment in both short-term and long-term MDD studies. The most common symptoms reported by patients after discontinuation of short-term desvenlafaxine treatment were dizziness, nausea, irritability, and diarrhea, which are characteristic of the serotonin reuptake inhibitor discontinuation syndrome. Symptoms associated with treatments of 6-month duration include fatigue, abnormal dreams, anxiety, and hyperhidrosis. About half of patients taking desvenlafaxine have some discontinuation symptoms, but they are relatively few and mild compared to short-acting SSRI withdrawal syndromes. At the recommended dose of 50 mg daily, discontinuation symptoms appear shortly after abrupt discontinuation and resolve within a week.

In summary, desvenlafaxine offers a few advantages over venlafaxine, although among them are ease of dosing—a single dose of 50 mg for initiation and maintenance, lower potential for pharmacokinetic drug interactions, and apparently a less severe discontinuation syndrome.

Duloxetine

Duloxetine is an antidepressant that inhibits both serotonin and norepinephrine reuptake. Although similar to venlafaxine, duloxetine's greater potency at norepinephrine reuptake is thought to contribute to its greater efficacy in pain treatment than venlafaxine. It is approved by the FDA for use in major depression, generalized anxiety disorder, diabetic neuropathic pain, and fibromyalgia. The recommended therapeutic doses range from 40-60 mg daily, but lower doses (20-30 mg daily) should be used for the first week of treatment to avoid adverse effects. Although clinical studies do not support doses higher than 60 mg daily, our experience suggests that higher doses are usually necessary for pain syndromes related to fibromyalgia and other autoimmune diseases. Common adverse effects are nausea, decreased appetite, constipation, headache, dry mouth, insomnia, and somnolence. Men, but not women, treated with duloxetine experience more difficulty achieving orgasm compared to placebo. Increases in both systolic and diastolic blood pressure of approximately 2 mm Hg and an increase in heart rate of 3-4 beats per minute. Some patients experience palpitations but clinically significant changes in electrocardiograms were not different in duloxetine and placebo groups in premarketing studies. The drug is among a class of agents that increase urethral resistance, which may lead to urinary hesitation. Duloxetine has an elimination half-life ranging from 8-17 hours, with hepatic metabolism by P450 isozymes CYP1A2 and CYP2D6. Numerous metabolites are produced, but it is believed that the primary therapeutic effect is from the parent compound.

Nefazodone and Trazodone

Nefazodone and *trazodone* are two closely related antidepressants. Nefazodone is a phenylpiperazine derivative of trazodone with lower α_1 activity. Trazodone is a triazolopyridine derivative developed in early 1980s as an alternative to TCAs, but its efficacy has always been questioned, and its most common use today is to promote sleep. Its antidepressant properties are believed to be related to its 5-HT₂ receptor antagonism and only partially from its weak serotonin reuptake inhibition (32, 187). Aside from its therapeutic actions, trazodone is a weak to moderate histamine H₁ receptor antagonist as well as α_1 -adrenergic antagonist, which makes it similar to TCAs in terms of the undesired side effects (187).

Nefazodone has three pharmacologically active metabolites: hydroxynefazodone (OHN), triazole-dione, and *m*-chlorophenylpiperazine (mCPP). Both triazole-dione and OHN contribute to the antidepressant effect of nefazodone. Like nefazodone, OHN is a very potent inhibitor of 5-HT_{2A} receptors as well as serotonin reuptake. The triazole-dione metabolite has weak 5-HT_{2A} antagonism. mCPP is an agonist at the 5-HT_{1A}, 1B, 1C, 1D and 5-HT_{2C} receptors but is not considered to have a significant impact on nefazodone's overall actions (182, 189). Nefazodone antagonizes and down-regulates postsynaptic 5-HT_{2A} receptors, which in turn leads to enhanced 5-HT_{1A} receptor-mediated postsynaptic neurotransmission (194). It is a moderate

presynaptic serotonin reuptake inhibitor (194). Nefazodone also inhibits presynaptic norepinephrine reuptake, but to a much lesser degree, and this probably does not contribute to its therapeutic actions (182). Nefazodone is a weak α_1 -adrenergic antagonist and has very little if any α_2 -adrenergic, antihistaminic, or dopamine receptor interactions (187, 195).

As discussed above, trazodone is a histamine H_1 receptor antagonist, as well as an α_1 -adrenergic antagonist, which makes it similar to TCA drugs in terms of the undesired side effects (187). Despite isolated case reports of conduction delay and arrhythmias with trazodone (especially in overdoses), studies have not found this effect even in patients with pre-existing cardiac disease. Anticholinergic and antihistamine effects are negligible (182, 187). Due to its α_1 -adenoreceptor blocking properties, trazodone may cause orthostatic hypotension (69). The most serious adverse effect of trazodone therapy in male patients is priapism, a urologic emergency (196). The incidence of trazodone-induced priapism is unknown with estimates ranging from 1 in 1,000 to 1 in 10,000 patients. It tends to occur early in treatment, usually within the first month, but has also been reported after 18 months of treatment. It can occur at doses as low as 50 mg daily. Approximately one-third of patients require surgical intervention. Priapism is believed to be due to α -adren-ergic blockade.

Nefazodone has weak α_1 and cholinergic receptor antagonism and virtually no α_2 -adrenergic, dopamine, or histaminic blockade (182, 190). Nefazodone does not cause sexual dysfunction, and it is a reasonable alternative to SSRI when this effect is of concern (97, 103). It has not been associated with priapism, despite its structural similarity to trazodone (34, 69). The most frequent side effects of nefazodone as compared to placebo in patients in clinical trials are nausea (21 vs. 14%), somnolence (19 vs. 13%), dry mouth (19 vs. 13%), dizziness (12 vs. 6%), constipation (11 vs. 7%), lightheadedness (10 vs. 4%), and blurred vision (6 vs. 3%) (195). It should be noted that occurrence of nausea and gastrointestinal distress in patients taking nefazodone or trazodone is usually less than that produced by either SSRI or venlafaxine treatment (185).

A study of hepatotoxicity of the newer antidepressants using the Spanish Pharmacovigilance System database reported a high incidence of hepatotoxicity with nefazodone, with 28.96 cases per 100,000 patient-years, compared to 1.28 for sertraline and 4.0 for clomipramine (72). The Canadian Adverse Drug Reaction Monitoring Program found 32 cases of hepatotoxicity associated with nefazodone, with 26 classified as severe (197). Patients were between 30 and 69 years old and were taking doses of 100–600 mg daily. Sixty-eight and eight-tenths percent were women; 88% developed toxicity within 6 months of beginning the drug. Toxicity is hepatocellular in such cases, with high serum aminotransferase levels and increased total bilirubin. Withdrawal of nefazodone may lead to improvement in liver function; however, deaths have also been reported (72, 198). It is likely that both pharmacovigilance studies suffer from underreporting (72). If this is so, the incidence of hepatotoxicity associated with nefazodone may be even higher. In the United States, nefazodone now carries a “black box” warning concerning hepatotoxicity, and some countries have

removed it from the market. It retains a niche market in the U.S. for anxious and depressed patients, often with substance abuse, who have not responded to several other agents.

Mirtazapine

Mirtazapine, is a 6-aza-analogue of mianserin but has a different pharmacologic profile (199). Mirtazapine is a less-potent noradrenergic reuptake blocker and 5-HT₂ antagonist than mianserin (199). Mirtazapine is an effective antidepressant and antianxiety agent, and some authorities believe it has a more rapid onset than other antidepressants.

Mirtazapine's mechanism of antidepressant action is believed to be related to enhancement of serotonin and norepinephrine neurotransmission through potent and direct blockade of α_2 -adrenergic autoreceptors and heteroreceptors (199, 200). This action results in increased noradrenergic transmission which stimulates α_1 -adrenergic receptors on the serotonergic cell body. Blockade of the α_2 -adrenergic heteroreceptor on the serotonin nerve terminal prevents this receptor from "turning off" the increased serotonin activity (199, 200). Mirtazapine is also a weak agonist of the 5-HT_{1A} serotonin receptor and causes some enhancement of 5-HT_{1A}-mediated serotonergic transmission through this mechanism (200). Another major action of mirtazapine is inhibition of 5-HT₂ and 5-HT₃ receptors postsynaptically, which may limit the adverse effects that are usually associated with increased serotonin activity and may also contribute to mirtazapine's anxiolytic and hypnotic effects. Because it has a unique pharmacodynamic profile, it is among the first agents used for augmentation and combination therapy with SSRI.

Mirtazapine is marketed as a racemate of R- and S-enantiomers (187). The R-enantiomer is more active, reaches higher plasma concentrations, and has a longer half-life than the S-enantiomer. Mirtazapine is rapidly absorbed from the gastrointestinal tract after oral administration with high bioavailability. It is 85% plasma protein bound and has an elimination half-life of 20–40 h (201). Mirtazapine's major metabolite is demethylmirtazapine, which has only weak activity compared to the parent compound. Hepatic and renal impairment may cause a 30 and 50% decrease in oral mirtazapine clearance, respectively, necessitating a dose adjustment in some patients (201).

Mirtazapine is associated with dry mouth, drowsiness, and sedation in about 25% of patients (199, 202). Because of its antihistaminic activity, this drug may also cause weight gain in approximately 10–20% of patients. A similar percentage of patients have elevated cholesterol and somewhat fewer have elevated triglycerides. Mirtazapine has low incidence of sexual side effects among antidepressants (103).

A causal association of mirtazapine with severe neutropenia (absolute neutrophil count less than 500/ml³) has been reported in three cases. Of these, 2 patients developed agranulocytosis. All 3 patients recovered upon discontinuation of the drug. It is therefore recommended that mirtazapine be stopped if any signs of infection with a low white cell count occur (201).

Overdose

As a group, the antidepressants introduced since 1985 appear to be safer in overdose compared to the cyclic antidepressants. Although reports of mortality in overdose can be found for most of these agents, fatal overdoses usually occur when they are combined with other agents. One review of venlafaxine reported 16 overdoses of up to 6,750 mg of venlafaxine, either alone or with other medications and/or alcohol without any deaths (201). The most common problems were somnolence and sinus tachycardia. On the other hand, a cohort study of 538 deliberate antidepressant overdoses found that both venlafaxine and SSRIs were more likely to cause serotonin syndromes, but less likely to cause coma, compared to TCAs (203). That study also found that 7 of 51 (14%) venlafaxine patients had seizures. There were no deaths reported. A study from the United Kingdom calculated fatal toxicity from antidepressants using the number of deaths per million prescriptions (204). A rate of 13.2 was reported for venlafaxine, which placed it at the low end of TCA death rates (5.5–200), but higher than SSRI death rates (0.7–3.0). These data must be interpreted with caution because they do not take into account selection bias. For example, patients with high suicide risk may be prescribed drugs that clinicians believe are safer (such as venlafaxine and SSRIs) or used preferentially in severe depression (dual action agents), and avoid those with a low therapeutic index (such as TCAs) or those that may not be as effective in endogenous depression (such as SSRIs).

Data on *mirtazapine*'s safety in overdose are limited. One review reported 8 patients in clinical trials who overdosed on mirtazapine either alone in doses from 100 to 315 mg, or with benzodiazepines, or "pain killers" (190). No fatalities or ECG changes occurred. Another study analyzed 6 cases of overdose with mirtazapine, including overdoses in a 3-year-old child and a 90-year-old man, which occurred during postmarketing surveillance and in clinical trials (205). Again, no serious sequelae were reported. Mirtazapine safety in overdose appears to be comparable to SSRI.

Seven overdose cases of *nefazodone*, with or without co-ingestion of other medications or alcohol, have been reported (195). The symptoms of overdose included nausea, vomiting, and somnolence. All of the patients recovered with general supportive care (195). The American Association of Poison Control Centers reported on 1,338 cases of nefazodone poisoning that were not associated with other drug use (206). There were no deaths, and the most serious effect was hypotension in 1.6% of cases. More common symptoms included drowsiness (17.3%), nausea (9.7%), and dizziness (9.5%), which resolved within 24 h.

A fatal case of *trazodone* overdose had been reported in European literature. The patient sustained arrhythmias (torsades de pointes and complete AV block) and multiple organ failure and died within 24 h after admission to emergency department (207).

Bupropion has been associated with fatalities when ingested with other medications or at very high doses. An overdose of 23 g resulted in death (208). In another report, a patient recovered after grand mal seizures, and sinus tachycardia occurred following intentional ingestion of 9 g of bupropion (209). A 3-year, multicenter, retrospective study of bupropion overdoses reported to poison control centers described 58 cases of bupropion ingestion alone and 9 cases of ingestion of bupropion and a

benzodiazepine (210). There were no fatal outcomes among these patients, but many had sinus tachycardia, hypotension, hypokalemia, lethargy, tremors, and seizures (210). The seizure risk of bupropion increases with dose (184), and higher seizure rates are seen in bulimic patients, with approximately one-third of overdoses with bupropion IR resulting in seizures in these individuals (34).

The Role of Mixed Action Antidepressants in Therapeutics

Recently marketed non-SSRI antidepressants are considered by most clinicians as second-line therapeutic options for treatment refractory patients or as augmenting agents. Since these antidepressant medications act on different neuronal systems, they are a rational choice in non-responders (182). They are also used as adjunctive agents to augment SSRIs in partial responders. Their overall efficacy as antidepressants is comparable to that of the standard antidepressant classes such as SSRIs, TCAs, and MAOIs, and some data indicate superiority compared to SSRI in depression with melancholic or endogenous features. They are second-line agents because the SSRI are easier to dose, are available in generic form, and have few medically serious adverse effects.

In addition to the efficacy of non-SSRI agents in depression, studies support efficacy in anxiety disorders (especially venlafaxine, mirtazapine, nefazodone) and ADHD (venlafaxine, bupropion). Bupropion's role in smoking cessation is well recognized (211) but it has also been used to treat neuropathic pain (212). Duloxetine and milnacipram are the preferred antidepressant agents in fibromyalgia. Bupropion and mirtazapine have become the agents of choice if SSRI-induced sexual dysfunction limits continued treatment with that class of drugs.

Trazodone has a limited role, but may be useful in promoting sleep in patients taking energizing antidepressants, or as an augmentation agent. Nefazodone is a very effective antidepressant but its use has declined since reports of hepatotoxicity have appeared. Mirtazapine is also an effective antidepressant and an anxiety agent that is frequently used in combination with other antidepressants as an augmentation strategy and to improve sleep, although with higher doses its hypnotic actions are eliminated.

The possibility of a more rapid onset of clinical effect for agents that have mixed actions, mirtazapine and venlafaxine in particular, has been the subject of much debate. At present, there are insufficient data to support such a claim.

Antidepressants Without United States FDA Approval

Reboxetine

Reboxetine is a selective norepinephrine reuptake inhibitor approved for use as an antidepressant in Canada and Europe, but not yet available in the United States. It is a racemic mixture of two stereoisomers, consisting of (S,S)-(+)- and

(R, R)-(–)-reboxetine; the (S,S) enantiomer is more potent as an antidepressant and has greater affinity to the norepinephrine receptor (213, 214).

Women have a 30% higher S, S to R, R ratio than men (215). Reboxetine down-regulates β -adrenergic receptors (213). Although it is somewhat less potent as a norepinephrine reuptake inhibitor than desipramine and nortriptyline (187), it has very low affinity for α -adrenergic and muscarinic cholinergic receptors, and no affinity for serotonergic or dopaminergic receptors (213).

Reboxetine has linear pharmacokinetics with either single or multiple oral doses. Its elimination half-life is approximately 12–13 h; absolute bioavailability is 94.5%. Reboxetine is rapidly absorbed; it reaches its maximal concentration in 2 h after administration (213, 214). It is 97% bound to plasma proteins, particularly α_1 -acid glycoprotein (213, 214). The suggested dosage for reboxetine is 8–10 mg/day in divided dose (216). It has no active metabolites. Plasma concentrations of reboxetine are increased in patients who are elderly or have hepatic or renal insufficiency (213, 214). The recommended dose for such patients is 4–6 mg/day. Reboxetine is metabolized hepatically by cytochrome P450 CYP 3A4 but has no known inhibitory or inducing effect on any of the CYP isoforms.

Adverse Effects

Clinical trials have established its safety (216, 217). The most frequent adverse effects include dry mouth, constipation, increased diaphoresis, insomnia, and urinary retention (187, 218–220). Most of these appear to be dose related (216, 219). Clinically insignificant orthostatic hypotension has been reported (218). Also, headache, palpitations, tachycardia, decreased appetite, dizziness, and abnormal sensation in the genitals have been reported with reboxetine use; the incidence of all side effects, except tachycardia, was dose related (219).

Reboxetine did not alter cardiac conduction in healthy volunteers in a randomized, open-label, placebo-controlled study, which was specifically designed to test reboxetine's effect on cardiac repolarization at different plasma concentrations, including those exceeding the normal therapeutic range (219). Subjects' ECGs were used to assess the QTc, PR, and QRS intervals; no changes in these parameters as a result of reboxetine treatment were reported (219). However, reboxetine resulted in heart rate increases of 8–11 beats per minute at doses of ≥ 8 mg/day (219).

Efficacy

Several double-blind, randomized clinical trials, conducted mostly outside the United States, showed superiority of reboxetine to placebo and/or to established antidepressants such as fluoxetine in patients suffering from moderate to severe MDD. In a 6-week randomized, double-blind, placebo-controlled study of reboxetine, hospitalized patients with MDD found that both the improvement in the mean HAM-D-21 total score and the response rate (defined as percentage of patients

achieving $\geq 50\%$ reduction in HAM-D-21 total score) were significantly greater in the reboxetine group than those in the placebo group (218).

In an 8-week double-blind, randomized, placebo- and active treatment-controlled, multisite clinical trial of 381 inpatients and outpatients with MDD and baseline HAM-D-17 scores 22 or higher, reboxetine, at daily doses of 8–10 mg, was shown to be as effective as fluoxetine, at 20–40 mg/day (as judged by a similar percentage of patients achieving $\geq 50\%$ reduction in HAM-D scores) (220). Both active drugs were shown to be significantly superior to placebo (220). Efficacy in severe depression was also found and replicated by Montgomery and associates (221). Some investigators have found reboxetine to have a faster onset of action than other antidepressants, improving patients' HAM-D scores as soon as 10 days after initiating treatment (217).

In general, however, the perception is that reboxetine has weak efficacy in MDD. An intriguing study found that a single 4 mg dose reduced negative information processing that is commonly seen in patients with mood and anxiety disorders (222). Reboxetine may share some actions with cognitive behavioral therapies. A related study found that reboxetine and citalopram (SSRI) both modulated information processing in depressed patients, although different brain areas were affected (223). These findings provide support for individualized assessment of depressed patients based on activity of specific brain regions assessed by fMRI. At present, it appears that an SSRI and an SNRI affect different brain regions that are important in emotional processing.

Mifepristone

Mifepristone is a progesterone-receptor antagonist and glucocorticoid antagonist, which in preliminary studies has been effective as short-term monotherapy for patients with psychotic major depression (PMD) at doses of 600–800 mg daily (224, 225). Adverse effects include fatigue, anorexia, and nausea. A maculopapular erythematous cutaneous eruption has also been reported (224, 225). Caution must be exercised when used in women because this agent induces abortion.

Substance P

Recent studies have examined compounds that inhibit substance P (SP)-neurokinin-1 (NK_1) receptor pathways as potential antidepressants (226). SP and NK_1 receptors are located in brain regions that regulate mood and are associated with neurotransmitter pathways thought to play a role in depression. In one postmortem study, higher concentrations of SP were found in the cerebrospinal fluid of depressed patients compared to controls (227). Aprepitant and compound A, SP- NK_1 antagonists, have a high affinity and selectivity for the NK_1 receptor, but have not been shown to inhibit other depression-related neurotransmitters. Both compounds have been studied for the treatment of depression with disappointing results.

Melantonergic Agents

Agomelatine is an agonist at melatonin MT_1 , and MT_2 receptors, an antagonist at 5-HT_{2C} receptors, and has very weak affinity for 5-HT_{1A}, and 5-HT_{2B} receptors. It is approved in Europe and marketed as Valdoxan. It has shown equivalency to sertraline and venlafaxine. It improves sleep without producing daytime drowsiness (228).

Sigma Agonists

Some currently marketed antidepressants such as fluvoxamine and sertraline, but not paroxetine, are sigma 1 agonists. The sigma agonist igmesine has shown efficacy and safety in early human studies (229).

MAOIs

History

Monoamine oxidase inhibitors (MAOIs) were the first antidepressants used in clinical practice. Iproniazid, the isopropyl derivative of isoniazid, was developed by Herbert Fox at Roche Laboratories in 1951 for the treatment of tuberculosis (230). The drug proved ineffective for tuberculosis, but did have a mood elevating effect in some patients (231). Its antidepressant properties are believed to be the result of the inhibition of monoamine oxidase (MAO), the enzyme that catalyzes oxidative deamination of monoamines such as dopamine, epinephrine, norepinephrine, and serotonin among others, thus rendering these amines inactive (31, 232–234). Inhibition of the enzyme results in increased availability of these biogenic amines by preventing their breakdown. Unfortunately, most United States clinicians who have entered practice over the last two decades have little experience using MAOIs for the treatment of depression. The efficacy of SSRI in atypical and mixed depression accounts in part for this phenomenon. However, as described below, the pharmacological actions of MAOIs are unique and should still be considered as alternative agents when other antidepressants are not effective.

In 1950s and 1960s, MAOIs became a primary treatment for depression. At their peak, there were five hydrazines (isocarboxazid, nialamide, mebanazine, phenelzine, and pheniprazine) which are structurally similar to iproniazid, one indole (etryptamine), and one cyclopropylamine (tranylcypromine) in clinical use. The first MAOI, iproniazid, and then pheniprazine were withdrawn from the market due to hepatotoxicity (31). As clinical experience grew, the serious adverse effects of MAOIs combined with the introduction of safer antidepressants led to a decline in MAOI use. Currently, only four MAOIs are approved by the FDA for treatment of depression in the United States. They are *phenelzine* (Nardil), *tranylcypromine* (Parnate), *isocarboxazide* (Marplan), and *selegiline* (EMSAM).

Pharmacology

A clinically relevant classification of MAOIs is based on three characteristics: (1) hydrazine vs. non-hydrazine structure; (2) selectivity for MAO-A or MAO-B; (3) reversibility of MAO inhibition. Phenelzine and isocarboxazid are hydrazines. The non-hydrazine MAOIs, tranylcypromine and selegiline, are arylalkamines. Hydrazine derivatives may be associated with hepatotoxicity, requiring monitoring of liver enzymes during treatment.

Monoamine oxidase is an enzyme located principally on the outer membrane of mitochondria. Its role is oxidative deamination of monoamines, many of which modulate mood states. The development of substrate selective MAOIs in the 1960s provided evidence for the existence of two forms of the enzyme: MAO-A and MAO-B. MAO-A selectively deaminates serotonin, norepinephrine, and epinephrine, whereas MAO-B selectively metabolizes tyramine, phenylethylamine, phenylethanolamine, and benzylamine. Both forms are involved in tyramine, tryptamine, and dopamine metabolism, although dopamine is the preferred substrate for MAO-B. Both MAO-A and MAO-B are widely distributed in the human body, with some cells containing both forms while others contain only one. The human brain MAO is 70–95% MAO-B; however, in other species, such as rodents, MAO-A may predominate in the brain. In humans, gut and platelet MAO is primarily Type A.

Although *selegiline* (referred to as *l*-deprenyl in the older research literature) has selectivity for MAO-B at low doses, as the dose increases, it affects both forms of the enzyme. The oral formulation is approved for use as an anti-Parkinson agent, but has also shown promise as an antidepressant at higher doses than used for Parkinsonism. The transdermal formulation of selegiline (EMSAM) is approved for the treatment of depression and offers less risk of food interactions than the antidepressant doses of oral selegiline. Pargyline, a drug that is no longer marketed, but was once used as an antihypertensive, is selective for MAO-B. All other clinically available MAOIs inhibit both MAO-A and MAO-B. An interesting compound is TV-3326, which is a cholinesterase inhibitor affecting both MAO-A and MAO-B, but it differentially inhibits Type A in the brain and does not inhibit Type A in the gut of rabbits (235). The reason for the selectivity is unclear, but possibly related to metabolites. It suggests that it may be possible to develop irreversible MAOIs that do not induce hypertensive crises with tyramine-containing foods. Another intriguing strategy to avoid the tyramine hypertensive reaction has been the development of a transdermal delivery system for selegiline that permits high brain concentrations of the drug to block both Type A and Type B MAO in the brain, but has no effect on intestinal MAO-A. Inhibition of Type A in the brain is necessary for antidepressant effects, whereas gut inhibition causes the tyramine reaction.

Other drugs have been developed that produce reversible MAO inhibition may be reversible, such as moclobemide and brofaromine, neither of which are marketed in the United States. This class of MAOIs is referred to as RIMA (reversible inhibitors of monoamine oxidase-A). The advantages of the reversible agents are fewer risks of tyramine-containing food interactions, because tyramine is able to displace RIMA from MAO-binding sites. In contrast, the agents available in the United

States are classified as irreversible or “suicide enzyme inhibitors” because they form covalent bonds at specific sites on the enzyme. Phenelzine inactivates the flavin group and phenelzine the sulfhydryl group. There is some evidence to suggest that MAO activity may return more quickly following discontinuation of tranylcypromine (3–5 days) compared to phenelzine. There is considerable variability among patients; therefore, most clinicians follow the manufacturer’s guideline of a 10- to 14-day interval after discontinuing an MAOI prior to starting a drug that has the potential for an adverse interaction.

The pharmacological properties of available agents have not been well studied, although there has been renewed interest in the area (236). Phenelzine (Nardil) is rapidly absorbed after oral administration, with maximum concentrations occurring 2–4 h post-dose and it has a short elimination half-life (1.5–4 h). On the other hand, the pharmacodynamic effects are long lasting, the result of irreversible MAO inhibition. The pathways of metabolism (236) are not well known; however, phenelzine is both a substrate and inhibitor of MAO, and this pathway may lead to the production of phenylacetic acid. Intermediate metabolites may be phenylethylidene hydrazine and 1-2-phenylethylidiazene, also resulting from the action of MAO. Another metabolite is believed to be phenylethylamine (PEA). Substantial levels of phenylethylamine may derive both from metabolism of phenelzine and from inhibition of endogenous metabolism (PEA is a substrate of MAO). Another pathway probably involves ring-hydroxylation leading to the formation of *p*-hydroxyphenelzine and via MAO to *p*-hydroxyphenylacetic acid. Contrary to early studies, it is now generally believed that despite its structural similarity to isoniazid, phenelzine acetylation is only a minor pathway, but low levels of *N*-acetyl phenelzine have also been reported. The contributions of the metabolites to clinical effects are not known.

Tranylcypromine (Parnate) is also rapidly absorbed with peak plasma levels occurring 1–2 h after an oral dose. It too is rapidly eliminated, with a $t_{1/2}$ of less than 2 h; however, a single 10 mg dose can produce MAO inhibition lasting as long as 1 week. Human metabolic pathways remain uncertain. Perhaps the most controversy has centered on the issue of whether tranylcypromine is metabolized to amphetamine, which was detected in the plasma of a patient who took an overdose of tranylcypromine (237). More recent studies have not detected amphetamine after any dose of tranylcypromine in humans or animals (238, 239). Most of the information on tranylcypromine metabolites is derived from animal studies, and their clinical relevance is not established. Tranylcypromine is marketed as a racemic mixture and studies indicate that S-tranylcypromine is absorbed more rapidly, metabolized more slowly, and reaches higher levels than R-tranylcypromine (240, 241). R-tranylcypromine is a more potent inhibitor of MAO, but is less potent in inhibiting catecholamine reuptake than S-tranylcypromine (236).

We are unaware of published studies on the human pharmacokinetics of isocarboxazid (Marplan).

Selegiline (Eldepryl) has antidepressant effects at oral doses of 40–60 mg daily, although it is not approved by the FDA for this use. Its absorption is increased by food, and its elimination half-life is 2 h after a single dose, but 10 h at steady state. With oral administration, there is wide variability in selegiline metabolism among individuals. Its primary metabolite, desmethylselegiline, possesses MAO-B inhibiting

activity; although it is less potent than the parent compound, it is present in higher concentrations. Other metabolites include L-amphetamine and L-methamphetamine; however, the concentrations of these metabolites are thought to be too low to contribute to the drug's therapeutic effects. Even at the 10 mg oral dose used to treat Parkinsonism, MAO-B selectivity is not absolute, and hypertensive reactions after ingestion of tyramine have occasionally been observed. As the dose increases, selectivity is lost, and although the exact dose at which selectivity is lost varies, at doses over 30 mg daily, tyramine restrictions should be instituted.

Emsam™ is FDA approved for major depressive disorder. Elimination half-life of selegiline with this transdermal delivery system ("patch") is 18 h in single dosing, and 22–30 h with chronic dosing. Time to reach steady state with the patch is 4–5 days. The Emsam™ patch is applied to dry, intact skin with a starting dose of 6 mg/24 h. If dose increases are indicated, they should occur in increments of 3 mg/24 h, up to a maximal dose of 12 mg/24 h at 2-week intervals. A tyramine-restricted diet is required with doses of 9 mg/24 h or higher and must be continued for 2 weeks after stopping the drug. As with other MAOIs, serious drug–drug interactions occur especially with serotonergic agents which can lead to a serotonin syndrome. Emsam™ should not be coadministered with other antidepressants, tramadol, methadone, meperidine, or drugs that have MAOI activity. It is not approved for use in children and has the same FDA black box warning concerning suicide as other antidepressants. The drug is generally well tolerated with the most common side effect being a skin reaction at the application site.

Reversible inhibitors of monoamine oxidase Type A (RIMAs) include moclobemide and brofaromine. Moclobemide and brofaromine both have proven antidepressant efficacy and are considered as effective and better tolerated than the tricyclic antidepressants (TCAs) (69, 242–244). RIMAs are also thought to have a much improved side effect profile due to their reversibility and selectivity. Although not entirely free of risk, they may be less likely to be associated with the serotonin syndrome based on significantly smaller number of reported cases compared to the traditional MAOIs (245). At this time, brofaromine is not being developed as an antidepressant for reasons unrelated to its adverse effects or efficacy. It had been studied as a possible treatment for panic disorder, and clinical improvements in anxiety symptoms and subsequent reduction in agoraphobic avoidance were found (246).

Moclobemide is widely used throughout much of the world except the United States (31, 247). Moclobemide was found to be comparable to the SSRIs in both efficacy and tolerability (243). It was also found to be better tolerated with an earlier onset of antidepressant activity when compared to clomipramine in a UK-based study (244).

Conventional explanations of the mechanism of MAOIs' antidepressant action are consistent with the biogenic amine hypothesis of depression, attributing their effects to inactivation of an enzyme responsible for catabolic metabolism of these amines which results in increased concentration of norepinephrine, dopamine, serotonin, and trace amines in the brain (31). In turn, these effects lead ultimately to changes in gene expression (see SSRI section, and Chapter "Biological Theories of Depression and Implications for Current and New Treatments", this volume). Although an integrative theory has appeal, it should not be misinterpreted to mean

that all MAOIs act identically. There are at least three related mechanisms that have been identified that may contribute to the therapeutic actions MAOIs: (1) inhibition of metabolism of brain biogenic amines, including trace amines such as phenylethylamine, tyramine, and octopamine; (2) enhanced neurotransmitter release, blockade of synaptic reuptake, and/or direct receptor effects; and (3) inhibition of other enzymes, altering other neurotransmitters.

Both phenelzine and tranylcypromine have direct effects on reuptake of dopamine, noradrenaline, and to a lesser extent serotonin. They have been reported to down-regulate β_1 , β_2 , and α_2 adrenoreceptors, and down-regulate the serotonin somatodendritic autoreceptor. Tryptamine receptors are reduced in rat cortex after chronic tranylcypromine administration, and 5-HT₂ receptors are decreased. Phenelzine and/or its metabolites inhibit γ -aminobutyric acid and alanine transaminases (leading to elevation in brain GABA and alanine), dopamine- β -hydroxylase, tryptophan pyrolyase, aromatic amino acid decarboxylase, and tyramine amino transaminase.

Clinical Use

MAOIs are now considered third or fourth-line agents in depression due to the potential for drug–drug and drug–food interactions. They have established efficacy in atypical depression, bipolar depression, and dysthymia, and some studies have even found them superior to other established antidepressants (244, 246, 248–252). MAOIs have also been effective in the treatment of depression in the elderly (253). MAOIs were as effective as the tricyclics in all recent controlled studies of depressed patients with either typical (unipolar) or atypical depression. Phenelzine’s superiority to imipramine, for example, was demonstrated in atypical depression (254). Other studies support MAOI’s advantages for treatment of patients with atypical depression (249, 250). Some have argued that higher than usual doses of MAOI may be needed in severely depressed patients and those who failed treatment with a TCA (255).

The use of MAOIs in patients who failed trials with other antidepressants is well supported (250, 255–257). In a double-blind crossover trial, phenelzine was effective in up to 67% of depressed outpatients who were not responding to treatment with imipramine (248). Tranylcypromine in combination with lithium was effective in treating depression in 12 treatment refractory patients (256). Tranylcypromine was found more effective than imipramine for bipolar depression and is often used to treat patients in the depressive phases of the illness (258). In bipolar patients, who developed manic states associated with antidepressant treatment, those treated with MAOIs experienced milder and shorter manic episodes than patients treated with SSRIs or TCAs (77).

MAOIs are also effective in dysthymia, anxiety, and phobic disorders (251). There are also some reports of efficacy in PTSD and personality disorders, although the data are conflicting (130, 259–261).

Adverse Effects

The older MAOIs have been limited in use as a consequence of their potential for toxicity. Of greatest concern have been drug–drug interactions with sympathomimetic amines and the food–drug interaction with tyramine, both of which may cause a hypertensive crisis. Another serious adverse effect is the serotonin syndrome, which can occur when MAOIs are coadministered with SSRIs (83). Other significant side effects include dizziness, hypotension, liver toxicity, dry mouth with GI upset, blurred vision, urinary retention/hesitancy, headache, fatigue late in the day, skin rashes, weight gain, pedal edema, and paresthesias. Muscle pain and paresthesias may respond to 100 mg of vitamin B6 (pyridoxine). Phenelzine is known to cause sedation, especially late in the day; tranylcypromine can cause insomnia. Hypotension, particularly orthostatic hypotension, is a major concern in treating elderly patients as this increases their risk for falls and fractures. We have not found a consistently effective way to manage orthostatic hypotension, although some clinicians recommend increased fluid and salt intake, fludrocortisone 0.3–0.8 mg daily dose, and support hose.

Sexual dysfunction such as decreased libido, erectile dysfunction, and inhibition of ejaculation in males and anorgasmia in females has been reported (97). These are common problems and have been shown to occur with all of MAOIs. Some of these are known to resolve over time; for example, spontaneous remission of MAOI-induced anorgasmia has been reported (262). It is also worth noting that rates of sexual effects with MAOIs seem to be equivalent to those of TCA drugs and significantly lower than those with SSRIs (96).

Hypertensive Crises

In the 1960s, there were several case reports of a sudden emergence of hypertension in patients taking MAOIs who were exposed to aged cheese. The name “cheese reaction” was coined by Asatoor et al. in 1963 who hypothesized that the combination of MAOIs with the pressor tyramine in cheese was responsible (263). Dietary precautions limiting ingestion of tyramine-containing foods have greatly increased the safety of MAOI treatment. It is generally accepted that greater than 10 mg of tyramine must be ingested to produce a clinically significant interaction. Symptoms may include severe headache, nausea, neck stiffness, diaphoresis, mydriasis, neuromuscular irritability, occasionally cardiac arrhythmias, and severe hypertension (263–265). Hypertensive crises are managed with intravenous phentolamine in closely monitored medical settings. Some clinicians advise patients to take oral nifedipine (10 mg) if hypertension develops.

Our dietary recommendations are shown in Table 11.

Table 11 Dietary restrictions with MAOI therapy (see (407, 408) for tyramine content of specific foods)

Contraindicated	Moderate restrictions	Relative restrictions	Unnecessary to restrict
<i>Aged cheese</i> (English Stilton, Blue Cheese, 3-year-old white, Old Cheddar and others)	<i>Bottled or canned beer</i> (highest contents have 1–1.5 mg tyramine per serving)	<i>Red or white wine</i> (most have less than 0.5 mg tyramine per serving)	<i>Bananas</i>
<i>Marmite yeast</i>	<i>Pizza</i> (caution patients about different types of cheeses that may be used)	<i>Banana peel or overripe bananas</i> (1.4 mg tyramine per peel)	<i>Chocolate</i>
<i>Sauerkraut</i>		<i>Distilled spirits</i> (most do not contain tyramine, but some MAOI inhibit acetaldehyde metabolism creating a potential for a disulfiram-like effect)	<i>Fresh/mild cheeses</i>
<i>Some aged/cured meats</i> (salami contains 5.6 mg, mortadella 5.5 mg, air-dried sausage 3.8 mg tyramine/30 g)			<i>Fresh meat</i>
<i>Tap beer</i>			<i>Pickled/smoked fish</i>
<i>Improperly stored meats or fish</i>			<i>Yeast extracts, except Marmite</i>
<i>Soy sauce</i> (tyramine content is highly variable)			<i>Chicken liver</i> (little evidence unless not fresh, by day 5 contains 1.5 mg tyramine/30 g, while undetectable at day 1)
<i>Soybean</i>			
<i>Tofu</i>			
<i>Fava Beans</i> (reactions not related to tyramine content, which is negligible)			

Drug–Drug Interactions

The “serotonin syndrome” has been reported with concurrent administration of MAOI and drugs that increase serotonin activity. Most common drug interactions associated with serotonin syndrome were combinations of an MAOI and L-tryptophan (removed from the US market because of an independent association with eosinophilia-myalgia syndrome), and fluoxetine (83). There is also a report of the development of serotonin syndrome in patients who were started on clomipramine 4 weeks after discontinuation of clorgyline (MAO-A inhibitor) (83, 266). A fatal case of serotonin syndrome occurred after combined moclobemide and citalopram intoxication in a Belgian patient with history of depression and prior suicide attempts (85). The serotonin syndrome consists of confusion or hypomania, agitation or restlessness, tremor, hyperreflexia, myoclonus, fever, diaphoresis, diarrhea, incoordination, and shivering. In general, the treatment for the serotonin syndrome should be immediate withdrawal of the offending agent and supportive measures.

Sympathomimetic amines, often contained in cold remedies, weight control products, and dietary supplements, can cause hypertensive reactions with MAOIs. Both indirect-acting sympathomimetics (more dangerous) as well as direct-acting (less dangerous) sympathomimetics may cause a hypertensive crisis when administered with MAOIs. The following indirect-acting vasopressors produce their pressor effects through the release of bound intraneuronal stores of norepinephrine and dopamine: amphetamine, methamphetamine, cyclopentamine, ephedrine, pseudoephedrine, L-dopa, dopamine, mephentermine, phentermine, metaraminol, methylphenidate, phenylpropanolamine, and tyramine. The indirect-acting agents are generally believed to be more dangerous than direct-acting amines, with the indirect agents, ephedrine, pseudoephedrine, and phenylpropanolamine, being especially hazardous (267). An additional concern is the use of MAOI antidepressants with drugs used for medical conditions that also inhibit monoamine oxidase, e.g., the antibiotic linezolid (Zyvox).

Overdose

MAOIs are dangerous in overdose, and suicidal patients may exploit the inherent toxicity to commit suicide (268). A fatal dose is considered to be 4–6 mg/kg body weight (69). The onset of symptoms usually occurs 6–12 h after ingestion of a toxic dose, but has been known to be delayed by 24 h. Clinical presentation of a patient who overdosed with an MAOI may include fainting, anxiety, flushing and sweating, headachy, tachycardia, and tremor in early stages; this will progress to agitation, coma, seizures, severe hypotension, and possible cardiac arrest (69). Also, physical tolerance and dependence has been reported with tranlycypromine, with one patient taking doses as high as 440 mg daily (269).

Augmentation Strategies

Combinations of Antidepressants

Some clinicians make a distinction between “combination” and “augmentation” therapies, with the former referring to the use of antidepressants in combination, and the latter referring to the use of drugs that are not antidepressants to augment-approved antidepressants. In our view, this is an artificial distinction, and prefer the term “augmentation” to refer to any combination of medications used to enhance antidepressant response. We recognize that a growing segment of clinical pharmacologists are recommending augmentation therapy at the initiation of treatment, with a rationale that the “best” treatment should be initiated at the start of treatment. This reflects, in part, that primary care providers provide initial pharmacotherapy for depression, and referral to psychiatrists occurs only after monotherapy with antidepressants have failed. The problem with this approach is that there are no augmentation therapies that have superior efficacy.

We recommend augmentation approaches only after monotherapy with two different antidepressants has failed, an opinion based on the observation that at least 50% of out-of-class switches result in treatment response (270–272). In instances of partial responders who have been taking adequate doses for sufficient time, we are inclined to follow an augmentation strategy. Once a decision has been made to augment, a number of options are available. The most common augmentation strategy is to combine antidepressants from different classes. With SSRI, our current practice is to add mirtazapine in doses of 15–30 mg, a strategy that is supported by the somewhat limited literature on the topic (273–275). Alternatively, we employ bupropion augmentation which has a small body of evidence supporting its efficacy in augmentation of SSRIs (276–278) and survey data that indicate it is the most popular SSRI augmentation strategy among clinicians (279). Addition of low doses of a TCA, such as desipramine or nortriptyline, has yielded mixed results (280–283).

Lithium has moderately strong evidence supporting its efficacy as an augmentation agent; however, it is less commonly used than other approaches. The STAR*D study found poor tolerability compared to T3 augmentation. Studies in the early 1980s found that the addition of lithium to TCAs in non-responding patients with unipolar depression resulted in improvement in depression (284, 285) and was comparable to thyroid (T3) supplementation, both of which were better than placebo (286). Other investigators reported similar results, including efficacy in potentiating MAOIs, although lack of efficacy and toxicity has also been reported (287–289). Most but not all studies have found that lithium is also effective in augmentation of SSRIs (281, 290–292). We suspect that the reasons for less frequent use of lithium are its low therapeutic index and the necessity for monitoring serum levels. Typical augmentation doses are 600–1,200 mg daily to produce a target serum level of 0.6–0.9 mEq/L.

Atypical Antipsychotic Augmentation of SSRI

The strongest efficacy data for augmentation of partial antidepressant response to SSRI is the growing clinical trial data on atypical antipsychotics. Despite the strong data for efficacy, it is rarely our first choice for augmentation because there are several unanswered questions regarding optimal dosing and long-term adverse effects. One of us (DAC) began using risperidone in doses of 0.5–1.0 mg as an adjunct to SSRI, and occasionally as a monotherapy in treatment-resistant depression following reports suggesting the effectiveness of this approach (293, 294). We limited it to patients with a partial SSRI response and those who demonstrated depressive features that had symptoms that were resistant to psychotherapy. These included guilt out of proportion to realistic events, inability to engage in introspection, perseveration of ideas of wrongdoing that were exaggerated, and recognition that their beliefs were not a reflection of reality (in other words, maintained capacity for introspection). While these symptoms resembled psychotic depression, the quality of their interpersonal relationships and level of impairment was not consistent with that diagnosis. Following the Ostroff and Nelson (1999) report, we used low doses of risperidone to treat depressive symptoms. To our surprise, the results were a dramatic improvement in symptoms, and since then we have used both risperidone and quetiapine with very good success. Aripiprazole would probably have produced similar results. Since that time, there is increasing evidence that four atypical antipsychotics are effective in augmentation of SSRI: olanzapine, quetiapine, aripiprazole, and risperidone (295–299). The combination product of olanzapine and fluoxetine, marketed under the trade name of Symbax, is approved by the US FDA for use in treatment-resistant depression (defined as failure to respond to treatment with two trials of antidepressants at adequate doses for sufficient time). Aripiprazole is approved by the FDA for adjunctive treatment of major depressive disorder “who had an inadequate response to antidepressant therapy during the current episode.” Quetiapine is also approved for use as an adjunct to SSRI, but there is strong evidence of its efficacy as monotherapy of depression, where it has a more rapid onset than duloxetine with fewer adverse effects leading to discontinuation (300).

The mechanism of antidepressant effect of atypical antipsychotics has not been established. The action of aripiprazole as a partial agonist at D2 and D3, 5-HT_{1A} receptors, and an antagonist at 5-HT₂ receptors is consistent with an antidepressant action. Quetiapine has moderate antagonism of D2 and serotonin 5-HT_{1A}, 5-HT_{2A} receptors and its metabolite norquetiapine inhibits the norepinephrine transporter. The antidepressant effects of risperidone may be due to its high affinity for α -2-adrenergic receptors which could enhance norepinephrine neuronal firing and release (301).

It appears that lower doses should be used for atypical antipsychotics when they are used as antidepressants as opposed to antipsychotic agents. For example, 300 mg of quetiapine, 0.5–2.0 mg risperidone, and 10 mg aripiprazole appear to be the optimal antidepressant doses. The combination product of olanzapine and fluoxetine (Symbyax) recommends doses of olanzapine of 6–18 mg of olanzapine with 25–75 mg of fluoxetine.

Despite strong data for efficacy, adequate dose response studies have not been done, long-term efficacy has not been studied, and antipsychotics as a class have been associated with serious adverse effects such as metabolic syndrome and extrapyramidal syndromes (although EPS are of a less concern with atypicals, they can occur).

Buspirone

Conflicting data exist concerning the efficacy of buspirone augmentation. Many open trials have suggested efficacy as an augmentation strategy (302–305); however, placebo-controlled trials have not fully supported the clinical reports. In a study of 102 outpatients with MDD who did not have an adequate response to 6 weeks of treatment with fluoxetine or citalopram, buspirone (doses of 10–30 mg b.i.d.) or placebo was added after a 2-week placebo wash-in period (306). Although buspirone was superior to placebo on the MADRS after 1 week, no difference was found at 6 weeks, except in patients with baseline MADRS scores greater than 30. In another study of 119 patients who failed to respond to paroxetine or placebo after a minimum of 4 weeks, buspirone or placebo was added for an additional 4 weeks (307). Although the combinations were well tolerated, there was no difference between groups, with both showing substantial improvement on the Clinical Global Impression Scale (50.9% buspirone, 46.7% placebo). An open-label, 2-week, follow-up phase with buspirone augmentation produced a response rate of 69.4%. Despite the lack of strong support for efficacy, we have found that the addition of buspirone in doses of 30–50 mg daily produces dramatic results in some patients; however, we recognize that this may be a placebo effect.

Psychostimulants

Methylphenidate is a secondary amine stimulant that exists as four isomers, with the marketed preparation containing the *d,l*-threo racemate, with *d*-threo believed to be responsible for therapeutic activity. The major metabolite is ritalinic acid (approximately 70%), with smaller amounts of *p*-hydroxyritalinic acid (1%) and 6-oxoritalinic acid (2%) also produced. It is believed that only the parent compound contributes to therapeutic effects. In its standard preparation, methylphenidate reaches peak plasma concentrations in 1–2 h and has an elimination half-life of 2–3 h, and exhibits dose proportionality through the therapeutic range (308). Newer preparations of methylphenidate include *d*-methylphenidate (Focalin®), and long-acting preparations (Metadate CD®, Concerta®, Ritalin-SR®). Dextroamphetamine is available as Dexedrine® and Dexedrine Spansule®. Adderall® and Adderall-XR® contain a mixture of *d*-amphetamine and *l*-amphetamine. Lisdexamfetamine (Vyvanse) is a prodrug of dextroamphetamine.

The pharmacologic actions of both methylphenidate and dextroamphetamine are complex. Both drugs affect dopamine and norepinephrine reuptake, although there may be subtle differences in the mechanism. Also, both drugs promote release of monoamines, but methylphenidate acts on reserpine-sensitive storage pools, while dextroamphetamine releases them from newly synthesized stores. Both drugs affect α -adrenergic receptors. Effects of stimulants on acetylcholine, serotonin, glutamate, and GABA result from the influence of dopamine on these systems and in some cases, from direct actions at receptors. Their actions in the brain during PET studies also suggest differences among stimulants.

There has been a long history of stimulant therapy in depression, both as monotherapy in the medically ill and as an augmenting agent (309–315). In the Boston area, it is not uncommon for stimulants to be prescribed as sole agents, or in combination with antidepressants. The scientific literature supporting the practice is weak, but clinical experience, as well as survey data of psychiatrists in the United States and Canada, provides support for the practice. The body of research in this area appears to be growing (316, 317).

In clinical practice, methylphenidate can be started at 10 mg doses and increased gradually up to 80 mg daily. We use approximately half that dose for dextroamphetamine therapy. Frequent patient monitoring, both for adverse effects and misuse, is necessary. Once the proper dose is achieved, response is rapid. Modafinil (Provigil®), a medication for the treatment of narcolepsy, has also been used in doses of 100–200 mg daily to augment and hasten antidepressant response (318, 319).

Thyroid Hormone

A series of studies of thyroid augmentation of antidepressant response have been reported by Prange and associates (320). In their first study, 20 euthyroid patients (16 women and 4 men) most of whom were diagnosed as unipolar retarded depression, were given imipramine (150 mg) plus 25 μ g of triiodothyronine (T3). Reductions in HAM-D scores were greater and occurred more rapidly in the T3 group. Other studies from the same research group found that women with nonretarded depressions also responded to T3 augmentation but men did not. In a study of T3 augmentation of amitriptyline, patients who were treated with 40 μ g of T3 with amitriptyline (100 mg) improved more rapidly than those on 20 μ g of T3 or placebo; women had better responses than men (321). An open trial using clomipramine had similar results (322). Several other studies have also found that patients who were unresponsive to tricyclic antidepressants improved with the addition of T3 in doses of 25–50 μ g (323–326). SSRI augmentation with T3 appears to be efficacious and well tolerated (327–329). On the other hand, some studies indicate a lack of efficacy (330) or efficacy only for those patients with elevated TSH response to TRH (331). It is not clear whether T3 augmentation is superior to thyroxine (T4) or lithium augmentation. One small study suggested that T4 augmentation should precede lithium augmentation

(332). The weight of the evidence suggests that T3 is more effective than T4 augmentation; however, some studies suggest that it may be necessary to administer high doses of T4 for long periods of time to obtain maximum benefit. An open-label study that administered T4 at a mean dose of 482 $\mu\text{g/day}$ for 8 weeks reported a substantial improvement in depression in over half of the sample (333).

A meta-analysis of 6 double-blind, placebo-controlled clinical trials evaluating coadministration of T3 and tricyclic antidepressants concluded that adjunctive T3 led to a more rapid clinical response (334). Women were more likely to benefit from the administration of T3 than men (334). The mechanism of action is believed to be related to correction of underlying subsyndromal thyroid dysfunction or direct effects on adrenergic activity.

In clinical practice, T3 (Cytomel) is begun in doses ranging from 12.5 to 25 μg and may be increased weekly up to 50 $\mu\text{g/day}$. One to 4 weeks is considered an adequate trial of T3 augmentation. It should be used with caution in patients with arrhythmias, hypertension, and cardiac disease. Some practitioners believe that the best response occurs in women, patients with mild thyroid abnormalities, and individuals with severe or retarded depression.

Testosterone

Testosterone supplementation may improve depressive symptoms for a subset of male patients with low or borderline testosterone levels suffering from refractory depression. A randomized, double-blind, placebo-controlled trial in 23 patients with a low or borderline serum testosterone level (range 100–350 ng/dl; normal range is 270–1,070 ng/dl) who met the DSM-IV criteria for current MDD and were being treated with antidepressant medications prior to and during the trial received either testosterone gel (1% gel, 10 g/day) or placebo for 8 weeks (335). There was significantly greater improvement in HAM-D scores in the testosterone-treated group compared to placebo in both the vegetative and affective symptom subscales of the HAM-D Scale. Overall, the testosterone gel was well tolerated. One patient in the study experienced exacerbation of benign prostatic hyperplasia, which may be attributed to testosterone supplementation and was withdrawn from the study, although the relationship of testosterone supplementation to prostate cancer has been challenged. The mechanism of testosterone's antidepressant action is not known.

Estrogen

The increased prevalence of depression in women during perimenopause and postmenopause has led to several studies examining estrogen replacement and

augmentation therapy for women during these stages of life. Perimenopause is the phase before menopause, which continues until menstruation has ceased for 12 consecutive months. Common symptoms include hot flashes, decreased libido, sleep disruption, and depression. In one study, perimenopausal women with major depression, dysthymic disorder, or minor depressive disorder received transdermal patches of 17[β]-estradiol (100 μ g) or placebo in a 12-week study (336). Sixty-eight percent of women treated with estradiol had remission of depression compared to 20% in the placebo group (336). An earlier study also found that estrogen was superior to placebo in reducing depressive symptoms in perimenopausal women (337). A small study of 16 perimenopausal women found that estrogen replacement therapy was effective in treating depression (338). Other studies have found that both transdermal patches and sublingual estradiol improved mood in women with premenstrual dysphoric disorder and postpartum depression (339–341). Other studies have not found efficacy of estrogen replacement therapy for depression (342–344). In a review of the literature, Epperson and associates (345) reported that five studies found estrogen replacement therapy more effective than placebo in a mixed group of perimenopausal and postmenopausal women and 5 found it as effective as placebo. One study (346) found that estrogen was superior to placebo in perimenopausal, but not postmenopausal women. In an early study, estrogen 5–25 mg/day, which is 5–25 times the replacement dose, was more effective than placebo in the treatment of women with depression that were unresponsive to antidepressants (347). A more recent study in postmenopausal Chinese women did not find differences between 1 and 2 mg of oral estradiol and placebo on symptoms of anxiety and depression (348).

In addition to estrogen replacement as a monotherapy, it has also been used as an augmentation strategy in women with menopausal depression. Fluoxetine in combination with estrogen replacement therapy proved superior to fluoxetine alone in a single study (349). On the other hand, Oppenheim and colleagues did not find estrogen augmentation effective when administered with imipramine (345, 350).

In summary, data are conflicting regarding the efficacy of estrogen replacement therapy in perimenopausal or postmenopausal women with depression. Some investigators have attributed inconsistent findings to the use of poorly bioavailable oral preparations, failure to use laboratory measures to confirm menopausal status, and wide variability of diagnostic and outcome measures (336). The mechanism of action of estrogen is unknown; however, a substantial body of evidence indicates that it influences monoamine and GABA systems. There is little evidence to support the use of estrogen augmentation with cyclic antidepressants, although some evidence supports its value in combination with fluoxetine. Its use as an augmentation agent is also limited by the risks of toxicity when used in combination with imipramine, which is most likely a consequence of a pharmacokinetic interaction. Increased risk of carcinoma and cardiovascular disease may be associated with estrogen replacement (351–354).

Amantadine

A small series of patients with a partial response to imipramine, SSRI, and mixed action antidepressants improved after amantadine was added to the antidepressant (355, 356). Larger controlled studies are required to replicate this finding; however, amantadine is a NMDA antagonist and promotes increased dopamine, which provides a rationale for studying this combination in adequately designed trials.

Alternative and Non-Traditional Antidepressants

St John's Wort

St John's Wort (*Hypericum perforatum*, available commercially as *Hypericum* alcohol extract standardized by level of hypericin) has been used as a traditional herbal medicine for more than 2,000 years. Pharmacologically, the plant contains naphthodianthrone (such as hypericin and pseudohypericin), phloroglucinols (such as hyperforin and adhyperforin), flavonoids, phenylpropanes, proanthocyanidins, xanthenes, and amino acids (357–359). It remains uncertain which of these constituents are responsible for antidepressant effects. Although extracts have been standardized for hypericin content, this component may not cross the blood–brain barrier (359). Consequently, hyperforin has been the focus of recent research. It inhibits reuptake of serotonin, dopamine, norepinephrine, GABA, and glutamate (360). It also has affinity for opioid receptors and 5-HT₆ and 5-HT₇ receptors. It may also have a direct effect on ion channels. Adhyperforin has similar effects on monoamine reuptake. Pseudohypericin inhibits dopamine- β -hydroxylase. Flavonoids and xanthenes inhibit MAO-A and the former also inhibit catechol-*O*-methyl-transferase (COMT). Amentoflavone binds to the benzodiazepine receptor. Similar to synthetic antidepressants, chronic administration of *St John's wort* down-regulates β -receptors in animal models.

Several standardized extracts are available in Europe; however, preparations available in the United States may vary in concentrations of active constituents. Of particular importance is that most preparations used in clinical trials have not been standardized to hyperforin. Typical doses range from 900 to 1,800 mg/day of the herb administered in 2 or 3 divided doses. Initial doses are typically one-third of that with weekly increases as needed to the maximum dose (296, 357, 358, 361, 362).

Adverse Effects

Extracts of *St John's wort* have been well tolerated under the conditions of physician supervision, monotherapy, and controlled doses of standardized extracts used in clinical trials (358, 361–363). The most common adverse effects reported in

clinical trials are headache, dry mouth, gastrointestinal upset, nausea, dizziness, sedation, fatigue, and insomnia (296, 364, 365). Among the more serious adverse effects, which are very rare, are photosensitivity and possible induction of manic symptoms (362). A serotonin syndrome due to St John's wort had been reported in patients using St John's wort together with an SSRI or other antidepressants such as nefazodone and venlafaxine (358, 366, 367).

Drug–Drug Interactions

Due to its induction of P-glycoprotein (a transporter protein in the blood–brain barrier and intestine) (38, 368) and its induction of P450 cytochromes 3A4, 1A2, and possibly 2C9, St John's wort has the potential to interact with other medications (358, 369). St John's wort can decrease plasma levels of many prescribed drugs, such as anticoagulants, oral contraceptives, and antiviral agents. An interaction between St John's wort and cyclosporine (metabolized by 3A4) resulted in cyclosporine's reduced activity and organ rejection after transplantation (370, 371). Interactions have resulted in decreased international normalized ratio (INR) in patients on warfarin (metabolized by CYP2C9 [S-warfarin] and CYP1A2 [R-warfarin]) (358, 372, 373), and decreased digoxin levels when these drugs are administered with St John's wort (374). Bioavailability of indinavir, cyclosporine, and digoxin may be altered as a result of P-glycoprotein induction (368).

In the United Kingdom and Sweden, where St John's wort is used extensively for medicinal purposes along with other herbal remedies, clinical interactions between St John's wort and other licensed medications were deemed serious enough to warrant a change in product labeling of the involved medications and to warn health care practitioners and patients about potential for such interactions (369).

Efficacy

Numerous European clinical trials examined efficacy of St John's wort. Most of these studies have found St John's wort more effective than placebo and at least as effective as a reference antidepressant for short-term treatment of mild to moderate depression (361, 363, 365).

A randomized, double-blind, multicenter clinical trial studied 263 German outpatients with the diagnosis of moderate depression according to International Classification of Diseases, 10th revision (ICD-10), who were randomized to either placebo, imipramine, 100 mg/day or St John's wort extract 1,050 mg/day, for 8 weeks (361). The investigators concluded that the standardized St John's wort extract was more effective than placebo and as effective as imipramine in reducing HAM-D scores, Hamilton Rating Scale for Anxiety (HAM-A) scores, and Clinical Global Impression (375) scores (361). The authors themselves note the study limitation of suboptimal dosing of imipramine (361).

Several meta-analyses and systematic reviews have supported efficacy of St John's wort in mild depression (364, 376, 377). Linde et al (376) conducted a

meta-analysis of 23 randomized clinical trials of acceptable methodologic quality that included a total of 1,757 outpatients with mild to moderate depression. They found that St John's wort extract was significantly superior to placebo and as effective as a standard antidepressant (imipramine, amitriptyline, or maprotiline).

Gaster and Holroyd (364) identified eight randomized, controlled, double-blind trials that were of acceptable methodological quality. They concluded that St John's wort is more effective than placebo in the treatment of mild to moderate depression. The investigators also noted that there were insufficient data to assess the efficacy of St John's wort in severe depression or to compare its efficacy to other antidepressants.

Kasper and Dienel (377) performed a meta-analysis on the original published data of three double-blind, randomized multicenter trials. In these trials, a total of 544 patients with mild to moderate depression based on DSM-IV diagnostic criteria received 900 mg/day of St John's wort (WS 5570 or WS 5572 standardized extracts) or placebo for 6 weeks. The authors found that St John's wort was significantly superior to placebo for treating mild to moderate depression and was especially effective in reducing the core symptoms of depression.

Serious methodological flaws exist in most published clinical trials (296, 364, 376, 377). Common problems are failure to use standardized diagnostic instruments or rating scales, short study duration, and administration of ratings by inexperienced investigators (296, 364, 376, 377). The earliest studies were limited by their small size, short duration, lack of either placebo or active reference drug arm, differences in preparation of the extract, failure to describe randomization and blinding methods, to measure compliance, or to report or explain the dropout rate (358, 378). In those studies using a well-established antidepressant for comparison, results may have been skewed by underdosing the reference drug. Doses such as 100 mg/day or less of imipramine or amitriptyline were used without plasma level monitoring to insure compliance or adequate dosing (296, 376). In many studies, the blind may have been transparent if care was not taken to mask the peculiar taste of St John's wort extract, or if a specific constellation of side effects allowed investigators to guess the treatment arm (296, 376).

The first major American randomized, double-blind, placebo-controlled clinical trial was conducted by Shelton et al. (296). While criticizing prior studies for methodological flaws and biases, these investigators succeeded in conducting a well-designed, large-scale, multicenter clinical trial. Two hundred patients were recruited through tertiary care centers associated with academic centers in the United States. Participants had a diagnosis of MDD according to DSM-IV criteria and a baseline HAM-D score of at least 20. Care was taken to assure similarity in outward appearance, taste, and smell of placebo and St John's wort preparations, protecting the blind. The study followed a 1-week, single-blind, run-in of placebo, done to minimize the effect of early placebo response, and the treatment arm lasted 8 weeks. The outcome measures were decrease in scores on HAM-D, Beck Depression Inventory (BDI), CGI, or HAM-A. The investigators failed to detect a significant difference in response rates between St John's wort and placebo after 8 weeks of the study; response rates were 26.5% for St John's wort and 18.6% for placebo. It was concluded that St John's wort was not effective in treating MDD.

The American and European study populations were quite different. Shelton and associates recruited subjects from tertiary care outpatient clinics affiliated with academic medical centers. Patients had a diagnosis of MDD and baseline HAM-D scores of at least 20, with an average duration of depression of more than 2 years (296). On the other hand, the population groups studied in Europe came mostly from primary care settings, were not suffering from chronic depression but had either first or recurrent episodes of “mild to moderate” depression with a lower baseline HAM-D scores (296, 377). All of these distinctions make the American patient sample quite different from the European populations studied previously; it may also explain lower response rate for both placebo and the studied compound. Kasper and Dienel (377) suggested that this difference of populations studied accounted for disparate findings of the American and European studies, noting that St John’s wort may not be appropriate for treatment of chronic MDD.

A randomized controlled trial by the Hypericum Depression Trial Study Group of 340 adult outpatients, with major depression and a baseline HAM-D score of at least 20, did not support the use of St John’s wort in the treatment of moderately severe major depression (379). The trial’s two primary outcome measures showed that neither sertraline nor St John’s wort differed significantly from placebo, which may have been due to the low sensitivity of the trial or inadequate doses of sertraline. The investigators indicated that St John’s wort may be most effective in treating less severe major depression, but that this cannot be supported until there are additional efficacy trials.

Conclusion

The efficacy of St John’s wort in major depression has not been established. There is evidence to suggest it may be effective in milder forms of depression. Its clinical use is limited by uncertainty concerning its active components, propensity for drug–drug interactions, and paucity of safety data. Currently, there is no available literature on using St John’s wort in children and adolescents, in patients with major psychiatric comorbidities, or in pregnant or lactating women. The drug–drug interactions associated with St John’s wort limit its use in patients with other medical or psychiatric comorbidities. Its efficacy is not established in moderate to severe major depression. Further research and well-designed clinical trials are needed to determine the efficacy of St John’s wort in the treatment of mood disorders.

SAMe

SAMe (*S*-adenosyl-*l*-methionine 1,4-butanedisulfonate) is a dietary supplement that has been used as an antidepressant by European psychiatrists for approximately 30 years (380). It is a naturally occurring compound which acts as a methyl group donor to multiple substances in the Central Nervous System; thus, it is involved in synthesis of various neurotransmitters (dopamine, serotonin, and

norepinephrine) as well as nucleic acids and proteins (380). SAME is synthesized in the brain from L-methionine, an amino acid. Both folate and methylcobalamin (vitamin B12) are necessary for its production (380). Deficiencies in folate and vitamin B12 have been linked to some types of depression (380). When low plasma concentrations of SAME are found in depressed patients, interventions that increase SAME levels are associated with improved mood (381). Although supporting evidence is lacking, several mechanisms have been suggested to explain SAME's effects in depression. Potentially, SAME could increase neurotransmitter synthesis (e.g., serotonin or norepinephrine synthesis), increase neurotransmitter receptor responsiveness, or increase phospholipid production, which would enhance cell membrane fluidity.

Two meta-analyses of clinical trials of SAME involving over 1,300 patients concluded that SAME had superior efficacy compared to placebo and was equivalent to tricyclic antidepressants (382, 383). More recently, two multicenter studies were conducted in patients with major depression and HAM-D scores 18 or higher (384). The first study compared 1,600 mg orally of SAME per day to 150 mg of imipramine per day orally in a double-blind design. The second study compared 400 mg of SAME per day administered intramuscularly (SAME has very poor oral availability) compared to 150 mg/day of oral imipramine. The primary efficacy measures were HAM-D scores and percent responders on clinical global impression scales. Secondary outcome measures were MADRS scores. Responders were defined as those patients demonstrating a decrease in HAM-D scores of 50% or greater from baseline (384). Responders in both studies ranged from 50 to 59% with no statistical difference between oral or intramuscular SAME and imipramine (384). The failure to include a placebo control group limits these findings. An earlier study reported that 400 mg/day of SAME administered intramuscularly produced an antidepressant effect at 7 and 15 days, which is more rapid than conventional antidepressants (385).

A recently published review of SAME's use in the treatment of depression concluded that doses of oral or parenteral SAME from 200 to 1,600 mg/day were a safe and effective alternative to tricyclics, with a faster possible onset of action and could have a role in augmentation of traditional antidepressants (380). Additional studies of the oral administration of SAME are necessary to establish the efficacy of the oral formulation (386). Evidence to date supports efficacy for parenteral SAME in depression; however, adoption of this route of administration will be difficult in mental health settings. Additional studies of SAME augmentation are needed.

Omega-3 Fatty Acids

The rationale for the use of *omega-3 fatty acids* (OFA) in the treatment of depression is based on converging evidence from diverse theoretical perspectives that seems to link OFAs and mood disorders. First, the epidemiologic evidence suggests that populations with low intake of dietary OFAs (e.g., fish oils) have a higher prevalence of depression than populations consuming large amounts (387). Second,

red blood cell membrane OFAs are lower in depression compared to healthy controls (388, 389) and are correlated with the severity of depression (390). Third, fatty acids are involved in signal transduction in the brain (391).

The OFAs in the brain consist of 6-OFAs (e.g., arachidonic acid) and 3-OFAs [e.g., decosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)]. A preliminary study of 3-OFAs (a combination of 6.2 g EPA and 3.4 g DHA daily) as adjunctive therapy in bipolar patients found it superior to placebo in improving mood and preventing relapse (392–394). In another study of depressed patients who were not responding to antidepressant therapy, the addition of EPA 1 g/day improved HAM-D, MADRS, and BDI scores, whereas placebo and higher doses of ECA did not (391). Both studies found 3-OFAs were well tolerated, with common side effects including loose stools and breath “fish odor.”

At the present time, the efficacy of OFAs in depression has not been established. Although preliminary evidence suggests that 1 g of EPA is effective as an adjunctive therapy, and most authorities believe that EPA is the active component for antidepressant response, neither OFA doses nor optimal composition of fatty acids have been established. There are ongoing clinical trials comparing the efficacy of DHA and EPA (395). In our clinical practice, we have not been impressed with the clinical response to OFAs, even as an adjunct. Many of our patients have been taking OFAs for the cardiac effects, and we have not observed significant changes in mood at the initiation of OFAs or when patients discontinue them. On the other hand, OFAs are unlikely to be associated with severe adverse effects and may be beneficial in preventing cardiovascular disease.

Conclusion

Appropriate clinical use of antidepressants relies on the ability of clinicians to make an accurate diagnosis, rule out medical conditions or substance-induced mood disorders, and differentiate subtypes of depression (e.g., unipolar and bipolar subtypes). Further, the ability to integrate knowledge of the pharmacology of specific drugs and the neuropathophysiology of depression forms the basis of rational prescribing.

Several multisite clinical trials have established approximate equivalent efficacy of all marketed antidepressants, with the clinically relevant differences related to adverse effects, ease of dosing, and safety. SSRIs remain the first-line agents under most circumstances, with mixed action, TCAs, heterocyclics, and MAOIs additional options. Antidepressants are effective across a range of disorders including depression, PTSD, anxiety, and chronic pain. Combination and augmentation therapies have been developed for depressions that are resistant to monotherapy, although evidence to date does not favor a specific approach. Novel treatments, whether developed from herbal preparations or new chemical compounds, are an exciting area for further research, but data supporting their efficacy and safety are limited. Combinations of antidepressants with Transcranial Magnetic Stimulation offers another potential augmentation strategy, however there is a paucity of data addressing this approach.

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