Pharmacology of Antidepressants: Focus on Nefazodone

C. Lindsay DeVane, Pharm.D.; Dale R. Grothe, Pharm.D., B.C.P.P.; and Sherry L. Smith, Pharm.D., B.C.P.P.

The past decade has witnessed the introduction of a diverse group of antidepressants from a variety of distinct chemical classes, each with their own specificity for neurochemical transmitters, receptors, and cytochrome P450 isozymes. This review focuses on nefazodone, a distinct antidepressant with efficacy for the treatment of depression with depression-related anxiety symptoms, an established tolerability profile, and a multimodal mechanism of action. Relevant pharmacologic and pharmacodynamic effects are summarized that support nefazodone as an attractive choice for both the short- and long-term treatment of depression. *(J Clin Psychiatry 2002;63[suppl 1]:10–17)*

Monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) were the primary antidepressants used in clinical practice until momentum for development of drugs to treat affective disorders increased substantially in the 1980s. This drive has been sustained now for more than 20 years. Noticeably, the availability of selective serotonin (5-HT) reuptake inhibitors (SSRIs) in the late 1980s stimulated subsequent development of an array of compounds with diverse structural, biochemical, and clinical characteristics (Table 1). The spectrum of therapeutic activity of the more recently developed drugs continues to be explored with clinical trials in subpopulations of depressed and anxious patients.

While all available antidepressants have been proved effective for short-term (6-week) treatment of recurrent major depression, their utility for relapse prevention in continuation and maintenance therapy and their efficacy in chronic forms of unipolar major depression are less well known.[6–10] Although evidence is accumulating, few clinical trials have extended evaluation for as long as 3 years of maintenance therapy, and only 1 small trial (imipramine vs. placebo) has continued for 5 years.[11] Nonetheless, a unanimity of opinion holds that most patients who have experienced multiple episodes of recurrent major depres-

sion should receive long-term or indefinite maintenance pharmacotherapy.[11] Thus, selection of the most appropriate antidepressant for a specific patient becomes critical for the management and prevention of recurrent major depression. The purpose of this review is to evaluate and compare the pharmacodynamic properties of nefazodone with those of other commonly used antidepressants and to summarize its pharmacologic and pharmacokinetic characteristics.

PHARMACOLOGIC PROFILE OF COMMON ANTIDEPRESSANTS

Most antidepressants exert their primary action on monoamines or their receptors (see Table 1). Affinity for ancillary receptors can often be related to a drug's adverse effect profile. The following discussion regarding several widely used antidepressants will provide perspective on the place of nefazodone among therapeutically useful drugs.

Monoamine Oxidase Inhibitors

Tranylcypromine, isocarboxazid, and phenelzine have all enjoyed widespread use, but the latter is the most fully investigated and clinically used drug. Phenelzine is considered superior to imipramine for the treatment of atypical depression.[12] Sheehan et al.[13] documented the usefulness of phenelzine in the treatment of panic anxiety. Phenelzine is further differentiated as one of the first effective treatments for social phobia.[14] However, unlike in the United Kingdom and elsewhere, MAOIs have not been widely used by American family practitioners, mainly because of the risk of hypertensive crisis, an effect that results from nonselective inhibition of both MAO-A and MAO-B subtypes.

Table 1. Salient Characteristics of Selected Currently Available Antidepressants[a]

Drug/Drug Class	Characteristics
Monoamine oxidase inhibitors (MAOIs) (eg, phenelzine, tranylcypromine)	Nonselective inhibition of MAO-A and MAO-B prevent catabolism of 5-HT and NE. Effective in depression, panic disorder, social anxiety. Relegated to treatment-resistant patients
Tricyclic antidepressants (TCAs) (eg, amitriptyline, imipramine)	Inhibit presynaptic uptake of 5-HT and NE; affinity for postsynaptic H_1, α_1, and muscarinic receptors. Lethal in overdose, poor patient tolerability, and narrow spectrum of antianxiety activity
Bupropion	Imprecise NE and DA reuptake actions; low risk of sedation, weight gain, and sexual dysfunction are clinical advantages. Contraindicated in patients with seizure disorder; seizure potential may limit use in some patients
Selective serotonin reuptake inhibitors (SSRIs) (eg, citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)	Selective pharmacologic effect; effective for depression and multiple anxiety states. Class-related adverse events include nausea, headache, sexual dysfunction, and a withdrawal syndrome
Venlafaxine	Dual 5-HT and NE uptake inhibitor. Rapid titration associated with nausea; high doses may elevate blood pressure. Effective for depression and generalized anxiety disorder
Mirtazapine	Multiple neurotransmitter effects; clinical use limited by drowsiness and weight gain
Nefazodone	Multimodal spectrum of action. Low incidence of sexual dysfunction; positive benefits on sleep parameters. Effective in short- and long-term treatment of depression with anxiety

[a]Data from references 1–5. Abbreviations: 5-HT = serotonin, DA = dopamine, H_1 = histamine type 1, NE = norepinephrine.

Attempts to market specific MAO subtype inhibitors in the United States for the treatment of depression have been unsuccessful. MAO-A is the predominant MAO form in the sympathetic nervous system; norepinephrine is preferentially deaminated in the human brain by MAO-A.[15,16] Preferential inhibition of MAO-A may be more important than MAO-B inhibition for antidepressant efficacy.[17]

At doses lower than recommended for antiparkinsonian effects (i.e., ≤ 10 mg/day), selegiline is selective for the MAO-B type and thus tends to raise dopamine levels relative to norepinephrine or 5-HT.[17] Clorgyline, an investigational agent, preferentially and irreversibly inhibits MAO-B. Clorgyline, initially used to differentiate MAO activity in rat mitochondria into its A and B types,[17] was available for a limited time in government-sponsored investigational studies.[18] Reversible MAOIs (RIMAs) such as moclobemide have been studied extensively although none are near introduction for general use.[1,19]

Tricyclic Antidepressants

Eight TCAs have been marketed in the United States, beginning with amitriptyline and imipramine in the 1960s. The other drugs in this class include nortriptyline, desipramine, doxepin, protriptyline, clomipramine, and trimipramine. Widespread familiarity from more than 30 years of data accumulation and low cost due to generic availability continue to be the most attractive features of the TCAs, making them the mainstay of treatment for thousands of depressed patients. Until only very recently, antidepressants in clinical development were tested against a TCA prototype.

Unfortunately, TCAs are lethal in accidental or purposeful overdose and can produce serious morbidity including generalized seizures and arrhythmias at doses only a few times higher than those used therapeutically. Their toxicity profile includes numerous adverse effects resulting from relatively high affinity for α-adrenergic, histaminic, and muscarinic receptors. Although their effective commercial life span was extended with a demonstration of effectiveness in panic disorder and the approval of clomipramine for treatment of obsessive-compulsive disorder, TCAs are rarely drugs of first choice except for patients who have a history of therapeutic failure to 2 or more new-generation antidepressants. Attempts to develop TCAs with better safety profiles (e.g., the 10-hydroxy metabolite of nortriptyline has much less cholinergic receptor affinity than its parent compound) were thwarted by the development of structurally distinct antidepressants.

Trazodone

Trazodone was introduced as a chemically and pharmacologically distinct alternative to TCAs in the early 1980s. It is a triazolopyridine derivative with antidepressant and some anxiolytic and hypnotic activity. Although trazodone is sometimes referred to as the first 5-HT reuptake inhibitor, its activity is partially due to other properties such as antagonism at 5-HT$_2$ receptor subtypes. The TCA-like adverse-effect profile of trazodone may be caused by histamine (H$_1$) receptor blockade and α$_1$-adrenoceptor blockade that are similar in magnitude to the affinity of these receptors found with TCAs.[2] The drug has a relatively benign cardiovascular risk profile compared with the TCAs and only weak in vitro anticholinergic activity.[2,3] Trazodone is a soporific compound that is widely and specifically used for this effect in combination with SSRIs (e.g., a single SSRI dose in the morning and a dose of trazodone in the evening). The reputation of trazodone for

causing priapism, a urologic emergency, has damaged its popularity in male patients. Indeed, trazodone should be used carefully in young male patients and also in the elderly or medically ill patient because of its TCA-like antihistaminic effects (e.g., sedation, weight gain) and its propensity to cause orthostatic hypotension.

Bupropion

Bupropion, an aminoketone, was introduced in the United States in 1988. Its mechanism of action was not promoted as a direct effect of reuptake inhibition of either 5-HT or norepinephrine, as the drug had apparently greater dopamine receptor affinity. Recently, its therapeutic effects have been proposed to be a result of more indirect effects on norepinephrine.[3,4] In vitro, bupropion is approximately twice as potent in inhibiting dopamine reuptake compared with its norepinephrine uptake action. In vivo, however, bupropion was considerably more potent in norepinephrine-mediated antidepressant models than in dopamine-mediated models. Bupropion does not enhance serotonergic actions, making a "serotonin syndrome" unlikely when combining it with other known serotonergic-enhancing drugs. The drug is associated with a low risk of cardiovascular events, sexual dysfunction, weight gain, sedation, and anticholinergic-like adverse effects. This safety profile has made bupropion attractive in combination with other antidepressants that cause those problems and in patients for whom potentiation of norepinephrine and dopamine actions may be desirable. Although the use of 2 antidepressants with complementary mechanisms of action has become popular recently, there remains a dearth of data to support this practice.

A higher-than-usual risk of seizures and a poor spectrum of activity as an anxiolytic have relegated bupropion to second-line status. In 1 small study, bupropion lacked efficacy as an antipanic compound.[20] The recent availability of a sustained-release formation allows twice-daily dosing, which lowers the risk of seizures,[21] although this potential may nonetheless limit its use in some patients. Until recently, bupropion was not thought to inhibit cytochrome P450 (CYP) enzymes. However, in volunteers, bupropion increased the plasma concentration of desipramine several-fold, thus implicating the drug as a potent CYP2D6 inhibitor.[21] Interaction reports involving patients receiving CYP2D6 substrates along with bupropion have yet to appear in the medical literature.

Amoxapine

Amoxapine, a dibenzoxazepine derivative, was one of the first drugs to provide an alternative to the familiar TCA mechanism of 5-HT and norepinephrine reuptake inhibition. The compound was initially touted as having a more rapid onset of clinical antidepressant effect than TCAs (an effect never substantiated), but more significantly, it possessed dopamine receptor antagonism, the likely result of

its major metabolite, 7-hydroxyamoxapine.[22] This pharmacologic effect was similar to that associated with typical antipsychotics and resulted in extrapyramidal symptoms (EPS), tardive dyskinesia, and neuroleptic malignant syndrome. Still marketed today, amoxapine is not recommended for clinical use because safer and more effective compounds are available.

Selective Serotonin Reuptake Inhibitors

A major transition in the clinical use of antidepressants occurred with the introduction of fluvoxamine in Europe in 1987 and fluoxetine in the United States in 1988.[23] The 5 SSRIs available in this country (also including sertraline, paroxetine, and citalopram) are effective for the treatment of depression and several anxiety disorders. Currently, 4 specific anxiety disorders are approved indications for 1 or more of the SSRIs, and results of clinical trials support their use in several obsessive-compulsive disorders.[24–26] Coincident with the introduction of the first SSRIs, other compounds that were selective for the uptake of either 5-HT or norepinephrine were developed (e.g., nomifensine, zimelidine), but problems with idiosyncratic toxicity halted their international development.

Although SSRIs have a wider spectrum of clinical benefit than TCAs and MAOIs, they lack all of the characteristics of an ideal antidepressant.[5] These deficits, especially the inability in randomized controlled trials to show consistently higher rates of efficacy in depressed patients of more than 60% to 70%, have stimulated the development of drugs in different pharmacologic classes.

Adverse effects of the SSRIs are related to their selective 5-HT reuptake inhibition. Multiple organ systems are affected, including the gastrointestinal (nausea, vomiting), central nervous (activation, nervousness), and urogenital (sexual dysfunction) systems. It has been appreciated that some differences exist among the SSRIs in the incidence of specific adverse events.[27] In a prospective multicenter study of 693 patients taking SSRIs, more than half of the patients reported sexual difficulty on the Sexual Dysfunction Questionnaire.[28] Fluoxetine does not appear to improve sleep characteristics in depressed patients, and it may worsen sleep electroencephalograph (EEG) parameters.[29,30] As the SSRIs continue to be extensively studied, their liabilities are becoming more apparent, including a recently described drug discontinuation syndrome.[31,32]

Venlafaxine

Venlafaxine was introduced in the United States in 1994. This drug and its major active metabolite, *O*-desmethyl venlafaxine, are potent inhibitors of the synaptosomal uptake of both 5-HT and norepinephrine. At low doses, venlafaxine displays SSRI-like effects on 5-HT, but as the dose is increased, reuptake inhibition of norepinephrine increases.[3] Inhibition of 5-HT uptake by venlafaxine is approximately 3-fold higher than that of norepi-

nephrine uptake.[1] Venlafaxine is a racemic mixture; the R-enantiomer is more potent than the S-enantiomer for both of its major pharmacologic effects. The actions of venlafaxine are fairly specific, as neither the parent drug nor its metabolite has appreciable activity at muscarinic, histaminic, or α_1- or α_2-adrenergic receptor sites. Nonetheless, like other antidepressants that lack appreciable muscarinic binding in vitro (trazodone, most SSRIs), venlafaxine may produce some anticholinergic-like effects such as sexual dysfunction and adverse effects on key sleep polysomnographic measurements.[30,33–36] Treatment with venlafaxine in the upper range of usual daily doses can result in increased blood pressure. This drug also causes nausea on initiation of treatment.

Venlafaxine is effective for the treatment of major depression with melancholia.[37] Its recent approval for the treatment of generalized anxiety disorder widens its clinical utility. Although its elimination half-life is fairly rapid (mean = 5 hours), a new sustained-release formation allows once-daily dosing, which reduces its adverse-effect burden.

Mirtazapine

Marketed in the United States in 1996, mirtazapine is the 6-aza-analogue of mianserin.[38] Mirtazapine is a racemic mixture with a unique pharmacologic profile. Mirtazapine differs from mianserin in that it does not inhibit norepinephrine uptake and it is about 20 times weaker as a $5\text{-}HT_2$ antagonist.[39] Mirtazapine is a selective antagonist at α_2-adrenergic autoreceptors and heteroreceptors in the locus ceruleus.[38–40] Blockade of these presynaptic α_2 receptors increases norepinephrine activity; as a consequence, increased firing of serotonergic neurons occurs in the raphe.[40] Mirtazapine also directly antagonizes $5\text{-}HT_2$ and $5\text{-}HT_3$ receptors.[40]

Mirtazapine is an effective antidepressant but causes drowsiness; some patients experience excessive sedation.[40] Although it has a relatively benign drug interaction profile, the drug has not been used extensively in this country, possibly because its clinical database (especially for treating anxiety disorders) is much smaller than those of alternative antidepressants.

Reboxetine

Reboxetine is a selective norepinephrine reuptake inhibitor marketed in several European countries; it is expected to gain approval for the United States market in the future. It weakly inhibits 5-HT uptake and does not inhibit dopamine uptake. Reboxetine is slightly less potent than desipramine and nortriptyline in terms of selective blockade of norepinephrine uptake.[41] The drug is active in classical models of depression, and clinical studies have supported its efficacy. Determining what advantages reboxetine may have compared with other antidepressants requires more extensive clinical trial testing. In trials conducted to date, the most frequently reported adverse events include dry mouth, constipation, increased sweating, insomnia, and urinary hesitancy and retention.[41] Drug interactions have not been reported.

FOCUS ON NEFAZODONE

In 1994, nefazodone was approved in the United States for treatment of depression. In pivotal trials, nefazodone demonstrated antidepressant efficacy similar to that of imipramine, but it improved depression-related anxiety symptoms significantly earlier and was better tolerated than its comparators. Other favorable characteristics of nefazodone included a low incidence of sexual dysfunction and treatment-emergent agitation. Additional studies conducted subsequent to marketing have further elucidated its pharmacodynamic effects and spectrum of clinical activity.

Neurochemical Actions

The pharmacologic actions of nefazodone within the serotonergic system are complex. Like the SSRIs, nefazodone blocks the presynaptic uptake of 5-HT. Nefazodone also blocks norepinephrine uptake. Its predominant pharmacologic effect, however, is blockade of the $5\text{-}HT_2$ postsynaptic receptor. This action probably contributes to antidepressant activity as well as leads to minimal treatment-emergent sexual dysfunction and sleep disruption. Thus, nefazodone has a multimodal mechanism of action. Nefazodone has minimal anticholinergic, antihistaminic, and antiadrenergic activity.

The antidepressant mechanism of nefazodone most likely relates to both its presynaptic and postsynaptic actions. Presynaptically, it inhibits 5-HT reuptake, which increases 5-HT levels within the synapse, prevents 5-HT metabolism, and results in an increased availability of 5-HT to interact with $5\text{-}HT_{1A}$ receptors. These receptors may be related to mood and anxiety homeostasis. Nefazodone also presynaptically inhibits norepinephrine uptake. Postsynaptically, nefazodone blocks $5\text{-}HT_2$ receptors. Recent findings show a decrease in $5\text{-}HT_2$ receptors in depressed patients.[42] Effective antidepressants and electroconvulsive therapy further down-regulate these receptors.[42] A decrease in baseline $5\text{-}HT_2$ receptor numbers might reflect a secondary compensatory response of the brain to the state of depression.[42]

The functional interrelationship between the $5\text{-}HT_2$ postsynaptic receptor and the $5\text{-}HT_{1A}$ receptor may be useful to exploit when developing drugs to treat both depression and depression-related anxiety symptoms. Blockade of the $5\text{-}HT_2$ receptor by nefazodone ultimately results in facilitation of $5\text{-}HT_{1A}$-receptor–mediated neurotransmission, which may be beneficial in the reduction of both depression and depression-related anxiety symptoms.[3] In support of this hypothesis, Fontaine and colleagues[43] found signifi-

Table 2. Pharmacokinetic Parameters of Nefazodone[a]

Parameter	Value
C_{max},[b] ng/mL	400–800
T_{max}, h	1.0–3.0
% Absorbed	15%–25%; assumed to be completely absorbed orally but ↓ bioavailability because of first-pass gut and hepatic metabolism
Mean steady-state plasma concentration,[c] ng/mL	150–1000
Therapeutic plasma concentration	Not established; no demonstrated value in plasma concentration monitoring
Half-life, h	4–8
Volume of distribution, L/kg	0.2–0.9
Mean plasma protein binding	99%
Active metabolites	3: hydroxynefazodone, desethyl hydroxynefazodone, and m-CPP
Changes in hepatic impairment	Exposure to nefazodone, m-CPP, and hydroxynefazodone higher in cirrhosis
Changes in renal impairment	Moderate renal impairment does not appreciably alter pharmacokinetics

[a]Data from references 45–47. Abbreviations: C_{max} = maximum plasma concentration, m-CPP = m-chlorophenylpiperazine, T_{max} = time to maximum plasma concentration.
[b]200-mg dose.
[c]Expected range for most patients receiving doses of 200 mg/day to 300 mg/day.

cant treatment differences favoring nefazodone in the Symptom Checklist-90 (SCL-90) Anxiety Factor scores as early as 1 week and sustained over 6 weeks as compared with placebo and imipramine. A meta-analysis of 6 randomized, placebo-controlled efficacy trials examined Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale for Anxiety (HAM-A) scores from a sample of 817 outpatients with major depression who received nefazodone (100–600 mg/day), imipramine (50–300 mg/day), or placebo. Statistically significant relief of agitation occurred in the nefazodone group as compared with the imipramine and placebo groups as early as week 1, and this benefit was sustained during the 6- to 8-week trials.[44] In addition to the beneficial antidepressant properties of nefazodone, 5-HT$_2$ antagonism may explain the less frequent treatment-emergent symptoms of activation (e.g., anxiety, agitation, insomnia) and sexual dysfunction.[42]

A further contribution to the mechanism of action of nefazodone may result from formation of its minor metabolite, m-CPP (m-chlorophenylpiperazine). Although the amount of m-CPP formed is low (approximately 7% of the area under the time-concentration curve [AUC] of nefazodone), its elimination half-life is 4 to 8 hours, similar to that of nefazodone (Table 2).[45–47] Pharmacologically, m-CPP is a direct 5-HT receptor agonist at 5-HT$_1$, 5-HT$_2$, and 5-HT$_3$ receptors, but with a 1 order of magnitude higher affinity for 5-HT$_{2C}$ receptors.[39] Studies of direct administration of m-CPP to patients with anxiety disorders, normal controls, and animals have yielded conflicting results.[39] The behavioral effects of m-CPP may depend on dosing, receptor sensitivity, and, perhaps, diagnosis. Attenuation or habituation following prolonged m-CPP exposure has been observed.[39] Thus, one may hypothesize that m-CPP could contribute a unique mechanism to the overall effects of nefazodone in the pharmacotherapy of various depression- and anxiety-related symptoms, possibly through down-regulation of specific 5-HT receptors. In addition, m-CPP may explain the weight-neutral properties of nefazodone.[48]

Nefazodone displays only weak α$_1$-adrenergic blockade and cholinergic receptor antagonism. Nefazodone lacks α$_2$-adrenergic antagonist activity, lacks dopamine antagonist activity, and displays only weak antihistaminic activity. The clinical implications of this receptor affinity profile include relatively low incidences of dry mouth, constipation, or urinary retention, relatively low sedation, and a lack of propensity to cause priapism or EPS. This adverse effect profile differs from that of nefazodone's chemical relative, trazodone, and of TCAs. In a study of the effects of nefazodone and imipramine on highway driving, cognitive functions, and daytime sleepiness in healthy adult and elderly subjects,[49] nefazodone did not impair highway-driving performance but imipramine did. Nefazodone does not appear to potentiate the sedative-hypnotic effects of alcohol.[50]

Additional Relevant Pharmacodynamic Effects

Data suggest a role of the 5-HT$_2$ receptor in sleep physiology.[51] In healthy controls, administration of a 5-HT$_2$ postsynaptic receptor antagonist, ritanserin, resulted in dose-related increases in slow-wave sleep. Thus, in the depressed state, the functional effects of a 5-HT$_2$ receptor antagonist would be enhanced slow-wave sleep.[51] Sleep abnormalities are common in patients with major depression. Objective measures of sleep collected by polysomnography or EEG show shortened rapid eye movement (REM) latency in depressed patients. Subjective and clinically observed target symptoms of insomnia, daytime sleepiness, fatigue, and difficulty falling asleep or staying asleep at night are also noted in depressed patients. About 70% to 90% of depressed patients have insomnia and 10% to 20% have hypersomnia.[34]

Whereas most antidepressants suppress REM sleep and increase REM latency, nefazodone does neither in healthy subjects. In a multicenter, randomized, double-blind, 8-week trial,[30] nefazodone was compared with fluoxetine in outpatients with major depression. Baseline sleep EEG recordings were compared with recordings taken through-

out the study. Nefazodone and fluoxetine equally reduced depressive symptoms, but nefazodone progressively increased sleep efficiency while fluoxetine reduced this parameter. Nighttime awakenings were reduced with nefazodone and increased with fluoxetine. These biological differences in sleep architecture were not mirrored in the subjective sleep quality differences reported by the patients, however. Polysomnographic studies with other antidepressants show that fluoxetine, sertraline, paroxetine, and venlafaxine worsen sleep quality.[33–37,52]

In 1 small polysomnographic study (N = 6),[53] mirtazapine improved sleep continuity by decreasing sleep latency and increasing total sleep time and sleep efficiency. As stated earlier, mirtazapine causes a high degree of sedation (54% versus 18% with placebo in short-term clinical trials).[54]

Another theorized role for the postsynaptic 5-HT_2 receptor involves regulation of sexual function. Clinical evidence comes from the observations that 58% to 80% of patients taking an SSRI reported sexual dysfunction on the Sexual Dysfunction Questionnaire.[28] Montejo and colleagues[28] conducted a prospective, multicenter study in 693 patients who were taking an antidepressant (clomipramine, various SSRIs, mirtazapine, or nefazodone). Patients taking an antidepressant that did not block the 5-HT_2 postsynaptic receptor and that increased 5-HT in the synapse reported a higher incidence of sexual dysfunction than did patients taking an antidepressant that raised 5-HT in the synapse but that also antagonized the 5-HT_2 postsynaptic receptor.[28] Feiger and associates[55] reported findings from a randomized, 6-week, double-blind study comparing nefazodone (100–600 mg/day) and sertraline (50–200 mg/day) in 160 outpatients who met DSM-III-R criteria for major depression. Data collected from a structured sexual dysfunction questionnaire indicated that both men and women experienced significantly more difficulty with ejaculation and orgasm, respectively, during sertraline treatment than during nefazodone treatment.[55]

Pharmacokinetic Characteristics

Nefazodone is rapidly and completely absorbed when taken orally; however, extensive presystemic metabolism reduces the absolute bioavailability to 15% to 25% (see Table 2). It is widely distributed in body tissues (volume of distribution = 0.2–0.9 L/kg)[45] and is approximately 99% plasma protein bound. Nefazodone is extensively metabolized by oxidative pathways (CYP3A4) and aromatic hydroxylation; the principal metabolites are hydroxynefazodone, a triazole-dione metabolite (desethyl hydroxynefazodone), and $m\text{-CPP}$.[45] The drug exhibits nonlinear pharmacokinetics (i.e., greater-than-proportional mean plasma concentrations and AUC with higher doses). Following an oral dose, peak plasma concentrations (C_{max}) occur in 1 to 3 hours, and the terminal elimination half-life is 4 to 8 hours. Thus, steady-state plasma concentrations are reached within 3 to 4 days with twice-daily dosing. Food delays the absorption of nefazodone and lowers the AUC by approximately 20%.[45]

Hepatic impairment increases the AUC and half-life of nefazodone and hydroxynefazodone by 2-fold. Renal impairment has no significant effect on the pharmacokinetic parameters of nefazodone or hydroxynefazodone. The disposition of nefazodone and its hydroxy metabolite is similar in both poor and extensive metabolizers of CYP2D6, but poor metabolizers eliminate $m\text{-CPP}$ more slowly. This finding implies that CYP2D6 is involved in the metabolism of $m\text{-CPP}$ but not in the conversion of nefazodone to its principal metabolites.

Drug Interactions

Extensive drug interaction studies have been conducted with nefazodone. Neither clinical nor pharmacokinetic interactions with cimetidine have been observed. No dosage reduction is required for cimetidine, propranolol, phenytoin, lorazepam, theophylline, warfarin, or digoxin.[46] With concurrent administration, nefazodone caused a 36% increase in haloperidol AUC, but the pharmacokinetics of nefazodone were not altered by the neuroleptic. Coadministration of nefazodone with MAOIs is not recommended.

Because nefazodone inhibits CYP3A4 in vitro, concomitant administration with some CYP3A4 substrates leads to clinically important drug interactions. Coadministration of nefazodone with terfenadine, astemizole, cisapride, or pimozide is contraindicated. However, terfenadine, astemizole, and cisapride have not been available in the United States since 1999–2000. Coadministration of carbamazepine and nefazodone also is contraindicated because carbamazepine induces CYP3A4 and lowers plasma nefazodone concentrations.[46] In a drug interaction surveillance program, the combination of carbamazepine with nefazodone did not result in a clinically significant interaction.[56]

Some benzodiazepines also are metabolized by CYP3A4. Nefazodone increased the C_{max} of triazolam by 1.7-fold, the elimination half-life by 3-fold, and the AUC by 4-fold and potentiated the psychomotor effects of the drug. Nefazodone increased the alprazolam C_{max} 1.6-fold and the AUC 2-fold and similarly potentiated the psychomotor effects of this benzodiazepine.[47] Neither triazolam nor alprazolam affected nefazodone pharmacokinetics. The manufacturer recommends avoidance of nefazodone and triazolam coadministration in most patients, including the elderly.[46] If alprazolam is coadministered with nefazodone, a 50% reduction in the initial alprazolam dose is recommended.[46]

SUMMARY

Older antidepressants, MAOIs and TCAs, work primarily in the synaptic space either by inhibiting the catalysis

of monoamines (5-HT, norepinephrine) or by inhibiting their presynaptic reuptake. For at least 2 decades, these antidepressants were used most often in clinical practice. Many of the newer compounds are variants on the monoamine-based antidepressants. These newer drugs generally act through multiple mechanisms of neurotransmission reuptake inhibition and receptor agonism or antagonism. Nefazodone has a unique pharmacologic profile and has demonstrated clinical efficacy for depression and depression with anxiety symptoms, beneficial effects on depression-related sleep disturbances, and a relatively low propensity to cause symptoms of sexual dysfunction and treatment-emergent activation symptoms. After 6 years of widespread clinical use, nefazodone has been proved to be a safe and effective antidepressant with unique pharmacodynamic properties.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), amoxapine (Asendin and others), bupropion (Wellbutrin), carbamazepine (Tegretol and others), cimetidine (Tagamet and others), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), digoxin (Lanoxin and others), doxepin (Sinequan and others), fluoxetine (Prozac and others), fluvoxamine (Luvox), haloperidol (Haldol and others), lorazepam (Loxitane and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), phenytoin (Dilantin and others), pimozide (Orap), propranolol (Inderal and others), protriptyline (Vivactil), selegiline (Eldepryl), sertraline (Zoloft), theophylline (Aerolate and others), tranylcypromine (Parnate and others), trazodone (Desyrel and others), triazolam (Halcion and others), trimipramine (Surmontil), venlafaxine (Effexor), warfarin (Coumadin).

REFERENCES

1. Feighner JP. Mechanism of action of antidepressant medications. J Clin Psychiatry 1999;60(suppl 4):4–11
2. Richelson E. Pharmacology of antidepressants: characteristics of the ideal drug. Mayo Clin Proc 1994;69:1069–1081
3. Horst WD, Preskorn SH. Mechanisms of action and clinical characteristics of 3 atypical antidepressants: venlafaxine, nefazodone, bupropion. J Affect Disord 1998;51:237–254
4. Coccaro EF, Siever LJ. Second-generation antidepressants: a comprehensive review. J Clin Pharmacol 1985;25:241–260
5. DeVane CL. Pharmacologic characteristics of ideal antidepressants in the 21st century. J Clin Psychiatry 2000;61(suppl 11):4–8
6. Frank E, Kupfer DJ, Perel JM, et al. Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1990;47:1093–1099
7. Kocsis JH, Friedman RA, Markowitz JC, et al. Maintenance therapy for chronic depression: a controlled clinical trial of desipramine. Arch Gen Psychiatry 1996;53:769–776
8. Keller MB, Gelenberg AJ, Hirschfeld RMA, et al. The treatment of chronic depression, pt 2: a double-blind, randomized trial of sertraline and imipramine. J Clin Psychiatry 1998;59:598–607
9. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000;342:1462–1470
10. Fava GA, Rafanelli C, Grandi S, et al. Prevention of recurrent depression with cognitive behavioral therapy. Arch Gen Psychiatry 1998;55:816–820
11. Kupfer DJ. Long-term treatment of depression. J Clin Psychiatry 1991;52(5, suppl):28–34
12. Quitkin FM, McGrath PJ, Stewart JW, et al. Atypical depression, panic attacks, and response to imipramine and phenelzine. Arch Gen Psychiatry 1990;47:935–941
13. Sheehan DV, Claycomb JB, Kouretas N. MAO inhibitors: prescription and patient management. Int J Psychiatry Med 1980;10:99–121
14. Levin AP, Liebowitz MR. Drug treatment of phobias: efficacy and optimum use. Drugs 1987;34:504–514
15. Goridis C, Neff NH. Monoamine oxidase in sympathetic nerves: a transmitter-specific enzyme type. Br J Pharmacol 1971;43:814–818
16. Kopin IJ, Gordon EF. Metabolism of (3)H-NE release by tyramine and reserpine. J Pharmacol Exp Ther 1962;138:351–359
17. Johnson JP. Some observations upon a new inhibitor of monoamine oxidase in brain tissue. Biochem Pharmacol 1968;17:1285–1297
18. Lipper S, Murphy DL, Slater S, et al. Comparative behavioral effects of clorgyline and pargyline in man: a preliminary evaluation. Psychopharmacology (Berl) 1979;62:123–128
19. Boerner RJ, Moller HJ. The importance of new antidepressants in the treatment of anxiety/depressive disorders. Pharmacopsychiatry 1999;32:119–126
20. Sheehan DV, Davidson J, Manschreck TC, et al. Lack of efficacy of a new antidepressant (bupropion) in the treatment of panic disorder with phobias. J Clin Psychopharmacol 1983;3:23–31
21. Wellbutrin [package insert]. Research Triangle Park, NC: Glaxo Wellcome, Inc; 2000
22. Cooper DJ, Gelenberg AJ, Wojcik JC, et al. The effects of amoxapine and imipramine on serum prolactin levels. Arch Intern Med 1981;141:1023–1025
23. DeVane CL. Pharmacokinetics of the selective serotonin reuptake inhibitors. J Clin Psychiatry 1992;53:(2, suppl):13–20
24. Jefferson JW, Griest JH. The pharmacotherapy of obsessive-compulsive disorder. Psychiatr Ann 1996;26:202–209
25. Dominguez RA. Serotonergic antidepressants and their efficacy in obsessive-compulsive disorder. J Clin Psychiatry 1992;53(10, suppl):56–59
26. Pigott TA, Pato MT, Bernstein SE, et al. Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive-compulsive disorder: behavioral and biological results. Arch Gen Psychiatry 1990;47:926–931
27. DeVane CL. Comparative safety and tolerability of selective serotonin reuptake inhibitors. Hum Psychopharmacol 1995;10:S185–S193
28. Montejo AL, Llorca G, Izquierdo JA, et al. Antidepressant-induced sexual dysfunction: a multicenter and prospective study using a questionnaire in 693 patients. In: New Research Program and Abstracts of the 152nd Annual Meeting of the American Psychiatric Association; May 20, 1999; Washington, DC. Abstract NR658:254
29. Armitage R, Yonkers K, Cole D, et al. A multicenter, double-blind comparison of the effects of nefazodone and fluoxetine on sleep architecture and quality of sleep in depressed outpatients. J Clin Psychopharmacol 1997;17:161–168
30. Rush AJ, Armitage R, Gillin JC, et al. Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. Biol Psychiatry 1998;44:3–14
31. Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry 1998;44:77–87
32. Therrien F, Markowitz JS. Selective serotonin reuptake inhibitors and withdrawal symptoms: a review of the literature. Hum Psychopharmacol 1997;12:309–323
33. Oswald I, Adam K. Effects of paroxetine on human sleep. Br J Pharmacol 1996;22:97–99
34. Saletu B, Frey R, Krupka M, et al. Sleep laboratory studies on the single-dose effects of serotonin reuptake inhibitors paroxetine and fluoxetine on human sleep and awakening qualities. Sleep 1991;14:439–447
35. Staner L, Kerkhofs M, Detroux D, et al. Acute, subchronic, and withdrawal sleep EEG changes during treatment with paroxetine and amitriptyline: a double-blind randomized trial in major depression. Sleep 1995;18:470–477
36. Luthringer R, Toussaint M, Schaltenbrand N, et al. A double-blind, placebo-controlled evaluation of the effects of orally administered venlafaxine on sleep in inpatients with major depression. Psychopharmacol Bull 1996;32:637–646
37. Effexor XR [package insert]. Philadelphia, Pa: Wyeth-Ayerst Laboratories; 2000
38. Frazer A. Norepinephrine involvement in antidepressant action. J Clin Psychiatry 2000;61(suppl 10):25–30
39. Stefanski R, Goldberg SR. Serotonin 5-HT$_2$ receptors antagonists: potential in the treatment of psychiatric disorders. CNS Drugs 1997;7:388–409
40. De Boer T, Raiteri MM, De Vos CJ, et al. Neurochemical and autonomic pharmacological profiles of the 6-aza-analogue of mianserin, ORG 3770 and its enantiomers. Neuropharmacology 1988;27:399–408

41. Anand A, Charney DS. Norepinephrine dysfunction in depression. J Clin Psychiatry 2000;61(suppl 10):16–24

42. Yatham LN, Liddle PF, Shiah I-S, et al. Brain serotonin 2 receptors in major depression: a positron emission tomography study. Arch Gen Psychiatry 2000;57:850–858

43. Fontaine R, Ontiveros A, Elie R, et al. A double-blind comparison of nefazodone, imipramine, and placebo in major depression. J Clin Psychiatry 1994;55:234–241

44. Fawcett J, Marcus RN, Anton SF, et al. Response of anxiety and agitation symptoms during nefazodone treatment of major depression. J Clin Psychiatry 1995;56(suppl 6):37–42

45. Dopheide JA, Stimmel GL, Yi DD. Focus on nefazodone: a serotonergic drug for major depression. Hosp Formulary 1995;30:205–212

46. Serzone [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2000

47. Greene DS, Salazar DE, Dockens RC, et al. Coadministration of nefazodone with benzodiazepines, 3: a pharmacokinetic interaction study with alprazolam. J Clin Psychopharmacol 1995;15:399–408

48. Sussman N, Ginsberg DL. Weight effects of nefazodone, bupropion, mirtazapine, and venlafaxine: a review of available evidence. Primary Psychiatry 2000;7:33–48

49. Laar MW, Willigenburg AP, Volkerts ER. Acute and subacute effects of nefazodone and imipramine on highway driving, cognitive functions, and daytime sleepiness in healthy adults and elderly subjects. J Clin Psychopharmacol 1995;15:30–40

50. Frewer LJ, Lader M. The effects of nefazodone, imipramine, and placebo, alone and combined with alcohol, in normal subjects. Int Clin Psychopharmacol 1993;8:13–20

51. Staner L, Kempenaeras C, Simonnet MP, et al. 5-HT$_2$ receptor antagonism and slow-wave sleep in major depression. Acta Psychiatr Scand 1992;86:133–137

52. Armitage R. Effects of antidepressant treatment on sleep EEG in depression. J Psychopharmacol 1996;10(suppl 1):22–25

53. Winokur A, Sateia MH, Hayes JB, et al. Acute effects of mirtazapine on sleep continuity and sleep architecture in depressed patients: a pilot study. Biol Psychiatry 2000;48:75–78

54. Remeron [package insert]. West Orange, NJ: Organon, Inc; 2001

55. Feiger A, Kiev A, Shrivastava RK, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. J Clin Psychiatry 1996;57 (suppl 2):53–62

56. DeVane CL, Markowitz JS, Liston HL, et al. Charleston Antidepressant Drug Interactions Surveillance Program (CADISP). Psychopharmacol Bull 2001;35:50–61