

# Six-Year Perspectives on the Safety and Tolerability of Nefazodone

## 33 Comparative Safety and Tolerability of Nefazodone.

David L. Dunner, M.D., and Lyle K. Laird, Pharm.D., B.C.P.P.

*From the Department of Psychiatry and Behavioral Sciences, University of Washington, and the Center for Anxiety and Depression, Seattle (Dr. Dunner); and the Neuroscience Medical Affairs Department, Bristol-Myers Squibb Company, and the School of Pharmacy, University of Colorado Health Sciences Center, Denver (Dr. Laird).*

*Reprint requests to: David L. Dunner, M.D., Department of Psychiatry and Behavioral Sciences, University of Washington, Center for Anxiety and Depression, 4225 Roosevelt Way, N.E., Suite 306C, Seattle, WA 98105-6099 (e-mail: ddunner@u.washington.edu).*

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John Zajecka, M.D., and LaGenia Bailey, Pharm.D.

*From the Department of Psychiatry, Rush-Presbyterian-St. Luke's Medical Center (Dr. Zajecka), and the Neuroscience Medical Affairs Department, Bristol-Myers Squibb Company (Dr. Bailey), Chicago, Ill.*

*Reprint requests to: John Zajecka, M.D., Department of Psychiatry, Rush-Presbyterian-St. Luke's Medical Center, 1725 West Harrison St., Ste. 955, Chicago, IL 60612 (e-mail: jzajecka@rush.edu).*

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Norman Sussman, M.D., and Julia L. Seabolt, Pharm.D.

*From the Department of Psychiatry, New York University School of Medicine (Dr. Sussman), and the Neuroscience Medical Affairs Department, Bristol-Myers Squibb Company (Dr. Seabolt), New York.*

*Reprint requests to: Norman Sussman, M.D., Department of Psychiatry, New York University School of Medicine, 150 E. 58th St., 27th Floor, New York, NY 10155 (e-mail: Sussman01@aol.com).*

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## Comparative Safety and Tolerability of Nefazodone

David L. Dunner, M.D., and  
Lyle K. Laird, Pharm.D., B.C.P.P.

Nefazodone is a novel antidepressant, belonging to the phenylpiperazine class. It is theorized to have potent antagonistic effects on postsynaptic serotonin type-2 (5-HT<sub>2</sub>) receptors and moderate presynaptic serotonin reuptake inhibitory effects. It is also believed to possess moderate presynaptic noradrenergic reuptake inhibition properties, but it has low affinity for muscarinic, cholinergic,  $\alpha$ -adrenergic, dopaminergic, and histaminergic receptors.<sup>1</sup> Since its approval in the United States in 1994, nefazodone has been found to have a well-established safety profile, and it is effective for short- and long-term use. To date, up to 9.4 million patients worldwide have used nefazodone, and the drug has been rigorously studied in worldwide clinical trials in at least 7000 patients with major depressive disorder. This article reviews available short- and long-term safety data that have accumulated since the release of nefazodone.

### TREATMENT-EMERGENT ADVERSE EXPERIENCES

By mid-1993, 1310 patients had received nefazodone in acute (6- to 8-week), placebo-controlled, clinical efficacy studies.<sup>2</sup> Active comparators included selective serotonin reuptake inhibitors (SSRIs) and imipramine. Nefazodone was generally well tolerated; treatment-emergent adverse experiences were considered mild or moderate in severity. Typically, the intensity of the event diminished over time or the event completely resolved.

In Table 1, adverse experiences that occurred at an incidence of 5% or higher and were significantly more common in nefazodone recipients than in placebo recipients are enumerated.<sup>3</sup> These findings reflect specific conditions existing at the time of each study and thus may not be useful to predict the incidence of adverse experiences across all patients. However, they do allow the clinician to better understand the relative contribution of nefazodone to the overall adverse experience profile in the patient being treated for major depressive disorder. Robinson and colleagues<sup>2</sup> noted that the number of patients who did not discontinue their nefazodone regimen after experiencing a treatment-emergent adverse experience in the first week decreased by 50% or more after 6 weeks. Of the 10 most commonly reported adverse experiences (see Table 1), only dry mouth tended to persist<sup>4</sup>; other adverse experiences tended to decrease in reported severity, if not resolve entirely. The adverse experiences were of mild-to-moderate

**Table 1. Treatment-Emergent Adverse Experiences Occurring at an Incidence of 5% or Higher in Short-Term (6- to 8-week), Placebo-Controlled Clinical Trials of Nefazodone (300–600 mg/d)<sup>a</sup>**

Adverse Experience	Patients (%)	
	Nefazodone (N = 393)	Placebo (N = 394)
Dry mouth	25	13
Somnolence	25	14
Nausea	22	12
Dizziness	17	5
Constipation	14	8
Asthenia	11	5
Light-headedness	10	3
Blurred vision	9	3
Confusion	7	2
Abnormal vision	7	1

<sup>a</sup>Adapted from the Serzone packet insert.<sup>3</sup> All adverse experiences significantly higher for nefazodone versus placebo ( $p \leq .05$ ).

**Table 2. Dose Relationship of Adverse Experiences<sup>a</sup> From Placebo-Controlled Clinical Trials<sup>b</sup>**

Adverse Experience	Patients (%)		
	Placebo (N = 212)	Nefazodone $\leq$ 300 mg/d (N = 211)	Nefazodone 300–600 mg/d (N = 209)
Somnolence	13	16	28
Nausea	12	14	23
Constipation	9	10	17
Dizziness	4	11	22
Blurred vision	2	3	9
Abnormal vision	2	0	10
Confusion	1	2	8
Tinnitus	1	0	3

<sup>a</sup>Adverse experiences for which a statistically significant difference ( $p \leq .05$ ) was apparent between the nefazodone groups.

<sup>b</sup>Adapted from the Serzone packet insert.<sup>3</sup>

severity and resulted in few to no clinically important sequelae. Thus, patients who continue treatment with nefazodone appear to develop increased tolerance to most adverse experiences.

### DOSE RELATIONSHIP ISSUES

Some adverse experiences reported with nefazodone appear to be dose related (Table 2).<sup>5,6</sup> An analysis was conducted on 3 placebo-controlled trials in which 2 dosage ranges of nefazodone were used (low  $\leq$  300 mg/day; high 300–600 mg/day) to permit maximum titration by week 2<sup>5,6</sup> (data on file, Bristol-Myers Squibb Company, Princeton, N.J.). Downward dose adjustments were allowed to help manage adverse experiences, if necessary. Although use of higher doses of nefazodone resulted in a greater incidence of adverse experiences than use of lower doses, their occurrence did not dampen the overall efficacy of nefazodone or its tolerability.<sup>5,6</sup> This finding underscores the importance of progressive titration of the depressed patient to higher doses of nefazodone (300–600 mg/day) to improve efficacy rates.<sup>6</sup>

Higher starting doses of nefazodone (e.g., 100 mg b.i.d.) have been reported to be associated with a higher frequency of early-onset, treatment-emergent adverse experiences (e.g., diarrhea and dizziness). Indeed, the manufacturer advocates titration, starting at a dose of 50 mg b.i.d. and increasing to 200 mg b.i.d. by the end of the third week, as tolerated.

### NEFAZODONE VERSUS SSRIs: DIFFERENTIATING COMMON ADVERSE EXPERIENCES

Safety data have also been gleaned from 6 head-to-head, double-blind, controlled studies comparing nefazodone with 3 SSRIs (fluoxetine, paroxetine, and sertraline)<sup>7-9</sup> (data on file, Bristol-Myers Squibb Company, Princeton, N.J.). Results of a pooled analysis of SSRI-treated patients demonstrated that adverse experiences that occurred at an incidence of 10% or more included agitation, dizziness, dry mouth, light-headedness, and sexual dysfunction (in men). The nefazodone group fared statistically better ( $p < .05$ ) in terms of agitation and sexual dysfunction, whereas the SSRI group experienced less dizziness, dry mouth, and light-headedness. Activating side effects such as agitation and insomnia are uncommon with nefazodone and are noted in controlled studies to occur at a frequency similar to that seen with placebo.<sup>2</sup>

### RELATIONSHIP OF ADVERSE EXPERIENCES AND AGE

When nefazodone was administered in controlled clinical trials in doses ranging from 100 mg/day to 200 mg/day and 500 mg/day to 600 mg/day, no clinically relevant difference in the rate of adverse experiences was observed between patients 65 years of age or older ( $N = 953$ ) and patients younger than age 65 ( $N = 6571$ ) (data on file, Bristol-Myers Squibb Company, Princeton, N.J.). Safety data from pediatric patients are not presently available.

### OTHER ADVERSE EXPERIENCES

Other safety aspects of nefazodone, including cardiovascular effects (e.g., electrocardiogram [ECG] changes), induction of hypomania/mania, seizure potential, induction of priapism, and abnormal vision, also have been examined.

#### Cardiovascular Effects

Nefazodone has limited effects on the cardiovascular system. In short-term, placebo-controlled trials, no clinically significant differences were apparent between nefazodone and placebo in terms of orthostatic blood pressure changes, whereas patients receiving imipramine had significant decreases in blood pressure.<sup>2</sup> Thus, while tricyclic antidepressants (TCAs), monoamine oxidase inhibitors,

trazodone, and venlafaxine can cause changes in blood pressure that warrant close clinical monitoring, special precautions are not necessary in patients taking nefazodone.

#### ECG Changes

No clinically significant ECG changes were noted in placebo-controlled trials involving 1153 patients taking nefazodone.<sup>2</sup> Nefazodone did not cause cardiac conduction disturbances, including QT prolongation. Asymptomatic sinus bradycardia on ECG was noted in 1.3% of nefazodone-treated patients and 0.4% of placebo-treated patients ( $p \leq .05$ ). The specific cardiac effects of nefazodone in patients with cardiovascular disease (e.g., history of recent myocardial infarction or unstable heart disease) are not fully known.

However, a potential for corrected QT interval prolongation exists if nefazodone is combined with terfenadine, astemizole, cisapride, or pimozone, drugs that are metabolized via this pathway.<sup>3</sup> Because nefazodone inhibits the cytochrome (CYP) 3A4 isoenzyme *in vitro*, coadministration increases the plasma levels of these drugs, which are associated with prolonged corrected QT intervals and rare cases of serious life-threatening cardiovascular events. Terfenadine, astemizole, and cisapride are no longer available in the United States.

#### Hypomania/Mania

All antidepressants carry a risk of inducing hypomania or mania, a phenomenon that most likely occurs when bipolar disorder (especially bipolar II) is mistakenly diagnosed as unipolar major depression. In premarketing clinical trials, hypomania/mania occurred in 0.3% of nefazodone-treated unipolar patients, 0.3% of TCA-treated unipolar patients, and 0.4% of placebo recipients. In bipolar patients, however, the rate of manic episodes was 1.6% with nefazodone, 5.1% with various TCAs, and 0% with placebo.<sup>3</sup> Thus, while the risk of inducing hypomania/mania with nefazodone is small, its use in patients with a history of bipolar disorder should be carefully considered, especially if the patient is not treated with a mood stabilizer.

#### Seizures

Nefazodone rarely exacerbates seizure disorders. Major motor seizures were not reported in 3496 patients treated in worldwide clinical trials, and only 1 patient with a preexisting absence seizure had a recurrence of that seizure type.<sup>2,3</sup> Rare postmarketing reports of nefazodone-associated seizures have arisen, although a causal relationship has not been established.<sup>3</sup>

#### Priapism

Priapism was not reported during premarketing trials of nefazodone, but rare cases have been noted since its approval in 1994. A literature search revealed only 1 case

of nefazodone-precipitated priapism (i.e., clitoral priapism).<sup>10</sup> Because of the extremely low number of reported cases of nefazodone-associated priapism and because of inherent confounding variables, a clear causal relationship has not been established.<sup>3</sup>

### Abnormal Vision

Abnormal vision, generally consisting of scotoma and visual trails (palinopsia), has been noted in case reports.<sup>11,12</sup> It was observed as a treatment-emergent adverse experience in the short-term, double-blind, placebo-controlled, nefazodone clinical trials described earlier. This adverse experience occurred in 10% of 209 patients taking nefazodone 300 mg/day to 600 mg/day (see Table 2) and in 0% of 211 placebo-treated patients.<sup>3</sup> Although this adverse experience is generally considered benign, it may be dose related (see Table 2) and can usually be managed by lowering the dose of nefazodone or by altering the time of day the dose is given.

### MEDICATION DISCONTINUATION DUE TO ADVERSE EXPERIENCES

Overall, discontinuation rates with nefazodone due to adverse experiences in short-term, placebo-controlled, clinical trials are similar to those observed with the SSRIs. Of the 1310 patients included in acute efficacy studies, 12% of those taking nefazodone stopped treatment because of adverse experiences as compared with 10.5% of those taking fluoxetine, 21.8% of those taking imipramine, and 7.4% of those receiving placebo.<sup>2</sup> Others have observed adverse experience-related discontinuation rates of 14% to 19% for nefazodone recipients, 12% for sertraline recipients, and 13% for paroxetine recipients.<sup>7,8</sup> Common adverse experiences ( $\geq 1\%$ ) that resulted in discontinuation of nefazodone in clinical trials (based on 3496 patients) were nausea (3.5%), dizziness (1.9%), insomnia (1.5%), asthenia (1.3%), and agitation (1.2%).<sup>3</sup> In a recent study of patients with chronic major depression, the dropout rate due to adverse experiences was 14% in the acute (12-week) treatment phase with nefazodone alone and 7% when nefazodone was combined with psychotherapy (the nefazodone dose in each group was about 500 mg/day).<sup>13</sup> During the 4-month continuation phase, only 2% of patients discontinued treatment due to adverse experiences (data on file, Bristol-Myers Squibb Company, Princeton, N.J.).

### LONG-TERM SAFETY ISSUES

Consideration of adverse experiences that may occur during long-term antidepressant use is critical when initiating therapy, as adverse experiences can significantly decrease patient compliance and otherwise negatively affect outcome. Altered sleep patterns and weight gain, important issues that may adversely affect long-term patient

compliance with therapy, are discussed in depth elsewhere in this supplement. The role of antidepressants in causing sexual dysfunction is reviewed below.

### SEXUAL DYSFUNCTION

Sexual dysfunction (abnormal ejaculation, anorgasmia, impotence, and psychosexual dysfunction) caused by antidepressants is underrecognized because it is gauged largely by patient self-reports. When it is measured by clinician-initiated methods, one gains a more realistic incidence of this important adverse experience. Feiger and colleagues<sup>8</sup> applied a sexual function questionnaire in a 6-week, double-blind, randomized study comparing nefazodone (100–600 mg/day) with sertraline (50–200 mg/day) in 160 depressed outpatients. While both medications were comparable in antidepressant response rates, nefazodone was better tolerated with respect to sexual function. For example, significantly more women taking sertraline (47%) reported difficulty in achieving orgasm than did women taking nefazodone (17%;  $p < .03$ ). Likewise, significantly more men reported greater ejaculatory difficulty while on sertraline treatment (67%) than did men taking nefazodone (19%;  $p < .01$ ). Mean overall sexual satisfaction scores at baseline and endpoint were similar in nefazodone-treated patients, but worsened in the sertraline group.

Ferguson and colleagues<sup>14</sup> have recently examined the reemergence of sexual dysfunction in depressed patients who had experienced this adverse event while taking sertraline (100 mg/day). Validated self-rating and clinician-rated scales were used to measure sexual dysfunction. In this 8-week, double-blind study, 105 patients were randomly assigned to receive nefazodone (titrated to 400 mg/day) or a rechallenge with sertraline (titrated to 100 mg/day) after a 7-day washout phase and a 7- to 10-day placebo phase. Antidepressant responses were similar in both treatment groups. However, 76% of the sertraline group (25/33) reexperienced sexual dysfunction whereas only 26% of patients (10/39) taking nefazodone did so ( $p < .001$ ). Although the rate of sexual dysfunction with nefazodone observed in this trial (26%) is higher than has been reported, the study population consisted wholly of patients who had developed this adverse experience while on sertraline treatment.

In addition to sertraline, other SSRIs (e.g., citalopram, fluoxetine, fluvoxamine, paroxetine) have been associated with sexual dysfunction.<sup>15–18</sup> The exact incidences of iatrogenic sexual dysfunction caused by SSRIs are not fully known. Estimates by some investigators of greater than 20% are probably more accurate than figures reported during the early SSRI experience and are a result of more accurate ongoing reporting.<sup>19</sup>

In the recent nefazodone chronic depression study,<sup>13</sup> sexual dysfunction occurred in 3.5% of patients taking

nefazodone alone and 3.5% of those receiving nefazodone plus psychotherapy. No patient receiving psychotherapy alone reported sexual dysfunction. Collectively, then, nefazodone appears to be associated with a relatively low incidence of sexual dysfunction.

### HEPATOTOXICITY ISSUES

Rare cases of hepatic necrosis and/or failure associated with nefazodone have been identified through postmarketing surveillance, and these findings prompted a revision of the nefazodone product labeling. Hepatotoxicity is not unknown with antidepressant therapy. Indeed, product labeling for many newer agents such as citalopram, fluoxetine, sertraline, and venlafaxine contains information regarding isolated and rare cases of hepatic necrosis and/or failure.

To date, at least 4 cases of acute hepatic failure and/or necrosis temporally associated with nefazodone use have been reported in the literature.<sup>20,21</sup> The reported rate in the United States is about 1 case of liver failure resulting in death or transplant per 250,000 to 300,000 patient-years of nefazodone treatment. This represents a rate of about 3 to 4 times the estimated background rate of liver failure (data on file, Bristol-Myers Squibb Company, Princeton, N.J.). This rate is an underestimate because of underreporting, and the true risk could be considerably greater than this. It is not possible to entirely discount nefazodone as an etiologic contributor in these cases. However, these reports are complicated by the presence of other confounding variables such as preexisting underlying hepatic conditions; use of concomitant illicit drugs, alcohol, other medications; or exposure to other hepatotoxic substances.

Worldwide, nefazodone has been used by up to 9.4 million patients since its introduction; approximately half of these patients are in the United States (data on file, Bristol-Myers Squibb Company, Princeton, N.J.). Routine serial testing for liver function abnormalities is not generally warranted for patients using an antidepressant. However, it is clinically prudent to obtain a complete pretreatment history to assess underlying liver disease. It is also important that patients who develop signs and symptoms suggestive of liver damage while on treatment with nefazodone or any antidepressant be promptly and appropriately evaluated and treated.

### SAFETY IN OVERDOSE

Nefazodone is similar to many newer antidepressants in that it is relatively benign when taken in overdose. In 7 cases of intentional nefazodone overdose (taken alone or with other substances) in amounts ranging from 1000 mg to 11,200 mg, all patients recovered without sequelae.<sup>3,4</sup> Symptoms of toxicity typically seen after nefazodone over-

dose include drowsiness and vomiting. Management of nefazodone overdose consists of supportive care.

### SUICIDAL IDEATION AND ATTEMPTS

No statistically significant differences have been noted between nefazodone, imipramine, and placebo in terms of treatment-emergent suicidal ideation or suicidal attempts in placebo-controlled studies.<sup>22</sup>

### SUMMARY: COMPARATIVE SAFETY AND TOLERABILITY

To date, nefazodone has been taken by up to 9.4 million patients worldwide and has been rigorously studied in clinical trials in 3496 patients with major depressive disorder (data on file, Bristol-Myers Squibb Company, Princeton, N.J.). This broad experiential base supports the unique safety and tolerability profile of nefazodone. In short-term, controlled clinical trials, nefazodone has a well-established adverse experience profile that often diminishes with continued use. Unlike SSRIs, nefazodone causes minimal activating side effects (insomnia, agitation, anxiety) or sexual dysfunction. The drug is well tolerated by depressed geriatric patients. Nefazodone is relatively devoid of adverse cardiovascular effects. As with many other antidepressants, isolated reports of hepatotoxicity with nefazodone have been published, but routine or special monitoring is not warranted. Nefazodone is relatively safe in overdose situations and does not increase suicidal ideation. Postmarketing and premarketing safety data consistently show that nefazodone has a well-established safety profile when used for acute and long-term treatment of depressed patients.

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## Nefazodone: Discontinuation Issues and Safety in Chronic Major Depression

John Zajecka, M.D., and  
LaGenia Bailey, Pharm.D., B.C.P.P.

Studies evaluating nefazodone for prevention of relapse in acutely depressed patients have established both the efficacy of the drug as well as the lack of a discontinuation syndrome on abrupt discontinuation.<sup>23</sup> The following sections discuss the evidence for antidepressant discontinuation syndrome in patients treated with TCAs and SSRIs. Data on the effect of abrupt discontinuation of nefazodone

**Table 3. Somatic and Psychological Symptoms Associated With Abrupt Discontinuation of Selective Serotonin Reuptake Inhibitors<sup>a</sup>**

Symptom	Examples
Somatic	
Disequilibrium	Dizziness, vertigo, ataxia, feeling "spaced out"
Gastrointestinal	Nausea, vomiting
Flu-like symptoms	Fatigue, lethargy, myalgia, chills
Sensory disturbances	Paresthesias, tremor, shock-like sensations
Sleep disturbances	Insomnia, vivid dreams
Psychological	
Core symptoms	Irritability, crying spells, anxiety
Also reported	Overactivity, depersonalization, difficulty concentrating, slowed thinking, confusion, low mood, memory problems

<sup>a</sup>Adapted with permission from Schatzberg et al.<sup>30</sup>

after 16 weeks of continuous treatment are presented. The long-term tolerability of nefazodone in chronically depressed patients also is reviewed.

### ABRUPT ANTIDEPRESSANT DISCONTINUATION

An antidepressant discontinuation syndrome has been well documented and described following acute discontinuation of some antidepressant therapies. The TCAs have been associated with a discontinuation syndrome consisting of general somatic distress, sleep disturbances, gastrointestinal disturbances, akathisia or pseudoparkinsonism, behavioral activation, and flu-like symptoms.<sup>24</sup> More attention has been given to discontinuation phenomena associated with the SSRIs and other antidepressants.<sup>25–29</sup> The discontinuation symptoms associated with SSRIs are unique (Table 3) and have been reported with varying frequency.<sup>30</sup> Incidences ranging from 0.06% to 5.1% have been reported in postmarketing surveillance. In some published reports, up to 50% of patients have experienced discontinuation symptoms on discontinuation of paroxetine.<sup>26</sup>

The elimination half-life, dose, and duration of the specific SSRI utilized appear to correlate with the frequency and severity of discontinuation symptoms. For example, in a randomized, double-blind, 5- to 8-day interruption study in 242 patients, those having used an SSRI (paroxetine, sertraline, or fluoxetine) for 12.5 weeks or more showed significant differences in the number and severity of discontinuation symptoms.<sup>29</sup> The severity of symptoms was most prominent with paroxetine followed by sertraline and fluoxetine. Among the SSRIs, fluoxetine may be least likely to cause discontinuation symptoms on abrupt discontinuation because of its long elimination half-life (4–6 days). Symptoms also may emerge with missed doses or during dose reduction. Although rarely dangerous, SSRI discontinuation symptoms may be perceived as a new side effect or reemergence of the underlying ill-

ness and may result in either premature discontinuation of treatment or increased use of emergency health services if the patient has not been properly educated about their potential.

In contrast to the SSRIs, nefazodone has minimal association with a discontinuation syndrome. Zajecka and associates<sup>31</sup> evaluated 259 patients who were maintained on nefazodone treatment for 16 weeks as part of a relapse prevention trial.<sup>23</sup> Patients who initially responded to nefazodone were randomly assigned to continuation treatment with nefazodone (N = 128) or placebo (N = 131). Patients were evaluated for relapse of depressive symptomatology as well as emergence of spontaneous, new-onset adverse experiences on either discontinuation of nefazodone (i.e., placebo substitution) or continuation of the active drug over a period of 36 weeks. Symptom emergence was measured using COSTART terminology and was rated on a severity scale from 1 (mild) to 3 (severe). Assessments were made 14 and 28 days after randomization. In the continued-treatment group, 22 (17.2%) reported at least 1 new-onset or worsened adverse experience at 14 days and 40 (31.3%) reported at least 1 new-onset or worsened adverse experience at 28 days, while in the placebo group, 27 (20.6%) reported at least 1 new-onset or worsened adverse experience at 14 days and 38 (29.0%) reported at least 1 new-onset or worsened adverse experience at 28 days. There was no statistically significant difference in the number of patients with new-onset or worsened adverse experiences between the continued treatment and placebo groups. Thus, nefazodone was not associated with discontinuation symptomatology on abrupt discontinuation of active drug.

### TOLERABILITY OF NEFAZODONE IN CHRONIC MAJOR DEPRESSION

Maintenance antidepressant treatment is recommended for patients at risk for recurrence by virtue of a history of frequent or multiple episodes, double depression, onset of depression after age 60 years, long duration of individual episodes, family history of mood disorder, poor symptom control during continuation therapy, and comorbid anxiety disorder or substance abuse.<sup>32–37</sup>

The long-term use of nefazodone in chronically depressed patients was recently examined in a comparative trial of nefazodone and the cognitive behavioral-analysis system of psychotherapy<sup>13</sup> (CBASP; discussed in detail elsewhere in this supplement). The 681 enrolled patients were randomly assigned to nefazodone, nefazodone plus CBASP, or CBASP alone. A 12-week acute treatment phase was followed by a 16-week continuation phase and a 52-week, placebo-controlled, randomized maintenance phase in which relapse rates were assessed. Nefazodone was selected as the active drug on the basis of its good tolerability profile. Nefazodone has minimal activation-type side effects, an incidence of weight gain comparable

Table 4. Adverse Experiences (%) Reported by  $\geq 10\%$  of Patients in the Nefazodone Chronic Depression Study<sup>a</sup>

Adverse Experience	Nefazodone/ Psychotherapy			p Value <sup>b</sup>
	Nefazodone (N = 225)	Psychotherapy (N = 221)	Psychotherapy (N = 226)	
Headache	56	45	65	< .001
Somnolence	40	1	36	< .001
Dry mouth	39	0	35	< .001
Nausea	30	6	36	< .001
Dizziness	25	2	29	< .001
Dyspepsia	21	12	19	.02
Insomnia	19	8	19	.004
Diarrhea	19	10	23	< .001
Asthenia	17	6	20	< .001
Constipation	16	1	17	< .001
Abnormal vision	15	< 1	20	< .001
Pain	14	12	21	.02
Abdominal pain	13	10	18	.08
Light-headedness	12	< 1	14	< .001
Pharyngitis	12	5	10	.05
Sinusitis	12	11	10	.89
Blurred vision	11	1	10	< .001
Agitation	10	2	8	< .001
Infection	9	13	12	.50
Difficulty concentrating	9	1	10	< .001
Back pain	8	10	12	.23

<sup>a</sup>Reprinted with permission from Keller et al.<sup>13</sup><sup>b</sup>Fisher exact test used to test for differences among the 3 groups.

to placebo, and, compared with placebo, lack of significant effect on sexual function in men and women. These attributes made nefazodone desirable for long-term maintenance treatment studies.<sup>38,39</sup>

During the 12-week acute phase, the most common adverse experiences occurring in the medication-treated groups were headache, somnolence, dry mouth, nausea, and dizziness (Table 4).<sup>13</sup> Weight gain did not occur in either the nefazodone group or the CBASP-treated group; weight gain occurred in 3.1% of the combined treatment group. Rates of withdrawal were similar: 26% (59/226) in the nefazodone group, 24% (55/228) in the CBASP group, and 21% (48/227) in the combination treatment group ( $p = .46$ ). Only 1% of patients from each group withdrew because of lack of efficacy. Fourteen percent of the nefazodone group withdrew because of adverse experiences, compared with 1% of those receiving CBASP and 7% receiving combination treatment.<sup>13</sup>

Sexual function was assessed with the Modified Rush Sexual Inventory, a validated self-rated scale. A statistically significant improvement in sexual function occurred in all 3 treatment groups from baseline to week 12. Patients receiving combination treatment showed significantly greater improvement in overall sexual satisfaction ( $p < .006$ ) than patients receiving either nefazodone or CBASP alone. The frequency of both initiation of sexual activity and sexual satisfaction improved in both men and women across all treatment groups. There was no reported worsening of any area of sexual functioning or satisfaction in any treatment group.<sup>40</sup>

## SUMMARY: DISCONTINUATION AND SAFETY IN CHRONIC DEPRESSION

On the basis of the data presented, nefazodone appears to be devoid of a discontinuation syndrome on abrupt discontinuation of 16 weeks of nefazodone treatment. In 1 study, sexual functioning improved in chronically depressed patients receiving nefazodone, CBASP, or the combination of nefazodone and CBASP. However, the greatest improvement was seen in the combination therapy group. This outcome of improvement in sexual function is what clinicians and patients hope to see with improvement in depressive symptoms.

## Effects of Nefazodone on Body Weight

Norman Sussman, M.D., and  
Julia L. Seabolt, Pharm.D.

Given the medical and cosmetic consequences of being overweight and the fact that many depressed patients require extended treatment, being "weight neutral" is an important property of an antidepressant drug. The sheer magnitude of antidepressant use makes this issue important to patients and prescribers alike. Both acute and long-term placebo-controlled or substitution studies of nefazodone have demonstrated a lack of significant treatment-associated weight gain.<sup>2,23</sup> The SSRIs have even been shown to briefly promote weight loss early in treatment. However, in the decade since their introduction, isolated reports have appeared implicating SSRIs as the cause of unexpected weight gain during long-term treatment.<sup>41-47</sup> These reports have been criticized as being anecdotal or from small, non-placebo-controlled trials and thus less reliable. The revised Practice Guideline for the Treatment of Patients with Major Depressive Disorder cites controversy in various postmarketing reports and notes a need to clarify "whether patients taking SSRIs beyond the acute phase do or do not experience weight gain as a medication side effect."<sup>48(p27)</sup> Nefazodone has not been implicated in published anecdotal reports or in studies as being associated with increases in body weight.

To resolve the uncertainty and controversy about the weight effects of the SSRIs, it would be useful if new long-term, placebo-controlled studies could be initiated with existing drugs. However, a number of obstacles to this suggestion exist. One difficulty is the expense of conducting the studies. Another is the need for a large enroll-

ment and completion rate to afford the statistical power to detect clinically significant differences. It is also difficult to enroll patients in a placebo-controlled trial in which the active treatment is readily available for clinical use. It might be possible to initiate prospective monitoring of patients in the clinical setting, but the outcome of such studies would be subject to criticism regarding lack of randomization and investigator bias.

In view of these difficulties, an alternative method has been to extract data from completed studies that compared active treatments. By using previously unanalyzed data from individual patients participating in a series of related trials, comparisons can be made about weight changes. At least 1 such analysis of SSRI studies has been conducted, and the results showed that paroxetine, but not sertraline or fluoxetine, caused clinically significant weight gain in 25.5% of patients over 26 to 32 weeks of treatment.<sup>44</sup> In contrast to these findings, however, an analysis of long-term fluoxetine (up to 50 weeks) and placebo therapy showed that weight gain was comparable with both treatments (approximately 3 kg [7 lb]).<sup>49</sup>

Because of the extensive degree of antidepressant drug use in our society, it is important to clarify differences between them with respect to their effects on body weight. Unwanted, excessive weight gain is a consequence of treatment with a broad range of psychotropic drugs, including the antipsychotic agents clozapine and olanzapine, the antidepressant mirtazapine,<sup>19</sup> and mood stabilizers such as lithium, valproic acid, and carbamazepine. Increased body weight associated with these agents has been observed in controlled trials and in the clinical setting, and these findings tend to arouse little controversy.

Nonpharmacologic factors, such as a nonspecific recovery effect, may explain weight gain during antidepressant therapy.<sup>50</sup> Thus, a modest increase in body weight may occur over time in patients recovering from depression. Reduction in anxiety and psychomotor activity has also been invoked as a possible source of reduced caloric expenditure and subsequent weight gain. Nefazodone has a comparable onset of action and response rate to selected SSRIs (fluoxetine, paroxetine, sertraline) and imipramine and was actually better than imipramine on some measures of depression-related anxiety.<sup>51</sup> However, these theories do not explain the differences in impact on weight gain observed between nefazodone and SSRIs. Part of the problem is that there is no accepted explanation as to why some SSRIs cause weight gain. Impact on the serotonin system, in particular the serotonin 5-HT<sub>2C</sub> receptor, has been suggested as the mechanism underlying SSRI weight effects. The effects of a nefazodone metabolite, *m*-chlorophenylpiperazine (*m*-CPP), may explain why nefazodone is considered "weight neutral."

Our analysis tends to support reports that the weight gain associated with SSRIs is a function of the duration of treatment. We postulate that the increased risk of weight

gain reported with paroxetine relative to fluoxetine<sup>44</sup> and sertraline<sup>41,44</sup> may be partially explained because patients taking fluoxetine or sertraline may gain weight later in the treatment course. We recently have shown, for example, that SSRIs cause more weight loss during short-term treatment than nefazodone but more weight gain during long-term treatment. We also demonstrated that, in comparative studies, imipramine caused more weight gain than nefazodone.<sup>52</sup>

Understandably, it is difficult to characterize the precise incidence of weight gain with a specific drug. In most studies, up to 10% of patients receiving placebo may experience clinically significant weight gain during long-term treatment. From a clinical perspective, the long-term effects of a drug on body weight may be more significant than its acute effects. These findings argue against the fact that weight gain during antidepressant therapy can be explained as merely a recovery effect.<sup>50</sup> In addition, a recent study has demonstrated clinically significant weight gain in paroxetine-treated patients with panic disorder.<sup>53</sup> Panic disorder does not usually result in weight loss, making it unlikely that significant weight gain during treatment is the result of a return to premorbid body weight.

#### EFFECTS OF NEFAZODONE ON BODY WEIGHT

Nefazodone has not been reported to cause significant increases or decreases in weight during acute or long-term treatment. In a pooled analysis of placebo-controlled, premarketing, acute-treatment studies, no differences were noted between nefazodone and placebo in the proportions of patients meeting criteria for potentially important increases or decreases in body weight (i.e., change  $\geq 7\%$ ).<sup>3</sup>

In a long-term treatment study, patients who responded to 16 weeks of open-label nefazodone treatment and who received nefazodone for up to an additional 36 weeks were no more likely to gain weight than those receiving placebo (0.6-kg [1.3-lb] gain in the nefazodone group, 0.9-kg [2.0-lb] gain in the placebo group).<sup>23</sup> When these data were pooled with those from another study,<sup>54</sup> no significant differences were noted between nefazodone and placebo in the proportion of patients meeting criteria for potentially important increases or decreases (i.e., change  $\geq 7\%$ ) in body weight (Table 5).

Analysis of body weight changes in a study of patients with chronic major depression also showed no statistically significant differences across treatment groups associated with acute or continuation nefazodone treatment alone or in combination with psychotherapy.<sup>13,55</sup> Following an acute 12-week phase, complete and partial responders were continued for a 28-week continuation phase. After 28 weeks, an increase in body weight of 7% or more occurred in 4% of patients receiving psychotherapy, 5% receiving nefazodone, and 4% receiving combination treatment. Reduction



**Table 5. Impact of Long-Term Nefazodone Treatment on Weight in Depressed Patients During Placebo-Controlled Trials<sup>a</sup>**

Patients	N	% of Patients With Weight Gain $\geq$ 7% From Baseline
All patients		
Nefazodone	119	10.9
Placebo	121	9.9
Females		
Nefazodone	79	7.6
Placebo	81	8.6

<sup>a</sup>Data from Feiger et al.,<sup>23</sup> Kornstein and McEnany,<sup>54</sup> and data on file, Bristol-Myers Squibb Company, Princeton, N.J.

in body weight of greater than 7% was observed in 8% of patients receiving psychotherapy, 9% of patients receiving nefazodone, and 15% of patients receiving combination therapy.<sup>56</sup> These results are congruent with other data that support a neutral effect of nefazodone on body weight.<sup>2,19</sup>

### SUMMARY: WEIGHT EFFECTS OF NEFAZODONE

Nefazodone has minimal effects on body weight in patients receiving the drug for acute or long-term treatment of major depression. Significant weight changes in these studies were comparable to placebo. In patients with chronic major depression receiving acute- and continuation-phase treatment with nefazodone, psychotherapy, or the combination, changes in weight were not statistically different among the groups. Thus, nefazodone can be considered weight neutral.

*Drug names:* carbamazepine (Tegretol and others), citalopram (Celexa), clozapine (Clozaril and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), mirtazapine (Remeron), nefazodone (Serzone), olanzapine (Zyprexa), paroxetine (Paxil), pimozide (Orap), sertraline (Zoloft), trazodone (Desyrel and others), valproic acid (Depakene and others), venlafaxine (Effexor).

### REFERENCES

- Davis R, Whittington R, Bryson HM. Nefazodone: a review of its pharmacology and clinical efficacy in the management of major depression. *Drugs* 1997;53:608–636
- Robinson DS, Roberts DL, Smith JM, et al. The safety profile of nefazodone. *J Clin Psychiatry* 1996;57(suppl 2):31–38
- Serzone [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2000
- Marcus RN. Safety and tolerability profile of nefazodone. *J Psychopharmacol* 1996;10(suppl 1):11–17
- 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
- Mendels J, Reimherr F, Marcus RN, et al. A double-blind, placebo-controlled trial of two dose ranges of nefazodone in the treatment of depressed outpatients. *J Clin Psychiatry* 1995;56(suppl 6):30–36
- Baldwin DS, Hawley CJ, Abed RT, et al. A multicenter double-blind comparison of nefazodone and paroxetine in the treatment of outpatients with moderate-to-severe depression. *J Clin Psychiatry* 1996;57(suppl 2):46–52
- 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
- Rioux P, Kibleur Y, Franchon O, et al. A double-blind comparison of nefazodone and fluoxetine in depressed patients. In: *New Research Program and Abstracts of the 149th Annual Meeting of the American Psychiatric Association*; May 7, 1996; New York, NY. Abstract NR359:164
- Brodie-Meijer CC, Diemont WL, Buijs PJ. Nefazodone-induced clitoral priapism. *Int Clin Psychopharmacol* 1999;14:257–258
- Kraus R. Visual “trails” with nefazodone treatment [letter]. *Am J Psychiatry* 1996;153:1365–1366
- Schwartz K. Nefazodone and visual side effects [letter]. *Am J Psychiatry* 1997;154:1038
- 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
- Ferguson JM, Shrivastava R, Stahl SM, et al. Reemergence of sexual dysfunction in patients with major depressive disorder: double-blind comparison of nefazodone and sertraline. *J Clin Psychiatry* 2001;62:24–29
- Mackle M, Kocsis J. Effects on body weight of the SSRI citalopram. Presented at the 37th annual meeting of the American College of Neuropsychopharmacology; Dec 14–18, 1998; Las Croabas, Puerto Rico
- Montejo AL, Llorca G, Izquierdo JA, et al. Antidepressant-induced sexual dysfunction: a multicenter and prospective study using a questionnaire of 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
- Montejo AL, Llorca G, Izquierdo JA, et al. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther* 1997;23:176–194
- Rudorfer MV, Manji HK, Potter WZ. Comparative tolerability profiles of the newer versus older antidepressants. *Drug Saf* 1994;10:18–46
- Sussman N, Ginsberg D. Rethinking side effects of the selective serotonin reuptake inhibitors: sexual dysfunction and weight gain. *Psychiatr Ann* 1998;28:89–97
- Aranda-Michel J, Koehler A, Bejarano PA, et al. Nefazodone-induced liver failure: report of 3 cases. *Ann Intern Med* 1999;130:285–288
- Schrader GD, Roberts-Thompson IC. Adverse effect of nefazodone: hepatitis [letter]. *Med J Aust* 1999;170:452
- Lader MH. Tolerability and safety: essentials in antidepressant pharmacotherapy. *J Clin Psychiatry* 1996;57(suppl 2):39–44
- Feiger AD, Bielski RJ, Bremner J, et al. Double-blind, placebo substitution study of nefazodone in the prevention of relapse during continuation treatment of outpatients with major depression. *Int Clin Psychopharmacol* 1999;14:19–28
- Kramer JC, Klein DF, Firdk M. Withdrawal symptoms following discontinuation of imipramine therapy. *Am J Psychiatry* 1961;118:549–550
- Anderson IM. SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress Anxiety* 1998;7(suppl 1):11–17
- Barr LC, Goodman WK, Price LH. Physical symptoms associated with paroxetine discontinuation [letter]. *Am J Psychiatry* 1994;151:289
- Lazowick A, Levin GM. Potential withdrawal syndrome associated with SSRI discontinuation. *Ann Pharmacother* 1995;29:1284–1285
- Price JS, Walker P, Wood S, et al. A comparison of the postmarketing safety of four selective serotonin reuptake inhibitors including the investigation of symptoms occurring on withdrawal. *Br J Clin Pharmacol* 1996;42:757–763
- Rosenbaum JF, Fava M, Hoog SL, et al. SSRI discontinuation syndrome: a randomized clinical trial. *Biol Psychiatry* 1998;44:77–87
- Schatzberg AF, Rosenbaum JF, Haddad P, et al. Serotonin reuptake inhibitor discontinuation syndrome: a hypothetical definition. *J Clin Psychiatry* 1997;58(suppl 7):5–10
- Zajacka J, Miles W, Cobb T, et al. The safety of abrupt discontinuation of nefazodone. In: *New Research Program and Abstracts of the 151st Annual Meeting of the American Psychiatric Association*; June 4, 1998; Toronto, Ontario, Canada. Abstract NR716:262
- Burrows GD. Long-term clinical management of depressive disorders. *J Clin Psychiatry* 1992;53(3, suppl):32–35
- Clinical Practice Guideline Number 5: Depression in Primary Care, vol 2. Treatment of Major Depression. Rockville, Md: US Dept Health Human Services, Agency for Health Care Policy and Research; April 1993. AHCPR publication 93-0551

34. Frank E, Kupfer DJ, Perel JM, et al. Three-year outcomes for maintenance therapies in recurrent depression. *Arch Gen Psychiatry* 1990;47:1093–1099
35. Hirschfeld RMA, Russell JM, Delgado PL, et al. Predictors of response to acute treatment of chronic and double depression with sertraline or imipramine. *J Clin Psychiatry* 1998;59:669–675
36. Lavori PW, Keller MB, Mueller TI, et al. Recurrence after recovery in unipolar MDD: an observational follow-up study of clinical predictors and somatic treatment as a mediating factor. *Int J Methods Psychiatr Res* 1994;4:221–229
37. Miller IW, Keitner GI, Schatzberg AF, et al. The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. *J Clin Psychiatry* 1998;59:608–619
38. Dubovsky SL. Beyond the serotonin reuptake inhibitors: rationales for the development of new serotonergic agents. *J Clin Psychiatry* 1994;55(2, suppl):34–44
39. Richelson E. Pharmacology of antidepressants: characteristics of the ideal drug. *Mayo Clin Proc* 1994;69:1069–1081
40. Zajecka J, Dunner DL, Hirschfeld RMA, et al. Sexual function and satisfaction in the treatment of chronic major depression with nefazodone, psychotherapy and their combination. In: *New Research Abstracts of the 153rd Annual Meeting of the American Psychiatric Association*; May 16, 2000; Chicago, Ill. Abstract NR443:176–177
41. Aberg-Wistedt A, Agren H, Eskelius L, et al. Sertraline versus paroxetine in major depression: clinical outcome after six months of continuous therapy. *J Clin Psychopharmacol* 2000;20:645–652
42. Amsterdam JD, Garcia-Espana F, Goodman D, et al. Breast enlargement during chronic antidepressant therapy. *J Affect Disord* 1997;46:151–156
43. Bouwer CD, Harvey BH. Phasic craving for carbohydrate observed with citalopram. *Int Clin Psychopharmacol* 1996;11:273–278
44. Fava M, Judge RA, Hoog SL, et al. Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. *J Clin Psychiatry* 2000;61:863–867
45. Fisher S, Kent TA, Bryant SG. Postmarketing surveillance by patient self-monitoring: preliminary data for sertraline versus fluoxetine. *J Clin Psychiatry* 1995;56:288–296
46. Fogelson DL. Weight gain during fluoxetine treatment. *J Clin Psychopharmacol* 1991;1:220–221
47. Joubert AF, Gagiano CA, Joubert G. Antidepressants and weight: comparative study of four antidepressants and their effect on weight. *Eur Neuropsychopharmacol* 1996;6(suppl 3):43
48. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder [Revision]. *Am J Psychiatry* 2000;0157(suppl 4):1–45
49. Michelson D, Amsterdam JD, Quitkin FM, et al. Changes in weight during a 1-year trial of fluoxetine. *Am J Psychiatry* 1999;156:1170–1176
50. Benazzi F. Weight gain in depression remitted with antidepressants: pharmacological or recovery effect? *Psychother Psychosom* 1998;67:271–274
51. 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
52. Sussman N, Ginsberg DL, Bikoff J. Effects of nefazodone on body weight: a pooled analysis of selective serotonin reuptake inhibitor- and imipramine-controlled trials. *J Clin Psychiatry* 2001;62:256–260
53. Dannon PN, Iancu I, Grunhaus LJ. Does weight change follow recovery from panic disorder? In: *New Research Program and Abstracts of the 151st Annual Meeting of the American Psychiatric Association*; May 18, 1999; Washington, DC. Abstract NR320:153–154
54. Kornstein SG, McEnany G. Enhancing pharmacologic effects in the treatment of depression in women. *J Clin Psychiatry* 2000;61(suppl 11):18–27
55. Dunner DL. Acute and maintenance treatment of chronic depression. *J Clin Psychiatry* 2001;62(suppl 6):10–16
56. Kocsis JH, Arnow BA, Borian FE, et al. Continuation treatment with nefazodone, cognitive behavioral analysis system of psychotherapy, and their combination for chronic major depression. In: *New Research Abstracts of the 154th Annual Meeting of the American Psychiatric Association*; May 8, 2001; New Orleans, La. Abstract NR388:105–106

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