Abstract

In spite of high prevalence of major depression, it is unrecognized or misdiagnosed in approximately 50% of affected individuals. The management of depression involves continued treatment (usually 3 to 6 months to prevent relapse) and maintenance treatment (usually 6 to 24 months to prevent reoccurrence of depression).

Although, development of TCAs was a major breakthrough in the treatment of depression, these agents are associated with undesirable anticholinergic, CNS and CVS effects. This prompted the researchers to look for new pharmacological agent with notably fewer side effects. SSRI, which came later, had similar therapeutic profile, but offered improved tolerability. Nefazodone, a new drug in the arsenal of antidepressants, has a dual mechanism of action, acting as an antagonist at post synaptic 5HT2A receptors and as an inhibitor of 5-HT and norepinephrine reuptake. In clinical trials, nefazodone has shown superiority in comparison to placebo and the same efficacy as imipramine, paroxetine, sertraline and fluoxetine. The tolerability profile of nefazodone is better than that of imipramine in clinical trials. The available data suggest that nefazodone is better than imipramine in clinical trials and that nefazodone represents a useful alternative to SSRI and TCA in the treatment of patients with major depression as it is associated with fewer side effects. It is also a promising drug in the treatment of post-traumatic stress disorder, social phobia and chronic fatigue syndrome.

Keywords: Nefazodone; depression.

Introduction

Depression is one of the most common psychiatric disorders. Many drugs like tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors etc., are available, which are used frequently in the management of depression. Nefazodone a novel drug, introduced for management of major depression can be a safe alternative to TCA and SSRI in patients with major depression. It has also been found to have beneficial effects in marked or severe depression, refractory depression and HIV and cancer-related depression. Few clinical studies have also demonstrated efficacy in managing symptoms of post-traumatic stress disorder, social phobia and chronic fatigue syndrome. However, controlled studies are required to investigate these preliminary findings as well as to compare nefazodone with currently available treatment.

Chemistry

Nefazodone hydrochloride is a phenyl piperazine derivative with a dual mechanism of action which is different from the other currently available drugs. It is a potent and selective blocker of post synaptic serotonin (5-HT), 5 HT2A receptors and moderately inhibits 5-HT and norepinephrine uptake. Like most clinically active anti-depressant drugs, long-term administration of nefazodone causes down regulation of 5HT2 receptors in the cortex.

Pharmacology

Pharmacodynamic properties

Various in vitro studies have demonstrated that nefazodone and its metabolites have potent antagonist effect on 5HT2A receptors and moderate inhibitory action on reuptake of 5-HT or norepinephrine, which together may result in modulation of serotonergic neurotransmission.

Effect on 5-HT Mechanism

Table I illustrates the high affinity of nefazodone for 5HT2A receptors, which is less than that of trazodone. In contrast, fluoxetine had little affinity for 5HT2A and 5HT1A receptors but a greater tendency to inhibit 5-HT uptake.

Table I: Receptor binding studies of nefazodone and 4 of its metabolites, trazodone and fluoxetine. Values indicate drug concentration in mmol/L
producing a 50% inhibition of 5-HT receptors.  

<table>
<thead>
<tr>
<th>Drug</th>
<th>Serotonergic receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5HT2A</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>52</td>
</tr>
<tr>
<td>Hydroxynefazodone</td>
<td>34</td>
</tr>
<tr>
<td>mCPP</td>
<td>433</td>
</tr>
<tr>
<td>Trazoledione</td>
<td>211</td>
</tr>
<tr>
<td>Trazodone</td>
<td>11</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>6170</td>
</tr>
</tbody>
</table>

A recent in-vivo study using rat or mouse brain confirmed that nefazodone is an antagonist at 5HT2A receptors.  

In addition, nefazodone (100 and 150 mg/kg) considerably inhibited 5-HT reuptake in rat brain synaptosomes.  

In a small clinical study, 20 healthy male volunteers were divided into 4 groups receiving either of the following: nefazodone (400mg or 100 mg/day), fluoxetine (20 mg/day) and placebo. The results showed that there was a significant reduction in the ex vivo rate of platelet 5-HT reuptake in the 1st and 3rd versus the 2nd and 4th group.  

**Receptor affinity**  

Results of receptor affinity studies show that nefazodone lacks affinity for muscarinic, cholinergic, adenosine, dopaminergic, benzodiazepine, opiate, aminobutyric acid A, calcium channel and N-methyl-D-aspartate receptors.  

However, it showed low affinity for H1 receptors.  

**Effects on sleep**  

Approximately 90% of patients suffering from depression show some form of sleep disturbance, which may be characterized by insomnia, short latency to the first phase REM sleep, multiple awakenings and decreased restorative slow wave sleep. Most antidepressants cause an increase in REM sleep latency and decrease in total duration of sleep. On the contrary, nefazodone does not bring about these changes. It decreases nocturnal awakenings and percentage of time awake.  

In a randomized 16-day double blind study comprising healthy volunteers, nefazodone 400 mg/day did not significantly suppress REM sleep and had little effect on sleep continuity as assessed by polysomnography.  

In another study (n=10), nefazodone (400 mg/day for 4 to 8 weeks) decreased duration of time awakening and stage I sleep and increased duration of stage II sleep. Similar effects on sleep architecture have been reported in various studies that analyzed the effect of nefazodone on sleep pattern.  

**Effects on psychomotor and cognitive functions**  

The effects of nefazodone on psychomotor and cognitive functions were assessed by a standard highway drinking test and battery of psychomotor tests including letter matching, memory scanning and letter/digit differentiation. Overall results indicated insignificant difference in driving performance between nefazodone or imipramine and placebo. Nevertheless,
similar to all other antidepressants drugs, patients taking nefazodone should be cautioned about engaging in any hazardous or risk bearing activity. Significant alterations in cardiovascular functions have not been observed with nefazodone treatment over short periods.21 Another advantage of nefazodone is its lower propensity to cause priapism as compared to trazodone.19

Pharmacokinetic properties

The pharmacokinetic properties of the nefazodone maybe described in following headlines.

Absorption

It is rapidly and completely absorbed from the intestine, when taken orally.22 Peak plasma concentration of nefazodone occurs within 2 hours after an oral dose.8,23,24 Pharmacokinetics of nefazodone are nonlinear and increase in plasma concentrations is not proportional to increase in dose. Steady-state plasma concentrations of nefazodone are attained within 4 days of the commencement of administration.24 The pharmacokinetic parameters have been compiled in table II.

Table II: Pharmacokinetic parameters of nefazodone

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters22,26</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax</td>
<td>1 hour</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>5-23%</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Plasma elimination half life</td>
<td>2-3.5</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>0.22-0.87 L/kg</td>
</tr>
</tbody>
</table>

Metabolism

The drug undergoes extensive first pass metabolism. As a result, absolute bioavailability is only 20% approximately.22 Oral bioavailability of nefazodone is increased by 18% in the presence of food, but this increase is not clinically significant and nefazodone can be administered without regards to meals.24 It is extensively metabolized in the liver and approximately 52% and 31% of the administered drug is excreted as free and conjugated nefazodone metabolites in the urine and faeces respectively. Less than 1% of the administered dose is excreted unchanged in the urine.22,25

There are 4 metabolites of nefazodone: hydroxynefazodone, triazoledione, metochlorophenylpiperazine (mCPP) (minor) and p-hydroxy- nefazodone (rare). The first three metabolites have some degree of 5HT2A antagonism. Hydroxynefazodone is the primary metabolite and shows equivalent activity as the parent compound on 5HT2A receptors and 5-HT reuptake sites.8 Triazoleidine metabolite has 7-fold lower affinity for 5HT2A receptors and no affinity for 5-HT reuptake sites in comparison to nefazodone. The amino metabolite, mCPP, has equivalent potency to block 5-HT reuptake but has no affinity for 5HT2A receptors as compared to nefazodone.1 Nefazodone and its metabolites have high affinity for cytochrome P450 3A4, which is a specific isoenzyme involved in the metabolism of nefazodone. The elimination half-life of nefazodone and hydroxynefazodone at steady state is similar - 2 to 3.5 hours after multiple doses of nefazodone (50 to 200 mg daily).26

Distribution

Nefazodone is widely distributed in the body tissue including the CNS. The volume of distribution ranges from 0.2 to 0.87 L/kg in humans.26 It is highly plasma protein bound (>99%). However, nefazodone does not alter in vitro protein binding of diazepam, phenytoin, lignocaine, prazosin, propranolol, verapamil or warfarin but it is not known whether displacement of either nefazodone or other drugs occur in vivo.26

Excretion

It is excreted mainly in urine and faeces, both in free as well as conjugated form. Less than one percent of the drug is excreted unchanged in the urine.25 Results of experimental studies based on AUC ratios suggest that conversion of nefazodone to hydroxynefazodone is not a saturable process while formation of mCPP is a saturable process.27
Pharmacokinetic in special population

Elderly

A single dose of nefazodone (300 mg) results in doubled Cmax and AUC values in elderly (>65 years) in comparison to younger (18 to 40 years) volunteers. Since nefazodone undergoes extensive metabolism, the increase in systemic exposure to the drug in elderly population probably reflects decreased metabolic clearance in this group. Keeping this in mind, the initial dose of nefazodone in elderly should preferably be kept low.28,29

Population with hepatic impairment

Two-fold increase in systemic exposure has been reported in patients with hepatic cirrhosis probably reflecting decreased clearance of the drug. Other studies assessing the pharmacokinetics of nefazodone on the basis of Cmax and mean AUC values have confirmed the increased systemic exposure in hepatic impairment.27,29 Therefore a lower daily dosage of nefazodone in this subset of patients is advised.

Adverse effects

Common adverse events seen in clinical trials include dry mouth, constipation and blurred vision. However, the incidence of these events was less in subjects taking nefazodone as compared to imipramine recipient's.30 Anti-cholinergic adverse effects occur at lower frequency in comparison with the imipramine. (See table III for adverse events in nefazodone versus placebo recipients).

Unlike TCA and trazodone, nefazodone has not been reported to cause abnormal weight gain. It is also associated with low incidence of cardiovascular effects eg, orthostatic hypotension, tachycardia and prolonged QTc interval than imipramine. However, in comparison to placebo, nefazodone was associated with a higher incidence of reduced systolic blood pressure (<90 mmHg and >20 mmHg change from baseline)30 and sinus bradycardia.26

Table III: Adverse events reported in a short-term double blind placebo controlled study30

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Nefazodone (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>21</td>
<td>151</td>
</tr>
<tr>
<td>Somnolence</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Asthenia</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Light headedness</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

No significant differences in the rates of suicidal ideation or suicidal attempts were noted between nefazodone, placebo and imipramine recipients in the placebo controlled trials.31 In comparison to nefazodone, SSRI was associated with a higher incidence of the activating symptoms (like agitation, anxiety, tremor, insomnia, nervousness), diarrhoea, sweating, anorexia, nausea and male sexual dysfunction. However, the use of nefazodone is generally associated with a higher incidence of dizziness, dry mouth, constipation, visual disturbances and confusion than SSRI. Three cases of subfulminant liver failure possibly associated with nefazodone therapy (14 to 28 weeks) have been reported. Histological appearance was similar in all the 3 cases with prominent necrosis in the centrilobular areas. Because of possible likelihood of nefazodone being the cause of severe hepatocellular injury, routine liver chemistries should be performed before starting nefazodone therapy and patients should be monitored regularly. Therapy should be discontinued if liver enzyme concentrations become abnormal.32,33
Drug interactions

Nefazodone being a potent inhibitor of CYP 3A4 isoenzyme has a higher propensity to interact with psychotropics, analgesics, hormonal cardiac, immunosuppressants, antineoplastic and antihistaminic agents. It is, however, a much weaker CYP2D6 inhibitor than the SSRI. Nefazodone is absolutely contraindicated with concurrent administration of terfenadine, astemizole, and cisapride and may not be suitable for all patient populations. Therefore, one has to be careful in prescribing novel antidepressants because of the risk of untoward drug-drug interactions, particularly in more diverse ethnic patient populations.

Although, concomitant prescription of nefazodone and BZ initially improves sleep pattern, it causes daytime sedation simultaneously. Moreover, the theory that temazepam, the only BZ not dependent on cytochrome mechanism for metabolism, will cause least sedation, and triazolam, because of its cytochrome metabolism interference with nefazodone will cause the most sedation is not confirmed as yet. However, triazolam (0.25 mg) is the safest BZ to be combined with nefazodone as compared to alprazolam, temazepam and diazepam. However, no pharmacokinetic or pharmacodynamic interactions have been observed with lorazepam.

Nefazodone should not be administered with or within 14 days after discontinuation of a MAO inhibitors. After discontinuation of nefazodone, at least 7-day drug-free period should be allowed before initiating therapy with MAO inhibitors. Co-administration of nefazodone does not modify pharmacokinetic parameters of lithium as evident by no significant differences between the AUC of nefazodone when administered alone or with lithium. Nefazodone does not affect the pharmacokinetics of theophylline, a compound cleared by CYP1A2. No clinically significant interaction was observed when nefazodone was administered with lorazepam, lithium, alcohol, cimetidine, warfarin, theophylline or propranolol. Refer table IV for drug interactions of nefazodone and their management.

Table IV: Common drug interactions of nefazodone

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>Significant increase in plasma concentration of alprazolam may result in increased psychomotor impairment and sedative effects.</td>
<td>Reduction of alprazolam dose by 10%.</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Significant increase in AUC of triazolam.</td>
<td>Reduction of triazolam dose by 75%.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Increased plasma carbamazepine levels resulting in toxicity.</td>
<td>Plasma concentration monitoring and/or dosage reduction of carbamazepine.</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>36% reduction in single dose AUC of haloperidol.</td>
<td>Dose reduction of haloperidol may be necessary.</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Increase in plasma digoxin concentration by 25%</td>
<td>Monitoring of plasma digoxin levels is recommended.</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Significant decrease in AUC and Cmax of propranolol.</td>
<td>Dose adjustment should be made on the basis of clinical response.</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Increase in plasma concentration of cyclosporin by 70%.</td>
<td>Plasma concentration monitoring of cyclosporin.</td>
</tr>
<tr>
<td>Terfenadine, Astemizole and Cisapride</td>
<td>Increase in plasma concentration of all the three drugs.</td>
<td>Caution is advised because of risk of cardiotoxicity.</td>
</tr>
</tbody>
</table>

Dosage and administration

The effective therapeutic range of nefazodone appears to be 300-600 mg/day. The recommended starting dose of nefazodone is 50 to 100 mg BD. The dosage should be increased after a minimum of 7 days with 100 to 200 mg increments, until the desired clinical response is observed (maximum of 600 mg/day). However, the results of a study suggests that nefazodone given once/day at bedtime maybe as effective as the currently accepted twice/day regimen, with less day time drowsiness.

In elderly, debilitated or drug sensitive patient, the recommended starting dose is 50mg BD and it is better to titrate the dosage slowly. Because of decreased metabolic clearance in patients with hepatic impairment, lower daily dosage of nefazodone in these patients is advised.

Therapeutic Efficacy

i. Major depression
Long-term clinical efficacy of nefazodone in depressed patients has been documented up to 1 year’s treatment and was accompanied by a good safety profile without any weight gain and with minimal symptoms of withdrawal upon abrupt discontinuation of treatment.

Efficacy was primarily assessed by Clinical Global Impressions (CGI) and 17-item Hamilton Rating Scale for Depression (HAM-D-17).

1. Versus placebo:
   Nefazodone was more effective than placebo in the treatment of hospitalized patients with severe depression.

2. Versus TCA:
   Clinical efficacy of nefazodone was similar to imipramine in various comparative studies.

3. Versus SSRI:
   Nefazodone showed equal efficacy to paroxetine, sertraline and fluoxetine in patients with depression. Both nefazodone and the SSRI achieved consistent and continuous improvements over the 6 to 8-week treatment periods.

Results of a case series suggests that methadone-maintained depressed patients who do not respond and/or suffer various side effects with other drugs, such as sertraline, risperidone, and bupropion may respond well to nefazodone.

ii. Marked or severe depression in hospitalized patients:

In a 6-week trial, 120 hospitalized patients of major depression (without psychosis) received either nefazodone or placebo. Efficacy of the treatment was evaluated using standard psychiatric rating scales. Nefazodone was found to be superior to placebo in the treatment of marked to severe major depression in patients requiring hospitalization. The clinical benefit of nefazodone was evident as early as the first week of treatment as judged by several measures of efficacy, with significant differences from placebo sustained throughout the trial. The mean nefazodone dose was 491 mg/day at the end of week 2 and 503 mg/day at the end of the treatment.

iii. Relapse of Depression:

In a 36-week double-blind, placebo controlled trial, 131 patients in stable remission after 16 weeks of acute, single-blind treatment with nefazodone were randomized in a 36-week double-blind trial to either nefazodone (n=65) or placebo (n=66). Those having a total score > or = 18 on the 17-item HAMD scale on 2 consecutive visits or if the treatment was discontinued for lack of efficacy were classified as relapse cases. Kaplan-Meier estimates of relapse rates 9 months (36 weeks) after the end of acute treatment were 1.8% for nefazodone versus 18.3% for placebo (P=0.009) by the HAMD Scale and 17.3% versus 32.8% (P=0.028) by discontinuation for lack of efficacy.

iv. Refractory depression:

It is associated with severe functional impairment, high morbidity and high cost of treatment. Nefazodone was evaluated as a therapeutic option in 20 patients (mean age 48.1+/-.9.4 years) of treatment-resistant and treatment-intolerant depression. Beck Depression Inventory (BDI) was completed before and after (> or = 4 weeks) initiation of nefazodone therapy along with CGI scores. After nefazodone administration, 11 of 20 patients (55%) were rated on the CGI as much or very much improved. In addition, 9 patients (45%) had >20% improvement on BDI, 3 patients (15%) had 10% to 20% improvement, and 6 patients (30%) had <10% change. Two patients (10%) discontinued nefazodone therapy due to adverse effects. In this study, approximately 50% of patients had substantial response to treatment with a smaller proportion having a more modest clinical response. However, larger and controlled studies are needed to confirm these preliminary observations.

v. HIV-related depression:

TCA and SSRI have shown comparable efficacy in treating major depression in HIV positive patients. Nefazodone was assessed in HIV related depression on the basis that it is more tolerable than TCA and SSRI. In an open 12-week trial, 15 HIV-seropositive outpatients with DSM-IV major depressive disorder and score of > or = 18 on 21 item HAMD Scale were treated with open-label nefazodone. The HAM-D-21, CGI, and Systematic Assessment for Treatment Emergent Events general inquiry (for safety and tolerability) scores were obtained at weeks 2, 4, 6, 8, and 12. Four patients discontinued treatment. Of the remaining eleven, 8 patients (73%) showed full response as assessed by 50% reduction in HAM-
D scores and final CGI score of 1 or 2. Nefazodone treated subjects experienced few total adverse effects (mean = 1.5), no sexual side effects, and low rates of adverse-effect-related dropout (1 subject, 7%). Thus, nefazodone may have a role in the treatment of depression in HIV-seropositive patients. Potential drug interactions with protease inhibitors indicate that it is essential to evaluate the appropriate dosing to avoid adverse effects and increase overall antidepressant efficacy.\textsuperscript{61}

\textbf{vi. Cancer-related depression:}

Nefazodone was found to be effective in major depressive episode in an elderly patient with small cell lung cancer. Moreover, during the course of therapy with nefazodone, the patient also experienced a remission of cancer chemotherapy-induced emesis, which could be related to 5-HT antagonistic property of nefazodone.\textsuperscript{62}

\textbf{vii. Post-traumatic stress disorder (PTSD):}

Nefazodone has been tried for symptom management in patients of post traumatic stress disorder (PTSD) because of its ability to block 5-HT\textsubscript{2} receptors postsynaptically and inhibit 5-HT reuptake presynaptically and/or its enhancement of sleep quality. In 6 open-label studies, involving both civilians and combat veterans, 105 outpatients with chronic PTSD were treated with nefazodone up to 600 mg/day. The response rate was assessed using 3 different criteria. The percentage drop in score between baseline and endpoint on main scale was used as a common measure to evaluate outcome. The response criterion of a drop in score of at least 30%, 40% and 50% revealed response rates of 46, 36 and 26%, respectively.\textsuperscript{63}

In one open-label 12-week study, 10 patients of PTSD initially received nefazodone 100 mg/day. The dose was gradually increased to achieve a maximal response or until reaching a maximum dosage of 600 mg/day. After 12 weeks, all the 10 patients showed significant improvement in PTSD symptoms (except self-reported PTSD re-experiencing symptoms), sleep, clinician-rated depression and overall improvement on the basis of CGI scores.\textsuperscript{64}

In another study, 17 patients with PTSD were treated with nefazodone up to 600 mg/day for a maximum total treatment period of 12 weeks. Treatment resulted in statistically significant improvement in mean scores on all six rating scales used to assess the changes from baseline in PTSD symptoms. Overall, there was a 43% response rate at endpoint, or 60% in treatment completers, by observer rating. These preliminary data suggest that nefazodone maybe effective in reducing the primary PTSD symptom clusters and maybe particularly helpful in improving sleep and decreasing anger. In these trials, nefazodone was well tolerated, and no significant changes in sexual function were reported. However, double-blind and placebo controlled studies should be undertaken to confirm these preliminary findings.\textsuperscript{65}

\textbf{viii. Social phobia:}

Preliminary findings support a role for nefazodone in the treatment of generalized type social phobia. In a 12-week open clinical trial, 23 patients who had a primary DSM-IV diagnosis of generalized type social phobia, 100 mg of nefazodone was administered daily and was increased according to clinical response and side effects. Twenty-one of the 23 patients completed the 12-week trial. Sixteen (69.6%) were considered responders (moderate or marked improvement), and 7 (30.4%) were considered to be nonresponders (minimal improvement or no change in symptoms). Measures of social anxiety, social phobic avoidance, and social functioning showed a statistically significant change at endpoint.\textsuperscript{66}

In yet another study (n=5), nefazodone (dose range: 200-600 mg/day) for 3 months has been found to be effective in the treatment of generalized social phobia.\textsuperscript{67} However, controlled studies are required to investigate these preliminary findings as well as to compare nefazodone with other pharmacological treatments of social phobia.

\textbf{ix. Chronic fatigue syndrome:}

It is characterized by musculoskeletal, neurocognitive, sleep disturbance and mood symptoms. In an open clinical study, 10 patients, who previously failed to respond to moclobemide and conventional antidepressant therapy, were treated with nefazodone (mean dose 370 mg/day) along with appropriate behavioural and sleep-wake cycle strategies to improve their level of functioning. Result indicated that eight (80%) patients reported at least some improvement in the key symptom of fatigue, with four (40%) reporting moderate or marked symptom relief. Moderate or marked improvement in sleep disturbance and mood occurred in 70% and 80% of the patients, respectively. Thus, nefazodone appears to have advantages in patients with this disorder.\textsuperscript{68}

\textbf{References}


