Antidepressant Dosing and Switching Guidelines: Focus on Nefazodone

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Dosing strategies form a fulcrum between patient-related and provider-related dimensions of treatment. The former focus on perceptions of efficacy and safety and adherence to the regimen, whereas the latter focus on symptom identification and appropriate drug selection. Appropriate dosing strategies may modulate adverse effects, allowing the patient to move more comfortably toward an efficacious response. Dosing also is an important dimension in switching between 2 antidepressants when the efficacy of the first agent is suboptimal. Nefazodone is effective for the management of acute, severe, and chronic major depression and relapse prevention. Response rates with nefazodone are comparable to those of imipramine and most SSRIs. In clinical trials, the efficacy of nefazodone was most clearly established at doses between 300 and 600 mg/day. At this dose range, discontinuations because of adverse events are low.
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Adherence to a prescribed treatment regimen involves a complex amalgam of variables encompassing both the provider and the person receiving treatment.[1] From the perspective of the patient seeking treatment, compelling dimensions of adherence to a specific regimen involve a perception of efficacy from the prescribed agent. Additionally, iatrogenic discomforts related to treatment will impact the willingness or reluctance of the individual to continue treatment. This willingness is usually strongly enhanced when accompanied by adequate preparation of treatment expectations addressed within a framework of symptom management.

From the prescriber's perspective, salient issues that are likely to enhance adherence include accurate symptom identification, discussion of the rudiments of symptom management, and selection of an appropriate medication. Ideally, the pharmacologic profile of the selected medication will dovetail with the presenting symptom constellation to provide the greatest effectiveness for resolving symptomatic dimensions of the illness. Once the patient has been instructed in symptom management and expectations have been established concerning the various dimensions of the treatment course, the pivotal task facing the clinician is selection of an appropriate dosing regimen. Dosing strategies become a fulcrum for the dimensions of adherence between the provider and the patient receiving treatment. Appropriate dosing requires adroit clinical skills and consideration of variables that influence the overall outcome of the intervention (Table 1).

Even when the provider and the patient mindfully address these issues, there are times when a suboptimal response is achieved. This consequence may be the result of unacceptable adverse effects or an inability to capture a full therapeutic response despite optimized dosing and use of augmentation strategies. A number of other cogent issues may influence a clinician's decision to recommend a change in the clinical strategy in light of a treatment failure. Such issues often lead to the decision to switch from one agent to another in an attempt to manage target symptoms more effectively and enhance efficacy for the treatment of the illness. The following sections address issues related to dosing and switching with a focus on the antidepressant nefazodone.

NEFAZODONE DOSING

Several investigations have examined the effectiveness of nefazodone compared with other antidepressants or

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Table 1. Variables That May Influence the Outcome of a Pharmacologic Intervention

Patient expectations concerning the perceived appropriate dose range
Selection of a dosing strategy that optimizes the possibility for effective management of target symptoms while minimizing iatrogenic effects
Proactively addressing issues of dose adjustment across the treatment trajectory, particularly in light of alterations in symptom presentation related to seasonal variance or other cyclic phenomena (e.g., menstrual cycle)

with placebo. For this discussion, these studies are addressed from the perspective of dosing patterns.

Placebo-Controlled Trials

Two double-blind, placebo-controlled trials provide the basis for discussion of nefazodone dosing.[2,3] In one trial, a 6-week, double-blind comparison of nefazodone with imipramine and placebo for the treatment of major depression, patients received 1 of 2 different dose ranges of nefazodone, termed low-dose (N = 45, 50–250 mg/day) and high-dose (N = 42, 100–500 mg/day).[2] The dosing ranges intentionally overlapped, because one of the study goals was to investigate the optimal dose range of nefazodone. Doses in both groups were rapidly titrated upward in the first 8 days such that the mean dosage in the low-dose group was 150 mg/day and in the high-dose group, 300 mg/day. By day 14, maximum dosages in both groups were achieved; in the low-dose group, the range was 200 mg/day (7%) to 250 mg/day (91%) and in the high-dose group, 400 mg/day (23%) to 500 mg/day (70%). Differences between the combined percentages in each group and the 100% total for each group are explained by attrition. Patients in the high-dose group (mean endpoint dose = 460 mg/day) showed efficacy comparable to those receiving imipramine (mean endpoint dose = 214 mg/day) based on Hamilton Rating Scale for Depression (HAM-D) and Clinical Global Impressions (CGI) scoring. Patients receiving low-dose nefazodone (mean endpoint dose = 242 mg/day) showed some benefit in HAM-D and CGI scores, but it was not significantly different from placebo.

Mendels and colleagues[3] also conducted a double-blind, placebo-controlled 6-week trial of 2 dose ranges of nefazodone for the treatment of depressed outpatients. Their design involved comparing 2 groups receiving nefazodone to placebo rather than to placebo and another active compound. Patients received either low-dose nefazodone (N = 78, 50–300 mg/day) or high-dose nefazodone (N = 78, 100–600 mg/day). Both groups were titrated to the maximum dosage by the end of week 2; in the last week of treatment, mean dosages were 239 ± 84 mg/day (low-dose group) and 392 ± 177 mg/day (high-dose group). Rapid titration to the maximum dosage was well tolerated in both groups. As above, significant improvement on standard efficacy measures (HAM-D, CGI, Inventory for Depressive Symptomatology) was observed in patients receiving the higher doses of nefazodone as compared with placebo. Improvement in patients receiving low-dose nefazodone was not different from those receiving placebo.

Comparative Selective Serotonin Reuptake Inhibitor Trials

Nefazodone dosing has been examined in several studies that compared the drug with a selective serotonin reuptake inhibitor (SSRI; fluoxetine, paroxetine, sertraline) in patients with moderate-to-severe depression. Three representative studies are reviewed below; in them, no statistically significant differences in overall response rates were observed between nefazodone and the SSRIs studied for any of the primary outcome measures.[4–6]

Feiger and colleagues[5] compared nefazodone with sertraline in patients with major depression to examine efficacy, tolerability, and effects on sexual function and satisfaction. Participants randomly assigned to nefazodone (N = 71) received between 100 and 600 mg/day. The initial dose in the nefazodone group was 100 mg/day for days 1 through 3. In the absence of significant clinical improvement or intolerable adverse events, the daily dose was then increased by 100-mg increments. The target dose was 400 mg/day at the end of the second week. At the end of week 4 or any time thereafter, the dose could be increased to a maximum of 600 mg/day. Doses were administered twice daily (b.i.d.), and the lower dose was administered in the morning. The mean modal daily dose for the nefazodone group at week 6 was 456 mg.

Baldwin and colleagues[4] conducted a multicenter, double-blind comparison of nefazodone and paroxetine in outpatients with moderate-to-severe depression. Participants were randomly assigned to receive nefazodone (N = 105, 200–600 mg/day) or paroxetine (N = 101, 20–40 mg/day) for 8 weeks. A double-dummy technique allowed the blind to be maintained and investigators to raise the dose of nefazodone to the required 400 mg/day (200 mg b.i.d.) by day 8 in the absence of intolerable adverse effects. At this point of dose escalation, the investigator could titrate the dose at set intervals if improvement was not seen and adverse effects did not preclude a dose increase. The mean final daily dose for the nefazodone group was 472 mg. Treatment discontinuations related to an adverse event occurred in 28 of the 206 participants, with similar proportions from each treatment group.

Rush and colleagues[6] reported a third comparative study of nefazodone and fluoxetine; results were combined from 3 identical, multicenter, randomized, double-blind, 8-week, acute-phase trials examining the effects of nefazodone (N = 64) and fluoxetine (N = 61) on sleep in outpatients with major depression. In contrast to the other trials, a fixed dosing regimen was used in this study. Patients who received nefazodone were given 100 mg b.i.d. on days 1

through 7. The dose was increased to 400 mg/day (200 mg b.i.d.) for days 8 through 56. At endpoint, 6 participants in the nefazodone group (9%) and 5 in the fluoxetine group (8%) discontinued treatment because of adverse events.

Dosing across the nefazodone/SSRI studies demonstrates trends that bear important implications for clinical practice. First, there was a low incidence of adverse events in patients receiving nefazodone across all studies. Second, whether on fixed or flexible dosing regimens, participants randomly assigned to nefazodone demonstrated similar patterns of tolerability. Third, the doses of nefazodone in these studies were titrated during treatment initiation.

A retrospective analysis of an integrated administrative claims database of a large commercial pharmacy benefit management organization compared the longitudinal dose increase from the index dose of nefazodone to that of fluoxetine, sertraline, and paroxetine over an 18-month period (data on file, Bristol-Myers Squibb Company, Plainsboro, N.J.). Nefazodone users were tracked only after entering a therapeutic dose range of greater than 300 mg/day. Differences observed in percentage increase at the 18-month timepoint were statistically significant ($p < .001$), suggesting that nefazodone use was predictive of lower relative dose increases than was use of the SSRIs. As practicing clinicians are aware, nearly all medications require titration. The difference rests with the timing of the titration, whether it is early or later in the treatment trajectory. Such trends are usually dictated by the clinical response of the patient throughout the course of a medication trial.

Inpatient Trials

Dosing information also is available from studies of nefazodone use in patients hospitalized for treatment of major depression. In one double-blind trial, participants were randomly assigned to nefazodone (N = 59) or placebo (N = 61) for 6 weeks after a drug-free baseline period of 1 to 4 weeks.[7] Nefazodone therapy was initiated with a 100-mg tablet, and the dose was increased by 1 tablet every 1 to 4 days to achieve a dose of 2 tablets (200 mg) b.i.d. (i.e., 400 mg/day). If a participant did not experience dose-limiting adverse effects, the dose was increased by an additional 1 or 2 tablets, yielding a total daily dose of 500 to 600 mg. At any time, if intolerable adverse effects emerged, the dose of nefazodone was reduced to a minimum of 100 mg/day. The mean modal doses of nefazodone in weeks 1 and 2, respectively, were 366 mg/day and 491 mg/day, with a mean endpoint dose of 503 mg/day. Fifty-one percent of the nefazodone group and 44% of the placebo group completed the study; lack of efficacy from a clinician perspective was the most frequent reason for discontinuation. However, given the possible dosing schedules, some participants in the nefazodone group may have been receiving as little as 100 mg/day. From phase 2 and 3 clinical trials, the mean effective dose was found to be greater than 300 mg/day (divided). It is unclear from the published report how many participants were receiving less than 300 mg/day of nefazodone and whether those participants were the ones classified as poor responders because of lack of efficacy. Nonetheless, the positive clinical response (50% reduction in the HAM-D score) demonstrated that significantly more nefazodone-treated outpatients (50%) responded than did placebo recipients (29%; $p = .017$).

Chronic Major Depression Study

In a recent *New England Journal of Medicine* publication, Keller and associates[8] described the acute phase results of a study comparing nefazodone with psychotherapy and with a combination of these interventions for treatment of chronic major depression. Participants who received nefazodone got an initial dose of 100 mg b.i.d., which was increased to 300 mg/day during the second week. Thereafter, the dose was increased weekly in 100-mg increments to a maximum of 600 mg/day to maximize the efficacy of the drug without producing intolerable adverse effects. In the modified intent-to-treat sample, the mean final daily dose in the nefazodone group (N = 216) was 466 ± 144 mg and in the combined treatment group (N = 221), 460 ± 139 mg. Among participants who completed the study and for whom dosing data were available, the mean nefazodone dose was 520 ± 100 mg/day in 92 responders in the nefazodone group and 479 ± 111 mg/day in 152 participants receiving combined treatment. The mean dose was 491 ± 125 mg in 73 nonresponders in the nefazodone group and 539 ± 96 mg in 27 nonresponders in the combined treatment group. Among the 519 participants who completed the study, response rates were 55% in the nefazodone group, 52% in the psychotherapy group, and 85% in the combined treatment group ($p < .001$ for both comparisons). These findings are a remarkable contrast to currently available data from studies of chronic depression, which is often treated with combined alternative agents and psychotherapy, and speak to the clinical utility of nefazodone for the treatment of chronic major depression.

Relapse Prevention Study

Feiger and colleagues[9] studied the effectiveness of nefazodone for relapse prevention during continuation treatment of outpatients with major depression in a double-blind, placebo-substitution study lasting 36 weeks in duration. After an initial 16-week, single-blind, open-label acute treatment phase, 467 participants were screened for response. Eligibility for participation in the 36-week, double-blind, placebo-controlled phase was based on depressive symptom stability as measured by the 17-item HAM-D. The 131 responders who met criteria were then randomly assigned to receive nefazodone (N = 65) or placebo (N = 66).

The dose of nefazodone during the acute, stabilization period was 100 mg/day or 200 mg/day (divided), titrated to 400 mg/day (divided) by the end of week 2. For patients who had no clinically meaningful response after the sec-

ond week, the dose was increased to a maximum of 600 mg/day (divided). The target dose of 400 to 600 mg/day was maintained throughout the remainder of the treatment period. The mean nefazodone dose at endpoint was 412 mg/day. Clinical relapse rates for nefazodone and placebo were 17.3% and 32.8%, respectively ($p = .031$). Rating scale relapse rates for nefazodone and placebo were 1.8% and 18.3%, respectively ($p < .01$). These findings clearly demonstrate the efficacy of nefazodone in relapse prevention in long-term treatment of depression and were accompanied by a good safety profile and an absence of discontinuation syndrome upon abrupt cessation of treatment.

GENERAL DOSING GUIDELINES FOR NEFAZODONE

Nefazodone therapy should be initiated with a dose of 100 mg b.i.d.[10] Doses may be increased in increments of 100 to 200 mg/day on a b.i.d. schedule at intervals of at least 1 week. The minimum effective dose range is considered to be 300 mg/day (divided) to 600 mg/day (divided).[10] In the clinical trials described earlier, the mean effective dose of nefazodone was 375 mg/day to 460 mg/day (divided). A lower initial dose and slower titration should be considered for patients with increased sensitivity to adverse central nervous system effects or for elderly or debilitated patients with reduced clearance mechanisms. For example, a conservative starting dose of 50 mg b.i.d. can be increased to 100 mg b.i.d. by week 2 and to 150 mg b.i.d. by week 3.

Some have suggested that higher starting doses of nefazodone (e.g., 100 mg b.i.d.) may be associated with a higher frequency of early-onset, treatment-emergent adverse events (data on file, Bristol-Myers Squibb Company, Plainsboro, N.J.). In one internal analysis of clinical trials in which 2 starting doses of nefazodone (50 mg b.i.d. and 100 mg b.i.d.) were directly compared with placebo, diarrhea and dizziness were significantly more frequent in the first 7 days of treatment in patients receiving the 100-mg b.i.d. dose than in those receiving the lower, 50-mg b.i.d. dose, although total patient numbers were small (200 patients per treatment arm) (data on file, Bristol-Myers Squibb Company, Plainsboro, N.J.). When patients from all nefazodone clinical trials were included, nausea, somnolence, dizziness, and light-headedness were more prominent in patients who started with a dosage of 100 mg b.i.d. In general, however, as with other antidepressants, the optimal clinical antidepressant response will emerge only after 4 to 6 weeks of nefazodone treatment. Using this lower dose (i.e., 50 mg b.i.d.), initiation of therapy may improve patient tolerability, while still achieving optimal relief of depression in similar time periods.

Once-Daily Dosing

Early studies documenting the efficacy of nefazodone used a b.i.d. dosing schedule partly based on the short half-life of the drug (i.e., 4–8 hours). More recent data, however, show no significant differences with once- versus twice-daily nefazodone.[11]

Table 2. Once-Daily (at bedtime [h.s.]) Versus Twice-Daily (b.i.d.) Dosing of Nefazodone[a]

Parameter	h.s. Dosing (N = 148)	b.i.d. Dosing (N = 61)
Titration schedule	50 mg (days 1–4)	50 mg (days 1–4)
	100 mg (days 5–8)	100 mg (days 5–8)
	200 mg (days 9–12)	150 mg (days 9–15)
	300 mg (days 13–19)	200 mg (days 16–22)
	400 mg (days 20–26)	250 mg (days 23–29)[b]
	500 mg (days 27–33)[b]	300 mg (day 30+)[b]
	600 mg (day 34+)	
Mean length of therapy	28.8 wk	36.1 wk
Mean daily dose	495.1 mg	468.8 mg

[a]Data from Markovitz and Wagner.[12]
[b]Further dosage increases (maximum 600 mg/day) made at weekly intervals if clinically indicated.

Markovitz and Wagner[12] conducted a study of 209 patients with major depression to compare once-daily dosing at bedtime with b.i.d. dosing of nefazodone. The titration schedules utilized, mean daily dose, and mean length of therapy are noted in Table 2. According to CGI scores, 77% of bedtime-treated patients and 75% of b.i.d.-treated patients improved (defined as > 50% improvement in depressive symptoms); 51% and 43% of bedtime- and b.i.d.-treated patients, respectively, were complete responders. Dropout rates were 11.3% and 8.2% for bedtime- and b.i.d.-treated patients, respectively. The investigators concluded that the efficacy and tolerability of nefazodone administered once daily at bedtime are comparable to those of b.i.d. administration.

To determine whether efficacy and tolerability would be maintained with the bedtime dosing, Preskorn and colleagues[13] conducted a 12-week, open-label continuation study in 47 depressed patients who responded to 12 weeks of nefazodone b.i.d. therapy (300–600 mg/day). At the end of the 12-week acute phase, patients' morning doses of nefazodone were halved and evening doses were increased by 50%; after 1 week, the entire daily dose was administered in the evening. Of 41 evaluable patients, antidepressant response was maintained or improved in 39 patients (95%) according to CGI-Improvement and -Severity of Illness subscales. Most patients (89%) tolerated the switch to a bedtime dose regimen without difficulty. Five patients (11%) discontinued treatment during the initial 2-week period of dose transition, primarily for adverse events. Overall, patients maintained good clinical response, or experienced further improvement, with bedtime nefazodone continuation therapy, based on results of both clinician and patient ratings. The tolerability of once-daily nefazodone dosing was excellent, and no safety concerns were evident during this extended treatment. This open study suggests that once-daily dosing of nefazodone is a convenient and safe treatment option.

SWITCHING

A clinician's decision to switch antidepressants is primarily based on an assessment of the efficacy, tolerability, and safety of the agent being used. Guidelines related to switching are readily available[14] and form the basis for the recommendations discussed here.

After 6 weeks of treatment, the patient's response should be evaluated. If there is no response or only a partial response, the diagnosis must be confirmed before other treatments are considered. If there is a partial response at 6 weeks and the patient is receiving an adequate dose of the antidepressant, most clinicians would change the antidepressant medication altogether and reevaluate the patient 6 weeks later.

If the decision is made to switch from another antidepressant to nefazodone, it is advisable to have a washout period equal to 4 to 5 times the elimination half-life of the drug being discontinued, but often this is not possible. When switching from nefazodone to another antidepressant, the same recommendations apply. Because of the lingering effects of cytochrome P450 isoenzyme inhibition by SSRIs and other antidepressants and the potential for pharmacodynamic effects, nefazodone therapy should be initiated at a low dose (e.g., 50 mg once-daily or less) if an adequate SSRI washout period is not clinically feasible. It is prudent to refer to prescribing information of the drug being discontinued and to follow recommendations for tapering to avoid discontinuation syndrome. Discontinuation/withdrawal symptoms have been reported following abrupt stopping of paroxetine and other SSRIs.[15–17] However, nefazodone has a low incidence of discontinuation syndrome or withdrawal-related emergent symptoms.[17]

Frequently, patients who are prescribed an antidepressant may also be receiving a benzodiazepine for treatment of anxiety or insomnia. If an individual is taking a benzodiazepine and needs to switch to nefazodone, the clinician should be alert to the possibility of additive sedation. If alprazolam is coadministered with nefazodone, the initial alprazolam dose should be reduced by 50%. If triazolam is coadministered with nefazodone, the initial triazolam dose should be reduced by 75%.

CUSTOMIZING A THERAPEUTIC REGIMEN

A critical dimension of any clinical strategy involving medication use requires that the clinician use a model of symptom management. Such a model clearly identifies the symptoms for which the medication is being prescribed and monitors the effectiveness of the selected agent against the given constellation of symptoms. Creativity is sometimes needed when designing a dosing strategy to marginalize the potential for adverse effects. For example, with medications that are sedating, the larger portion of the total daily dose may be administered at bedtime. Alternatively, the dose could be given earlier in the evening to allow the patient to sleep through the greater part of the given effect. Slower or faster titration may be used to assure patient comfort at the outset of a given medication trial.

Patient education is a critical dimension of any medication trial. Education begins with teaching about the manifestations of the illness itself, reviewing principles of symptom management, and preparing the patient for expectations of the medication trial including dosing strategies and the course of treatment. The single most common challenge in the early phase of therapy is dealing effectively with treatment-emergent adverse effects and collaborating with the patient to assure the greatest level of adherence to the prescribed regimen. As a patient progresses through the acute phase of antidepressant treatment and moves into continuation therapy, the goal becomes prevention of relapse, which is often due to early discontinuation of the prescribed agent. Lastly, during the maintenance phase, the clinician will continue to work with the patient in recovery from the existing episode of depression to prevention of a new episode.

SUMMARY

Dosing strategies form a fulcrum between patient-related dimensions of adherence to the regimen, which involve perceptions of efficacy and safety, and provider-related dimensions, which focus on symptom identification and appropriate drug selection to achieve the greatest efficacy. Appropriate dosing may modulate adverse effects, allowing the patient to move toward an efficacious response. Dosing also is an important dimension in switching between 2 antidepressants when the efficacy of the first agent is suboptimal.

With respect to nefazodone, an effective antidepressant for the management of acute, severe, and chronic major depression and relapse prevention, dosing strategies also are important. In general, response rates with nefazodone are comparable to those of imipramine and selected SSRIs. In clinical trials, the efficacy of nefazodone was most clearly established at doses between 300 and 600 mg/day. At this dose range, discontinuations because of adverse events are low and comparable to those observed with SSRIs.

Drug names: alprazolam (Xanax and others), fluoxetine (Prozac and others), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), triazolam (Halcion).

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