Which Depressed Patients Respond to Nefazodone and When?

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Background: Retrospective data analyses were conducted of a single-blind trial of 993 outpatients with nonpsychotic major depression (DSM-III-R) treated for 12 weeks with nefazodone to provide a more specific picture of the nature and timing of response or remission to acute-phase treatment.

Method: All patients participated in a single-blind, 16-week lead-in to obtain responders eligible for a subsequent double-blind, randomized continuation phase trial. Outcomes were defined by the 17-item Hamilton Rating Scale for Depression (HAM-D). A ≥ 50% reduction from baseline defined response, and a total HAM-D exit score of ≤ 8 defined remission.

Results: Of all patients who entered the trial, 41.8% (last observation carried forward) responded at or before week 4 (early responders), and an additional 25.2% responded thereafter; 18.3% achieved remission at or before week 4; 33.6% achieved remission after week 4. Thus, 77.3% of those responding ultimately remitted. On average, remission followed response by 2 weeks. The average end-of-treatment dose was 376 mg/day at exit (last observation carried forward). Responders or remitters (as opposed to nonresponders or nonremitters) had lower baseline depressive symptomatology and were more likely to be married or cohabiting.

Conclusion: The full symptomatic benefit of antidepressant medication may not be apparent until completion of an 8- to 10-week trial. A high number of responders ultimately attained remission. Baseline demographic and clinical features were not highly predictive of who would or would not benefit from nefazodone. For routine care, a minimal acute-phase trial, using a 50% reduction in baseline symptom severity to define response, should be 8 weeks. Whether ultimate nonresponders can be identified earlier than 8 weeks deserves further study.

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The range of antidepressant medications from which to choose has increased dramatically in the last decade. Four to 7 "classes" of agents are now recognized on the basis of their presynaptic and postsynaptic effects on neurotransmitter release, reuptake, metabolism, or presynaptic or postsynaptic receptor blockade.[1,2] These agents appear to be largely equal in both overall efficacy and speed of onset of action. Most of the newer agents are associated with lower attrition due to side effects than the older agents,[3–6] and they are far safer in overdose than tricyclic antidepressants. Further, there is evidence from case reports and consecutive case series,[7–10] but rarely from randomized, controlled, double-blind trials,[11] that when patients cannot tolerate or do not respond satisfactorily to one agent, one from another class is likely to provide a 50% or better chance of response. Most, but not all, studies suggest that a within-class switch may be of equal utility to an out-of-class switch in patients who fail to benefit from initial treatment with selective serotonin reuptake inhibitors.[7–10]

With the many therapeutic choices, recent attempts to define a preferred sequence of medication options (stepwise disease management plans or medication algorithms) have been reported.[12–16] Inherent in such algorithm efforts, however, and germane to the treatment of all patients in general, are several specific questions, not yet well addressed by the scientific literature: (1) can one identify patients, using baseline clinical or other characteristics, who have a greater than average chance of responding to a particular agent; (2) after treatment has begun, how can one identify, as early and accurately as possible, those in-

dividuals who will not ultimately benefit from the selected agent (i.e., those who will need to proceed to another agent or receive an augmenting agent); and (3) after what point in the treatment trial can one expect no further benefit without changing the treatment?

Nefazodone is a recently marketed antidepressant that inhibits both serotonin (5-HT) and norepinephrine reuptake and potently blocks postsynaptic 5-HT_2 receptors. A series of placebo-controlled studies show that nefazodone is effective for treating patients with major depression[17] and that it is equal in efficacy to fluoxetine,[18–20] imipramine,[21,22] sertraline,[23] and paroxetine.[24,25] However, efficacy and safety data are only part of the information clinicians need to most effectively use any medication.[26,27] They need to know who will respond, when the response can be anticipated, and since symptom remission is the aim of treatment, whether and when those who initially respond will ultimately remit fully.[28,29]

We anticipated that there would be 2 groups of patients who responded or remitted: (1) those showing response/remission at or before week 4 (earlier) and (2) those responding or remitting after week 4 (later). Some clinicians opt to switch or augment an agent as early as week 3 or 4 for those not responding. Therefore, we wished to know whether and how often patients responded later and who these patients were. Secondly, since the ultimate goal of treatment is symptomatic remission (not just response),[29] we wished to know when remission occurred and which patients achieved this status.

Our specific questions were (1) when does response occur, (2) when does remission occur, (3) are there earlier responders and later responders, (4) are there earlier remitters and later remitters, (5) are earlier responders different from later responders, (6) do earlier remitters differ from later remitters, and (7) what percentage of responders go on to a sustained response, remission, or a sustained remission?

METHOD

Study Design

This retrospective data analysis relies on pooled data gathered as part of 2 multicenter, 16-week, acute-phase portions of 2 double-blind, placebo-controlled trials of nefazodone in the prevention of relapse during continuation-phase treatment in adult outpatients with DSM-III-R nonpsychotic major depression. Each trial was divided into 3 phases: (1) a 1- to 4-week baseline observation phase to ensure patients met eligibility criteria, (2) a 16-week stabilization phase with single-blind nefazodone therapy to select patients in remission, and (3) a 36-week, double-blind, randomized continuation phase trial of nefazodone or placebo for acute-phase remitters. A single-blind extension of 36 weeks was made available to those not randomly assigned to the placebo substitution.

Patients were recruited via advertisements, referral from other health professionals, and self-referral. All patients gave written informed consent prior to beginning the study. All patients were ≥ 18 years of age and had DSM-III-R major depression (single or recurrent). For those with recurrent depression, they had to be in the current episode for ≥ 6 months or had to have a history of depressive episodes lasting ≥ 6 more months. For single-episode patients, the current episode had to exceed 1 year in duration. All patients were diagnosed by Structured Clinical Interview for DSM-III-R (SCID).[30] Excluded were pregnant or lactating women and sexually active women of childbearing potential who were not using adequate contraception; patients with current organic mental syndromes or any psychotic disorders, bipolar disorder, or seasonal depression; patients with significant current general medical conditions that increased the risk of adverse events during the trial; those with any psychoactive substance use disorder within the 6 months prior to the study; those with allergies to trazodone or *m*-CPP (*m*-chlorophenylpiperazine); those previously participating in a nefazodone trial; and those who were a significant suicidal risk.

Acute trial outcome was assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D),[31,32] the 28-item Inventory of Depressive Symptomatology, Clinician Rated (IDS-C) and Self-Report (IDS-SR),[33,34] the 14-item Hamilton Rating Scale for Anxiety (HAM-A),[35] and the Clinical Global Impressions-Severity of Illness and -Improvement scales.[36] Primary outcomes were measured at baseline (week 0) and at weeks 1, 2, 3, 4, 6, 8, 10, 12, and 16.

Eligible patients began nefazodone and were titrated between 100 and 600 mg/day. The study therapy was given in divided doses (generally b.i.d.). Patients initially took 100 mg/day. The dose was increased by one 100-mg tablet every 1 to 4 days so that all patients were receiving the target dose of 200 mg b.i.d. (400 mg/day) by the end of the first or second week. By the end of week 2, patients without a good response and no rate-limiting adverse effects were titrated to 500 or 600 mg/day.

For the purpose of randomization and entry into the double-blind trial, patients were defined to be in stable remission at the end of single-blind treatment if they had (1) achieved a HAM-D total score ≤ 10 on 2 consecutive visits at least 7 days apart from week 6 through week 10, with no 2 consecutive HAM-D scores > 10 thereafter; and (2) had a HAM-D score ≤ 10 at the week-16 visit and at the previous week (occurring at least 7 days earlier).

Definitions of Response and Remission

We defined response and remission using itemized symptom severity ratings completed by clinicians. We chose the 17-item HAM-D as the preferred measure, given its wide historical use. A ≥ 50% reduction from baseline total score was declared a response. Two consecutive rat-

Table 1. A Comparison of Baseline Demographic and Clinical Features for Early and Late Responders and Remitters[a]

Variable	All Patients (N = 993)	Early Responders (N = 415)	Late Responders (N = 250)	p Value[b]	Early Remitters (N = 182)	Late Remitters (N = 334)	p Value[c]
Female, %	64.4	64.8	63.6	.75	68.7	61.7	.11
Not married, %	56.0	52.5	53.6	.79	48.9	50.9	.67
Positive family history, %	32.6	35.7	32.4	.39	36.8	32.0	.27
	Mean SD	Mean SD	Mean SD		Mean SD	Mean SD	
Age, y	40.9 10.9	40.3 10.6	42.5 10.3	.01*	40.3 10.3	41.4 10.5	.27
Age at onset, y	28.0 12.9	28.7 12.8	28.0 13.1	.47	28.1 12.8	28.3 13.1	.83
No. previous hospitalizations	0.1 0.5	0.1 0.6	0.1 0.4	.66	0.09 0.04	0.09 0.04	.87
No. prior episodes	2.5 3.7	2.2 3.0	2.7 4.1	.10	2.3 2.9	2.4 3.4	.53
Baseline measures							
HAM-D	24.8 2.9	24.8 3.0	24.9 2.9	.83	24.1 2.6	24.9 2.9	.001*
HAM-A	18.4 5.1	18.4 5.2	18.7 5.0	.42	17.9 5.0	18.4 5.2	.42
IDS-C	37.2 7.2	36.2 7.5	37.6 6.8	.02*	35.0 7.3	36.9 7.2	.005*
IDS-SR	37.0 9.4	35.9 9.6	36.4 8.6	.49	34.8 9.9	36.3 8.9	.09
Exit measures (LOCF)							
HAM-D	11.7 7.4	7.7 5.4	9.1 4.8	.001*	6.3 5.0	7.1 4.3	.08
HAM-A	10.3 5.9	7.7 4.8	10.0 4.7	.001*	6.3 4.2	8.0 4.4	.001*
IDS-C	20.4 11.8	14.6 9.6	19.8 9.5	.001*	11.3 8.4	15.6 8.8	.001*
IDS-SR	23.4 11.6	18.5 10.3	23.4 9.4	.001*	14.8 9.0	20.2 9.4	.001*

[a]Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, IDS-C = Inventory of Depressive Symptomatology, Clinician Rated, IDS-SR = Inventory of Depressive Symptomatology, Self-Report, LOCF = last observation carried forward.
[b]Early response (occurred at or before week 4) vs. late response (occurred after week 4).
[c]Early remission (occurred at or before week 4) vs. late remission (occurred after week 4).
*Significant difference.

ings at ≤ 50% of baseline were "sustained" responses. Remission was declared if the 17-item HAM-D total score was ≤ 8, while a "sustained remission" was declared if 2 consecutive ratings met this threshold. In these analyses, we focused on weeks 0 to 12, since that time period was sufficient to answer the questions posed. We choose 4 weeks (or earlier) to define "early" response a priori based on our prior findings with tricyclic antidepressants.[37]

For responders and remitters, the time at which the subject met criteria for response or remission defined their status for analysis. Status was defined a priori independent of how long the patient stayed in the treatment trial. Since we have also used the definition of sustained response and sustained remission, some subjects who were identified as responders or remitters may not have been defined as sustained responders if they did not meet the latter definition. For nonresponders, on the other hand, all available data that defined group membership were used. That is, subjects were defined as nonresponders if they remained in treatment beyond the first visit and never met criteria for response regardless of the timing of their exit from the study.

Statistical Methods

Statistical methods employed in this study included t test, chi-square, survival analysis, and logistic regression. The baseline measures in Table 1 were compared between earlier and later responders and remitters using t test or χ^2 as appropriate. Kaplan-Meier[38] survival curves were conducted for time to response and remission,[39] and the Kaplan-Meier type estimate of the hazard function was graphed. Patients who dropped out of the study without attaining response or remission were considered censored at the point they left the study. Logistic regression analysis was used to identify factors related to response versus nonresponse. Four analyses were carried out, with one analysis each for level of benefit: response, sustained response, remission, and sustained remission. We used a p value of .05 to determine which factors were added or deleted from the model. All models were evaluated for the assumption of linearity, the need for interaction terms, and the presence of outliers. The factors included age, age at onset, length of illness, gender, marital status (married/not married), previous hospitalization (yes/no), family history of depression (yes/no/unknown), prior depressive episodes (yes/no), and baseline HAM-D, HAM-A, IDS-C, and IDS-SR scores.

RESULTS

Sample Features

Table 1 shows the baseline demographic and clinical features of all patients (N = 993), as well as for earlier (≤ 4 weeks) and later (> 4 weeks) responders and earlier and later remitters. The average end-of-treatment dose was 376 mg/day at exit (last observation carried forward). Of the 993 patients included in this study, 415 patients (41.8%) responded in the first 4 weeks and an additional 250 (25.2%) responded after week 4. Thus, of those who responded (N = 665), 250 (37.6%) did so after week 4. Altogether, 516 patients remitted. A total of 182 patients (18.3%) were classified as earlier remitters, while 334 patients (33.6%) were classified as later remitters. Thus, of those who remitted, 64.7% did so after week 4. Altogether, 77.3% of respond-

Table 2. Timing of Response and Remission[a]

Variable	Week 1 (N = 881)	Week 2 (N = 845)	Week 3 (N = 806)	Week 4 (N = 766)	Week 6 (N = 678)	Week 8 (N = 609)	Week 10 (N = 548)	Week 12 (N = 556)
Visit wise								
Mean HAM-D score	20.3	17.4	14.8	14.1	11.1	10.4	8.7	8.3
Responders, %	5.5	17.9	34.6	38.5	62.1	67.2	77.5	81.2
Sustained responders, %	3.8	14.8	27.5	35.7	57.7	65.4	76.2	81.2
Remitters, %	1.4	5.2	13.6	16.3	35.6	41.6	57.0	57.4
Sustained remitters, %	0.6	3.9	9.2	14.5	28.6	37.6	51.4	57.4
Last observation carried forward								
Mean HAM-D score	20.8	18.2	16.0	15.4	13.6	13.2	12.5	12.4
Responders (N = 989), %	4.9	17.0	33.1	41.8	55.9	61.5	64.9	67.2
Sustained responders (N = 989), %	3.3	12.8	24.2	32.5	47.7	54.1	58.9	61.9
Remitters (N = 993), %	1.2	5.1	12.9	18.3	32.3	40.4	48.3	52.0
Sustained remitters (N = 993), %	0.5	3.3	8.0	12.5	23.4	30.3	39.2	44.5
Mean HAM-D score at exit	22.4	19.3	17.1	17.5	15.1	16.3	13.4	8.3

[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression. Response defined as a ≥ 50% reduction in baseline HAM-D total score. Remission defined as a HAM-D total score ≤ 8.

Figure 1. Time to Response and Remission by 17-Item Hamilton Rating Scale for Depression (HAM-D) Score (N = 993)

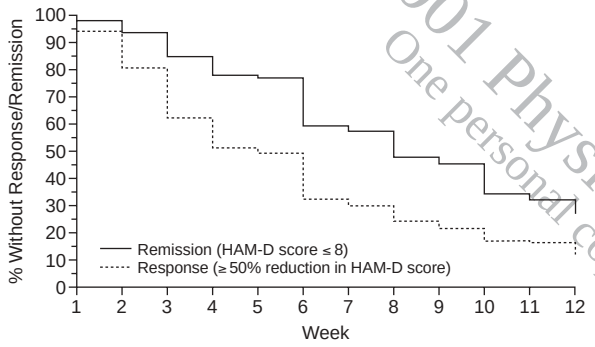
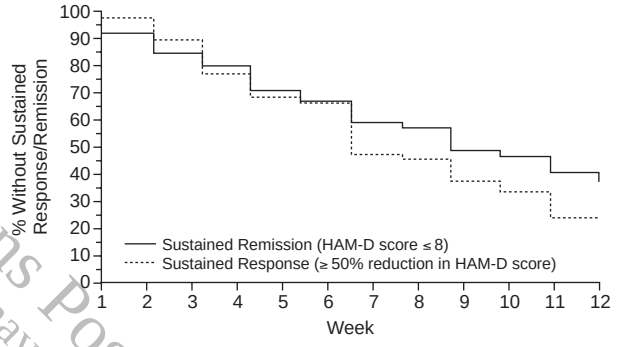


Figure 2. Time to Sustained Response and Remission by 17-Item Hamilton Rating Scale for Depression (HAM-D) Score (N = 993)



ers also remitted. Of the 665 responders, only 514 remitters had a known response status.

Table 1 compares baseline features of both earlier and later responders and earlier as opposed to later remitters. Earlier responders were younger than later responders, and they were less severely ill by IDS-C baseline total score. Later responders tended ($p < .10$) to have more prior depressive episodes than earlier responders. Later remitters were significantly more depressed than earlier remitters at baseline by HAM-D and IDS-C total scores.

At week 12 (or exit) last observation carried forward (LOCF), scores on the HAM-D, HAM-A, IDS-C, and IDS-SR were lower for earlier as opposed to later responders ($p < .001$). Similarly, the HAM-A, IDS-C, and IDS-SR scores were lower for earlier as opposed to later remitters ($p < .001$).

When Does Response/Remission Occur?

Table 2 shows the percentage of responders and sustained responders, as well as the percentage of remitters and sustained remitters using HAM-D criteria at each measurement occasion. Of note, only 556 patients (56%) initially beginning treatment completed 12 weeks. About two thirds (67.2%) of the intent-to-treat patient sample responded at or before week 12. This is the percentage of patients who responded at any time and, thus, includes those who dropped out after achieving response but prior to the completion of the study. Of those who achieved a response, 92.0% achieved a sustained response.

In this sample, 176 patients experienced response and remission at the same visit. This number is 17.7% of the total sample (N = 993) and 34.2% of the 514 patients who ultimately attained response or remission.

Nearly one third (32.3%) of the sample achieved remission by week 6. Ultimately, over 50% of the patients remitted by week 12. While only 23.4% achieved a sustained remission by week 6, nearly one half (44.5%) achieved sustained remission by week 12.

Figure 1 shows hazard curves using HAM-D to define response and remission. The probability of response remains fairly constant after week 2, while the probability of remission shows an upward trend through week 12. Figure 2 shows hazard curves using HAM-D to define sustained response and sustained remission.

Table 3. Summary of Results of Logistic Regression Analysis of 4 Different Response Definitions (based on HAM-D score)[a]

Predictor	Response	Sustained Response	Remission	Sustained Remission
Marital status[b]	0.71 (0.54 to 0.93)	0.72 (0.55 to 0.94)	0.60 (0.46 to 0.78)	0.61 (0.47 to 0.80)
IDS-C[c]			0.82 (0.74 to 0.90)	0.84 (0.76 to 0.92)
IDS-SR[c]	0.85 (0.79 to 0.92)	0.86 (0.81 to 0.93)		
Presence of prior episode[d]			1.37 (1.02 to 1.83)	1.36 (1.02 to 1.83)

[a]Values shown as odds ratio (95% confidence interval). Abbreviations: HAM-D = Hamilton Rating Scale for Depression, IDS-C = Inventory of Depressive Symptomatology, Clinician Rated, IDS-SR = Inventory of Depressive Symptomatology, Self-Report.
[b]Unmarried patients had a lower odds of responding or remitting.
[c]Odds ratio for a 5-point increase in the predictor.
[d]Presence of a prior episode increases the odds of remission.

Who Attains Response and Who Attains Remission?

Table 3 shows the results of a variable selection procedure carried out for each logistic regression analysis of the 4 levels of benefit (response, sustained response, remission, and sustained remission) to find predictors of those patients who benefit versus those who do not. Unmarried patients had lower odds of response or remission than married patients for all 4 levels of benefit. The odds of response/remission for unmarried patients were about 60% to 70% of the odds for married patients. The findings for other variables included (1) the odds of response or sustained response to nefazodone decreased by about 15% as the baseline IDS-SR score was increased by 5 points (i.e., the higher the baseline IDS-SR total score, the lower the odds of response or sustained response), and (2) for remission and sustained remission, higher baseline IDS-C total score lowered the odds by about 13% for every 5-point increment. Patients with prior episodes of depression had greater odds of remission than patients without such prior episodes.

DISCUSSION

This retrospective data analysis revealed that response to nefazodone occurred both earlier (at or before 4 weeks) and later (5–12 weeks) during acute-phase treatment. In fact, 37.6% of those who ultimately responded did so after week 4. Few patients (8.6%) who ultimately responded did so after 8 weeks. Remission followed response by a mean ± SD of 2.1 ± 2.2 weeks. Nearly two thirds (63.6%) of those who ultimately remitted did so at or after 6 weeks of treatment. Nearly all responders (92.0%) attained a sustained response, and nearly all remitters (85.7%) attained a sustained remission. Most who initially responded (N = 665) ultimately attained remission (N = 514) (77.3%). This is consistent with other observations in that about one half of depressed patients entering acute-phase trials experienced a response by week 6.[37,40]

A comparison of baseline demographic and clinical features for earlier as opposed to later responders or remitters revealed that patients in the earlier response group were younger than later responders. Baseline depressive symptom severity (i.e., IDS-C total score) for both earlier responders and earlier remitters were lower than for later responders or remitters. Finally, the patients whose depression responded earlier (as opposed to later) had lower anxiety and depressive symptoms as measured by the HAM-D, HAM-A, IDS-C, and IDS-SR at exit. This finding of a better clinical benefit for those responding early mirrors another recent report.[41]

The present results suggest that the length of acute-phase nefazodone therapy in outpatients with minimal general medical or psychiatric current comorbidity should be at least 6 weeks to identify responders. The response rate of 67.2% is equal to or exceeds that of other medications (see Depression Guideline Panel[28] and Keller et al.[42]). To determine if remission will occur with medication alone, 10 weeks of treatment are recommended. Of note is the fact that 77.3% of those who responded ultimately remitted. Quitkin et al.[43,44] and Nierenberg et al.[45,46] have also reported on the pattern of symptom change in acute-phase treatment with antidepressants. Their approach has generally been designed to understand the basic prediction of response. Conversely, we have chosen to focus on the question of when in the course of treatment do patients respond or remit.

Logistic regression analyses revealed that greater symptom severity at baseline, whether by clinician rating or by self-report, was associated with poorer outcomes defined either as response or as remission. Patients who were married had a greater likelihood of response or remission than unmarried patients, perhaps due to greater social support for married patients. Those with prior depressive episodes had a greater likelihood of remission with nefazodone, perhaps because those with single episodes were required by protocol to be depressed for a longer time period than those with recurrent episodes. The presence or absence of prior episodes was unrelated to the likelihood of response. Of note, age, length of illness, age at onset of illness, gender, and family history were unrelated to the likelihood of either response or remission. Importantly, level of baseline anxiety was also unrelated to the likelihood of response or remission.

There are several limitations to the current report. Without a placebo group, one cannot attribute cause to the drug itself. In fact, it is likely that results include both those who responded to a specific drug effect and those who responded to nonspecific drug effects, since both kinds of patients are likely to be found in this cohort. Conversely, clinicians are treating patient groups much like the one in this study. Thus, this retrospective analysis does provide tentative answers to current clinical questions.

In summary, (1) nefazodone results in a 67.2% response rate and a 52.0% remission rate in outpatients with moder-

ate to moderately severe nonpsychotic major depression; (2) the length of acute-phase antidepressant drug treatment should be at least 6 weeks to capture the 20% to 30% of patients who do not respond in the first 4 weeks of treatment but who will respond by week 6; (3) patients who ultimately responded did so between weeks 6 and 8; and (4) the clinical and demographic features associated with response versus nonresponse are not powerful enough to form the basis for patient selection.

Drug names: fluoxetine (Prozac), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft).

REFERENCES

1. Delgado PL, Gelenberg AJ. Antidepressant and antimanic medications. In: Gabbard GO, ed. Treatments of Psychiatric Disorders, vol 1. 2nd ed. Washington, DC: American Psychiatric Press; 1995:1131–1168
2. Preskorn SH. Selection of an antidepressant: mirtazapine. J Clin Psychiatry 1997;58(suppl 6):3–8
3. Nelson JC. Treatment of refractory depression. Depress Anxiety 1997;5: 165–174
4. Montgomery SA, Henry J, McDonald G, et al. Selective serotonin reuptake inhibitors: meta-analysis of discontinuation rates. Int Clin Psychopharmacol 1994;9:47–53
5. Frazer A. Antidepressants. J Clin Psychiatry 1997;58(suppl 6):9–25
6. Srisurapanont M. Response and discontinuation rates of newer antidepressants: a meta-analysis of randomized controlled trials in treating depression. J Med Assoc Thailand 1998;81:387–392
7. Thase ME, Blomgren SL, Birkett MA, et al. Fluoxetine treatment of patients with major depressive disorder who failed initial treatment with sertraline. J Clin Psychiatry 1997;58:16–21
8. Zarate CA Jr, Kando JC, Tohen M, et al. Does intolerance or lack of response with fluoxetine predict the same will happen with sertraline? J Clin Psychiatry 1996;57:67–71
9. Joffe RT, Levitt AJ, Sokolov STH, et al. Response to an open trial of a second SSRI in major depression. J Clin Psychiatry 1996;57:114–115
10. Brown WA, Harrison W. Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? J Clin Psychiatry 1995; 56:30–34
11. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. J Clin Psychiatry 1997;58(suppl 13): 23–29
12. Gilbert DA, Altshuler KZ, Rago WV, et al. Texas Medication Algorithm Project: definitions, rationale, and methods to develop medication algorithms. J Clin Psychiatry 1998;59:345–351
13. Rush AJ, Crismon ML, Toprac MG, et al. Consensus guidelines in the treatment of major depressive disorder. J Clin Psychiatry 1998;59 (suppl 20):73–84
14. Rush AJ, Rago WV, Crismon ML, et al. Medication treatment for the severely and persistently mentally ill: the Texas Medication Algorithm Project. J Clin Psychiatry 1999;60:284–291
15. Rush AJ, Crismon ML, Toprac MG, et al. Implementing guidelines and systems of care: experiences with the Texas Medication Algorithm Project (TMAP). J Pract Psychiatry Behav Health 1999;5:75–86
16. Crismon ML, Trivedi MH, Pigott TA, et al. The Texas Medication Algorithm Project: report of the Texas Consensus Conference Panel on Medication Treatment of Major Depressive Disorder. J Clin Psychiatry 1999; 60:142–156
17. 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
18. Rush AJ, Armitage R, Gillin JC, et al. Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. Biol Psychiatry 1998;44:3–14
19. Armitage R, Yonkers KA, Cole D, et al. A multicenter, double-blind comparison of the effects of nefazodone and fluoxetine on sleep architecture and quality of sleep in depressed outpatients. J Clin Psychopharmacol 1997;17:161–168
20. Gillin JC, Rapaport M, Erman MK, et al. A comparison of nefazodone and fluoxetine on mood and on objective, subjective, and clinician-rated measures of sleep in depressed patients: a double-blind, 8-week, clinical trial. J Clin Psychiatry 1997;58:185–192. Correction 1997;58:275
21. 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
22. Rickels K, Schweizer E, Clary C, et al. Nefazodone and imipramine in major depression: a placebo-controlled trial. Br J Psychiatry 1990;164: 802–805
23. 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
24. Baldwin DS, Haley 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
25. Gunasekara NS, Noble S, Benfield P. Paroxetine: an update of its pharmacology and therapeutic use in depression and a review of its use in other disorders. Drugs 1998;55:85–120
26. Rush AJ, Prien R. From scientific knowledge to the clinical practice of psychopharmacology: can the gap be bridged? Psychopharmacol Bull 1995;31:7–20
27. Rush AJ, Kupfer DJ. Strategies and tactics in the treatment of depression. In: Gabbard GO, ed. Treatments of Psychiatric Disorders, vol 1. 2nd ed. Washington, DC: American Psychiatric Press; 1995:1349–1360
28. 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, Public Health Service; 1993. AHCPR publication 93-0551
29. Rush AJ, Trivedi MH. Treating depression to remission. Psychiatr Ann 1995;25:704–705, 709
30. Spitzer RL, Williams JBW, Gibbon M, et al. The Structured Clinical Interview for DSM-III-R (SCID), 1: history, rationale, and description. Arch Gen Psychiatry 1992;49:624–629
31. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
32. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296
33. Rush AJ, Giles DE, Schlesser MA, et al. The Inventory of Depressive Symptomatology (IDS): preliminary findings. Psychiatry Res 1986;18: 65–87
34. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med 1996;26: 477–486
35. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
36. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
37. Rush AJ, Gullion CM, Roffwarg HP, et al. When do patients respond to tricyclic antidepressants? [abstract] Biol Psychiatry 1994;35:711
38. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–581
39. Collett D, ed. Modeling Survival Data in Medical Research. London, England: Chapman & Hall; 1994
40. Schweizer E, Rickels K, Amsterdam JD, et al. What constitutes an adequate antidepressant trial for fluoxetine? J Clin Psychiatry 1990;51:8–11
41. Stassen HH, Angst J, Delini-Stula A. Delayed onset of action of antidepressant drugs? survey of results of Zurich meta-analyses. Pharmacopsychiatry 1996;29:87–96
42. Keller MB, Gelenberg AJ, Hirschfeld RMA, et al. The treatment of chronic depression, pt 2: a double-blind, randomized trial of sertraline and imipramine. J Clin Psychiatry 1998;59:598–607
43. Quitkin FM, Rabkin JG, Ross D, et al. Identification of true drug response to antidepressants. Arch Gen Psychiatry 1984;41:782–786
44. Quitkin FM, Rabkin JG, Markowitz JM, et al. Use of pattern analysis to identify true drug response. Arch Gen Psychiatry 1987;44:259–264
45. Nierenberg AA, McLean NE, Alpert JE, et al. Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. Am J Psychiatry 1995;152: 1500–1503
46. Nierenberg AA, Farabaugh AH, Alpert JE, et al. Timing of onset of antidepressant response with fluoxetine treatment. Am J Psychiatry 2000;157: 1423–1428