Partial Response, Nonresponse, and Relapse With Selective Serotonin Reuptake Inhibitors in Major Depression: A Survey of Current "Next-Step" Practices

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Background: Many patients treated for major depression require more than one antidepressant trial to achieve or sustain response. However, the literature provides few treatment algorithms or effectiveness studies that empirically support "next-step" options available to clinicians. We conducted a survey of psychiatrists and other medical specialists who treat depression to ascertain what clinicians actually do when faced with patients who suboptimally respond to an adequate course of selective serotonin reuptake inhibitor (SSRI) therapy.

Method: Attendees at a psychopharmacology course (N = 801) were queried about their top choices for antidepressant-treatment nonresponders: a minimal responder after 4 weeks of adequate SSRI treatment, a partial responder after 8 weeks of adequate SSRI therapy, a nonresponder after 8 weeks of adequate SSRI therapy, and a relapser on long-term SSRI maintenance therapy. Choices included raising the dose, augmenting or combining with another agent, switching to a second SSRI, or switching to a non-SSRI agent.

Results: 432 (54%) of the surveys were returned. Raising the dose was the most frequently reported next-step strategy for a patient with minimal response after 4 weeks of adequate SSRI therapy, partial response after 8 weeks of adequate SSRI therapy, and relapse on long-term SSRI therapy. Switching to a non-SSRI agent was the most frequently chosen option for nonresponders to an adequate trial of SSRI therapy.

Conclusion: Our findings suggest that clinicians select different next-step strategies when patients are nonresponders versus when patients are partial responders or relapsers.

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First-line treatment of depression has shifted over the past decade from the tricyclic antidepressants (TCAs) to the selective serotonin reuptake inhibitors (SSRIs). Although antidepressant efficacy is comparable among the different classes of drugs,[1] the SSRIs appear to be more effective than TCAs in clinical practice due to their relatively greater safety and tolerability.[2] Nonetheless, 29% to 46% of depressed patients fail to respond fully to antidepressant medication. Specifically, it has been suggested that 12% to 15% are partial responders and 19% to 34% are nonresponders.[3]

The "next-step" strategies available to clinicians—raising the dose, augmenting or combining with other agents, and switching classes of antidepressants or switching to another antidepressant within the same class—may be employed for partial responders, nonresponders, and relapsers during SSRI treatment.[4] Unfortunately, the literature provides few "real world" effectiveness studies of patients resistant to SSRIs.[5] Although randomized clinical trials are important because they provide investigators

with methodological controls over potentially confounding factors and maximize internal validity, they typically require relatively rarefied research patient populations, such as those who are drug free and without significant psychiatric comorbidity, and mainly have power only to examine one drug's efficacy over placebo instead of comparing multiple alternate strategies simultaneously.

The design of research studies of clinical relevance to practitioners may be enhanced by knowing what strategies community-based clinicians actually employ in their own practices. Surveying practitioners who treat depression is one potentially informative means of gathering this information. Several surveys have been conducted previously. Nearly 10 years ago, Nierenberg[6] queried 118 Northeastern psychiatrists who were presented with a case vignette of a depressed patient who had failed to respond to 4 weeks of nortriptyline at 100 mg daily and were asked what treatment they would use next. Lithium augmentation was the most popular strategy among psychiatrists in that study. One limitation of that survey is that it was conducted prior to the widespread use of SSRIs first-line for the treatment of depression; therefore, next-step strategies described in that study were most likely specific to TCA failure and may not reflect current prescribing practices.

Shergill and Katona[7] conducted a similar survey in the United Kingdom in which the clinical vignette was of a patient refractory to initial treatment with amitriptyline, 150 mg daily. Unlike in the Nierenberg survey,[6] the most popular next-step strategies were to raise the amitriptyline dose or switch to an SSRI. Mischoulon and colleagues[8] conducted a small study in which they asked 20 expert psychopharmacologists in Boston, Mass., to rate the perceived effectiveness of different augmentation strategies when an SSRI failed to produce or sustain response among depressed patients. They found that bupropion, methylphenidate, and dextroamphetamine were perceived as the most effective agents to add to the treatment regimen. This sample, however, was limited to psychopharmacologists who practiced mainly in an academic teaching hospital in the same city. Byrne and Rothschild[9] also surveyed psychiatrists in Massachusetts to ascertain their top choices in the treatment of breakthrough depressive symptoms among patients taking 20 mg of fluoxetine, 100 mg of sertraline, 100 mg of nortriptyline, or 40 mg of fluoxetine. The authors reported that for all drugs and doses, raising the dose was the most commonly chosen strategy among those surveyed. As in the Nierenberg[6] study, this study surveyed clinicians from a limited geographical region and posed only one clinical vignette.

The goal of the present study was to extend the findings of earlier surveys by presenting several different clinical vignettes of treatment-resistant depressed patients to psychiatrists and other practitioners working in a wide variety of practice settings (private practice, hospital, health maintenance organization [HMO], academic centers) across a broad geographical distribution in the United States.

METHOD

Attendees at an annual psychopharmacology course sponsored by Harvard Medical School (N = 801) were asked to fill out a questionnaire prior to the lectures on depression and its treatment. Approximately 790 questionnaires were distributed, and 432 (54% of 801 attendees) were returned. The questionnaire consisted of 4 clinical vignettes of depressed patients who did not achieve full response to treatment with an SSRI: a patient who has minimal response after 4 weeks of adequate SSRI treatment, a patient who is partially responsive after 8 weeks of adequate SSRI treatment, a patient who is nonresponsive after 8 weeks of adequate SSRI treatment, and a patient who relapses while taking long-term SSRI therapy (see Appendix 1 for list of questions). Adequate dose was specified as 20 mg/day of fluoxetine, 100 mg/day of sertraline, or 20 mg/day of paroxetine.

Clinicians were asked to indicate and rank their top 3 choices for next-step strategies in response to each of the 4 vignettes. For the minimal responder vignette, the choices were wait more time and observe the patient, raise the dose, or add another agent. For the partial responder, nonresponder, and relapser vignettes, options included raising the SSRI dose, augmenting, or switching agents. Clinicians were also able to fill in which agents they would augment with or switch to, if that option was among their top choices.

The data were harvested and grouped in the following manner:

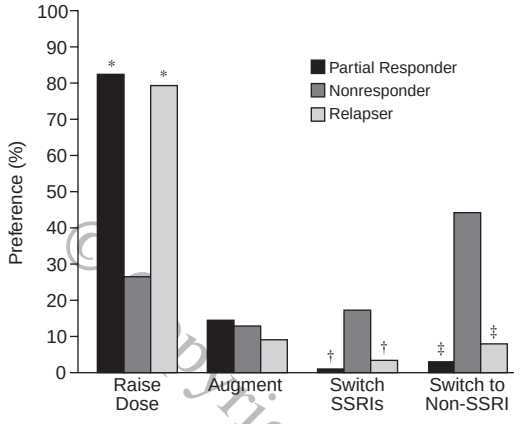
Medical specialty. Attendees identified themselves as working in 1 of following medical specialties: psychiatry, internal medicine/primary care, other medical specialty, or nonmedical specialty (e.g., nurse, psychologist).

Practice setting. Practice setting was considered hospital based or non–hospital based. Hospital-based practices referred to those in which clinicians worked in hospitals, academic teaching centers, community clinics, and mental health treatment centers. Non–hospital-based practices included those where clinicians worked exclusively in private practice (solo or group) or at an HMO.

Geographical region. The city and state where the clinicians practice were classified as belonging to 1 of 4 regions: New England, MidAtlantic/South/Southeast, West (Midwest, Northwest, Southwest, and West Coast), and Other (locations outside of the contiguous United States, i.e., Alaska, Hawaii, Canada, and Puerto Rico).

Next-step options. For the partial responder, nonresponder, and relapser vignettes, respondents' first choices for next-step options were classified as 1 of the following:

Figure 1. Next Step After 8 Weeks of Treatment[a]



[a]Abbreviation: SSRI = selective serotonin reuptake inhibitor.
*p < .004: Raise dose: partial vs. nonresponder; relapser vs. nonresponder.
†p < .004: Switch to SSRI: partial vs. nonresponder; relapser vs. nonresponder.
‡p < .004: Switch to non-SSRI: partial vs. nonresponder; relapser vs. nonresponder.

raise the dose, augment/combine (add another agent that may or may not be an antidepressant), switch to another SSRI, or switch to a non-SSRI antidepressant. When the option of choosing to switch to a non-SSRI agent was selected, the agents listed were classified as dual-acting agents (venlafaxine, mirtazapine, and clomipramine), bupropion, nefazodone, a TCA, a monoamine oxidase inhibitor (MAOI), or a non-SSRI agent (if the respondent was nonspecific in regard to which non-SSRI agent to choose). Some observations were dropped if the respondent did not discriminate among his or her first, second, or third choices or did not complete a section of the survey.

Statistical comparisons across clinical vignettes. In addition to descriptive statistics, we conducted pairwise comparisons using the McNemar chi-square analysis with Bonferroni corrections for multiple comparisons. Statistical significance was therefore set at $p < .004$.

RESULTS

Of the 801 individuals registered for the course, 681 were physicians (630 psychiatrists, 33 internists/primary care physicians/D.O.'s, and 18 other medical specialists). One hundred twenty of the attendees were not physicians, including 70 nurses, 20 clinical psychologists, and 30 other nonmedical specialists. Among the 432 attendees who completed and returned the survey, 93% of those who indicated their medical specialty in our sample identified themselves as psychiatrists and in practice for a mean ± SD duration of 16.7 ± 10.6 years. Sixty-three percent of respondents identified themselves as men and 37% as women.

Table 1. First-Choice Next-Step Strategies After 8 Weeks[a]

	Partial Responders (N = 412)		Nonresponder (N = 392)		Relapser (N = 384)	
Treatment Option	N	%	N	%	N	%
Raise dose	338	82	104	27	306	80
Augment/combine	56	14	49	12	35	9
2nd SSRI	0	0	0	0	1	0.3
TCA	10	2	6	2	6	2
Dual-acting agent	4	1	2	0.5	0	0
Bupropion	15	4	13	3	12	3
Non-SSRI/atypical antidepressant/ other antidepressant	1	0.2	3	0.8	1	0.3
Nonspecific agent	5	1	4	1	2	0.5
Stimulant/ dopaminergic agent	0	0	1	0.3	0	0
Lithium/ mood stabilizer/ benzodiazepine	13	3	11	3	10	3
Thyroid	4	1	5	1	1	0.3
Buspirone/pindolol	4	1	4	1	2	0.5
Switch	18	4	239	61	43	11
2nd SSRI	6	1	67	17	12	3
Non-SSRI	12	3	172	44	31	8
TCA	4	1	20	5	7	2
MAOI/RIMA	0	0	0	0	1	0.3
Dual-acting agent	2	0.5	53	14	7	2
Bupropion	0	0	46	12	4	1
Non-antidepressant	0	0	2	0.5	1	0.3
Nefazodone	0	0	6	2	0	0
Unspecified non-SSRI agent	6	1	45	11	11	3

[a]Abbreviations: MAOI = monoamine oxidase inhibitor, RIMA = reversible inhibitor of monoamine oxidase, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant. Total Ns are different and < 432 because some questionnaires were incomplete or uninterpretable with respect to the options chosen in response to each vignette.

Minimal responder. The most commonly endorsed strategy for a minimal responder after 4 weeks of SSRI therapy was to raise the dose, which was selected by 80% of the respondents. The options of waiting more time and adding a second agent were chosen at rates of 16% and 4%, respectively.

Partial responder. The most commonly chosen first-choice strategy for a partial responder after 8 weeks of adequate SSRI treatment was to raise the SSRI dose (82%), followed (in order of decreasing preference) by augmentation/combination (14%), switching to a non-SSRI agent (3%), and switching to another SSRI (1%) (Figure 1). The most popular augmentation/combination agents were bupropion (4%), lithium/mood stabilizer/benzodiazepine (3%), and a TCA (2%) (Table 1).

Nonresponder. Switching to a non-SSRI agent was the most popular choice for the treatment of a nonresponder after 8 weeks of adequate SSRI treatment and was selected by 44%. Raising the dose was the next most popular strategy (27%), followed by switching to another SSRI (17%) and augmenting

with another agent (12%) (see Figure 1). Among those switching to a non-SSRI agent, the medications selected in order of decreasing preference were a dual-acting agent (14%), bupropion (12%), unspecified non-SSRI agent (11%), a TCA (5%), and nefazodone (2%). As in the partial responder vignette, the most frequently chosen augmentation/combination agents were bupropion (3%), lithium/mood stabilizer/benzodiazepine (3%), and a TCA (2%) (see Table 1).

Relapser. Raising the dose was the most commonly chosen first-choice strategy for the treatment of patients who relapse while on long-term SSRI treatment (80%). Augmentation was chosen by 9%, switching to a non-SSRI agent by 8%, and switching to another SSRI by 3% (see Figure 1). Similar to the partial responder and nonresponder vignettes, the favored augmentation/combination agents for a relapser were bupropion (3%), lithium/mood stabilizer/benzodiazepine (3%), and a TCA (2%). The most popular agents to switch to were a second SSRI (3%), a non-SSRI agent (3%), and a dual-acting agent (2%) (see Table 1).

For each of the 4 clinical vignettes, rankings for first-choice next-step strategies remained the same after controlling for gender, geographical region, and practice setting (i.e., there were no significant differences in first-choice next-step treatments across gender, geographical regions, and practice settings). Therefore, we are confident that our results are not based on these biases among respondents in our sample.

Figure 1 shows our pairwise comparisons, which revealed statistically significant differences ($p < .004$, significant after Bonferroni correction) in the rates of choosing particular strategies depending on the patient vignette presented. Differences were observed in the rates of raising the dose, switching to an SSRI, and switching to a non-SSRI agent between the partial responder and nonresponder vignettes as well as between the nonresponder and relapser vignettes. More specifically, raising the dose was chosen more frequently in the case of a partial responder than a nonresponder; similarly, raising the dose was chosen more frequently in the case of a relapser than a nonresponder. However, switching to a non-SSRI agent was chosen more often in the case of a nonresponder than either a partial responder or a relapser. A similar trend emerged with respect to switching to another SSRI. No statistically significant differences were detected in the rates of augmentation/combination strategies in response to the 3 vignettes, nor were there significant differences between the partial responder and relapser vignettes with respect to the rates of choosing to raise the dose, switch to an SSRI, or switch to a non-SSRI agent.

DISCUSSION

On the basis of the findings of this survey, it appears that psychiatrists approach the treatment of depressed patients differently, depending on the particular type of failure to respond. When asked about the first-choice next-step options for a minimal responder after 4 weeks, a partial responder after 8 weeks, and a patient who relapses while on long-term medication treatment, 80% or more of respondents indicated that their first choice would be to raise the SSRI dose. This was in contrast to the vignette in which the patient is a nonresponder after 8 weeks of treatment. In response to this vignette, clinicians indicated that the most popular next-step would be to switch to a non-SSRI agent. Raising the SSRI dose for a nonresponder was selected by only 27% of those surveyed, substantially less than the rates of choosing this option for the other 3 vignettes.

One caveat in interpreting these results is that these data represent the perceptions clinicians have of their own prescribing practices, and they are not necessarily a true reflection of their actual behavior. Because we relied on clinician self-report in response to hypothetical clinical vignettes, we cannot absolutely infer that the clinicians actually do what they say they would. Additionally, only 54% of the course attendees responded to our survey; therefore, we are unable to say with certainty that the responses we received generalize to all clinicians at the course. In the absence of sociodemographic data on the course participants who did not complete the survey, we cannot rule out the possibility that a significant selection bias occurred. Nonetheless, the response rate of 54% is comparable with or better than the rates for other large surveys of clinicians' approaches to treatment-resistant depression, which reported rates of 63%,[7] 56%,[9] and 24.5%.[10] Lastly, the course attendees, from whom our sample respondents were derived, were clinicians who were particularly interested and motivated to learn about psychopharmacology. Having devoted 3 days and a minimum (tuition only) of $650 to attend the course, these clinicians may not be representative of community practitioners in terms of their knowledge of psychopharmacology or the extent to which they use pharmacologic agents in the treatment of depression.

These limitations notwithstanding, there are several possible implications of these findings. First, this study underscores the importance for research reports on treatment resistance to clearly specify the type of suboptimal response on which results are based. Depending on the type and level of response of a particular patient, clinicians appear to choose different therapeutic strategies. Given that physicians may employ certain treatment options based on findings from studies reported in the literature and that research findings may be translated into clinical practice, there is a clear need for operationalized

definitions of treatment resistance. In particular, it is important to distinguish between partial response and nonresponse.

Second, our findings suggest that antidepressant prescribing trends change over time, perhaps influenced by results from clinical research and expert practitioner recommendations. The results from our study are somewhat different from those of Nierenberg[6] with respect to treating antidepressant nonresponders. For instance, the most popular strategy in the Nierenberg[6] study was to add lithium to nortriptyline (34%), whereas in our study, augmenting an SSRI with lithium was chosen by fewer than 3%. There also appears to be an increased trend in the use of bupropion, as reflected by the fact that only 1 person in the Nierenberg study[6] (0.8%) chose to switch to bupropion, whereas this option was chosen by 12% of our sample, and augmentation/combination with bupropion was chosen by 3% of our sample. In addition, bupropion was consistently the first-choice augmentation/combination agent for partial responders, nonresponders, and relapsers.

Third, it appears that clinicians' use of differential next-step strategies is actually empirically supported in the literature. For minimal responders and partial responders, the vast majority of respondents in our survey indicated that they would raise the dose. In a controlled study, Fava and colleagues[11] found that among partial responders to fluoxetine, 20 mg/day, raising the dose to 40 to 60 mg/day was significantly more effective than adding either lithium or desipramine.

Consistent with psychiatrists' responses reported by Byrne and Rothschild[9] in a survey of psychiatrists about the treatment of breakthrough depressive symptoms during maintenance treatment, most clinicians in our survey reported that they would raise the dose if the patient experienced a relapse or recurrence while on longer-term antidepressant therapy. A trial by Fava and colleagues[12] provides preliminary support for this approach as well. In an open study of 18 patients who relapsed with fluoxetine, 20 mg/day, the authors observed that 83% of patients responded when the fluoxetine dose was raised to 40 mg/day.

Moreover, duration of treatment appears to be associated with a clear contrast in the choice of next-step treatments for minimal and nonresponders. An overwhelming majority (80%) of respondents chose to raise the dose for minimal responders after 4 weeks of treatment, while only 27% selected the same treatment option for nonresponders after 8 weeks of treatment. In addition, among clinicians surveyed in our sample, the most popular choice for nonresponders after 8 weeks of SSRI treatment was to switch to a non-SSRI agent (44%). This is consistent with empirical findings that suggest the usefulness of this approach in patients resistant to SSRIs.[13–15]

The results of our survey may be of use in designing additional controlled clinical research trials that empirically compare next-step strategies commonly used in the pharmacologic treatment of depression. Our findings suggest that it may be useful to conduct head-to-head studies that directly compare raising the dose with augmentation and combination as well as with switching to a different agent in all 3 subpopulations of depressed patients.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), buspirone (BuSpar), clomipramine (Anafranil and others), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), fluoxetine (Prozac), methylphenidate (Ritalin and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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Appendix 1: Enhancing Response to Treatment

1. You have a patient on an adequate dose of an SSRI (20 mg Prozac, 20 mg Paxil, or 100 mg Zoloft) for *4 weeks*, but the patient has only shown *minimal improvement*. Please rank the following strategies for usual next step treatments in order of preference (from 1 to 3).
   _____ wait more time and observe the patient
   _____ raise the dose
   _____ add another agent

2. You have a patient on an SSRI for *more than two months* and consider the patient to be a *partial responder*. Please rank the following strategies for usual next step treatments in order of preference (from 1 to 3).
   _____ raise the dose (please fill in below)
   _____ augment or combine with _____
   _____ augment or combine with _____
   _____ augment or combine with _____
   _____ switch to _____

3. You have a patient on an SSRI for *more than two months* and consider the patient to be *a non-responder*. Please rank the following strategies for usual next step treatments in order of preference (from 1 to 3).
   _____ raise the dose
   _____ augment or combine with _____
   _____ augment or combine with _____
   _____ augment or combine with _____
   _____ switch to _____

4. You have a patient on an SSRI for *more than two months*, and the *patient was a responder but then worsened* clinically while still on medication. Please rank the following strategies for usual next step treatments in order of preference (from 1 to 3).
   _____ raise the dose (please fill in below)
   _____ augment or combine with _____
   _____ augment or combine with _____
   _____ augment or combine with _____
   _____ switch to _____