Response Rates to Fluoxetine in Subjects Who Initially Show No Improvement

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Objective: This study sought to investigate the likelihood that subjects will respond to continued antidepressant therapy when little or no benefit has yet been observed.

Method: Six hundred twenty-seven subjects diagnosed with *DSM-IV* major depressive disorder were recruited in a 12-week open-label trial with fluoxetine, which was designed as a preliminary phase to a subsequent 52-week continuation trial, which was conducted in 1997–2003. For each week of the study, a calculation was made for all subjects who had heretofore demonstrated little or no improvement as to the likelihood of converting to a positive response in subsequent weeks as measured by the Clinical Global Impressions scale, the primary outcome measure. In order to compare our findings with prior research, we focused primarily on outcomes at weeks 6, 8, and 12.

Results: The likelihood of converting to a positive response decreased the longer subjects remained unimproved. When week 6 was used as the end point, the likelihood of converting to a positive response for unimproved subjects at week 1 was 36% (n = 302); the respective conversion rates for weeks 2–5 were 29% (n = 208) at week 2, 18% (n = 151) at week 3, 17% (n = 120) at week 4, and 9% (n = 91) at week 5. When week 8 was used as the end point, the likelihood of converting to a positive response for unimproved subjects at week 4 was 23% (n = 118) and, at week 6, was 10% (n = 61). Finally, when week 12 was used as the end point, the likelihood of unimproved subjects at weeks 4, 6, and 8 converting to a positive response at week 12 was 50% (n = 117), 33% (n = 60), and 30% (n = 46), respectively.

Conclusions: The study adds to a small, but growing literature that gives clinicians some guidelines to help decide whether to continue an antidepressant trial when little or no benefit has yet been observed.

Trial Registration: clinicaltrials.gov Identifier: NCT00427128

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A significant minority of patients do not respond to antidepressant therapy. It remains unclear how long an antidepressant trial should be continued when no signs of improvement have yet been observed. If clinicians give up too soon, they risk aborting a trial potentially just when it was on the verge of being helpful. If clinicians extend a trial too long, they risk unnecessarily prolonging morbidity while engendering disillusionment with somatic treatment. Despite its clear clinical relevance, only a handful of studies to date have attempted to address this issue directly (Table 1).

In their seminal article[1] on the topic, published in 1984, researchers from Columbia University sought to determine the prognosis at week 6 for subjects who were unimproved through the first 4 weeks of treatment. The most salient finding presented was that 27% (25/92) of subjects who had demonstrated no improvement through 4 weeks of treatment subsequently responded when the antidepressant trial was continued for 2 additional weeks. In contrast, only 9% (8/92) of nonresponders to placebo at week 4 converted to a positive response by week 6 ($\chi^2_1 = 3.38$, $P = .03$ using a 1-tailed test). The investigators concluded that even if there are no signs of improvement after 4 weeks of antidepressant treatment, antidepressant trials should be continued for at least another 1–2 weeks.

Twelve years later, the same group published findings culled from data they had collected over a 10-year period.[3] In this study, the investigators depicted the likelihood of response at week 6 for subjects (n = 382) who were unimproved in each prior week. For nonresponders at weeks 1, 2, 3, 4, and 5, the likelihood of converting to a positive response at week 6 was 52%, 44%, 32%, 13%, and 3%, respectively. Here, the investigators suggested that a 13% conversion rate was too low to justify extending trials beyond 4 weeks. In contrast to their initial study then, they now recommended abandoning an antidepressant trial after 4 weeks if no signs of improvement have yet been observed.

In 1995, Nierenberg et al[2] published a report examining response rates at week 8 for subjects (n = 143) who had not demonstrated any improvement with fluoxetine 20 mg/d prior to that point. They found that 36%, 19%, and 6% of subjects who had shown no improvement after week 2, 4, and 6, respectively, ultimately responded at week 8. The authors suggested that antidepressant trials should probably not be extended beyond 4–6 weeks if no signs of improvement have been observed.

In 2003, Quitkin et al[4] examined remission rates after 12 weeks of treatment with fluoxetine 20 mg/d in subjects (n = 840) who had not improved in previous weeks. For weeks 4, 6, and 8, the likelihood of unimproved subjects converting to remission by week 12 was 38%, 33%, and 16%, respectively. Since the 33% remission rate at week 6, but not the 16% remission rate at week 8, was deemed acceptable, the authors concluded that unimproved patients should be continued on their antidepressant medication for 8 weeks, but not longer.

Clinical Points

- A significant minority of depressed patients respond to continued treatment with fluoxetine even when no improvement has yet been observed after 4, 6, or 8 weeks of treatment.
- The optimal trial duration for antidepressant therapy remains largely unknown, though clinicians can offer prognostic guidelines for converting to a positive response with continued antidepressant therapy.

Most recently, Mulsant et al[5] published a study examining the probability of response at week 12 in 472 geriatric patients with depression who had derived little or no benefit from either nortriptyline or paroxetine in prior weeks. Of 168 unimproved subjects at week 4, 14% subsequently responded by week 6. Using week 8 as the end point, 31% and 9% of unimproved subjects at weeks 4 and 6, respectively, converted to a positive response by week 8. Finally, if week 12 was chosen as the end point, 30%, 20%, 10%, and 10% of nonresponders at weeks 4, 6, 8, and 10, respectively, ultimately responded.

In sum, there have been relatively few data published to date to guide clinicians as to how long to continue an antidepressant trial when little or no benefit has yet been observed. Not surprisingly then, there exists a wide disparity of opinions regarding how long unimproved patients should be maintained on their antidepressant medication.[4,6,7] In the present study, we analyzed the results of a 12-week trial with fluoxetine in a large cohort of subjects in order to better ascertain the benefits of continued antidepressant therapy in previously unimproved subjects, and we examined outcomes at multiple end points, which also allowed us to compare our results to each of the prior comparable studies.

METHOD

A total of 627 subjects 18 to 65 years of age who met *DSM-IV* criteria for a current episode of major depressive disorder were recruited into a study conducted in 1997–2003 by research programs at the New York State Psychiatric Institute in New York City and the Depression Clinical and Research Program of the Massachusetts General Hospital in Boston. The study is registered at clinicaltrials.gov (identifier: NCT00427128). The study was approved by institutional review boards at both sites, and all participants provided written informed consent. Diagnoses were established using the Structured Clinical Interview for *DSM-IV* Axis I Disorders—Patient Edition.[8] No minimum score for severity of depressive symptoms was required for inclusion in the study. Baseline medical screening included medical history, physical examination, electrocardiogram, complete blood count, blood chemistry profile, thyroid function tests, urinalysis, and urine drug screen. Subjects were excluded from the study if they were at significant risk of suicide; were pregnant or breastfeeding; were women not using effective contraception; had an unstable physical disorder; had a lifetime history of any organic mental disorder, psychotic disorder, or mania; had a history of seizures; had a neurologic disorder that significantly affects central nervous system function; had been active substance abusers or had substance dependence in the previous 6 months, other than nicotine dependence; were taking medications that may cause or exacerbate depression; had clinical or laboratory evidence of hypothyroidism without adequate and stable replacement therapy; or had a history of nonresponse to an adequate trial of a selective serotonin reuptake inhibitor (defined as a 4-week trial of ≥ 40 mg of fluoxetine or the equivalent daily).

After a 1-week medication-free washout, subjects who continued to meet inclusion criteria and whose symptoms had not improved significantly began a 12-week course of open-label treatment with fluoxetine. They were seen weekly by a research psychiatrist during the first 6 weeks, every 2 weeks for the next 4 weeks, and weekly for the remaining 2 weeks. Target fluoxetine dosages were 10 mg/d for the first week, 20 mg/d for weeks 2–4, 40 mg/d for weeks 4–8, and 60 mg/d for weeks 5–12. The dose was increased to meet the target only if the subject tolerated the medication well, and it was increased to 40 mg daily for all subjects who could tolerate it. Treatment response was rated on the 17-item Hamilton Depression Rating Scale (HDRS-17)[9] that was modified to assess for reversed neurovegetative symptoms, as well as the Clinical Global Impressions scale (CGI).[10]

Subjects who responded to the medication by week 12 entered a double-blind discontinuation phase for up to 52 weeks. Findings from the discontinuation phase were not deemed relevant for the purposes of this article and are not discussed further.

We chose to use the CGI scale rather than the HDRS-17 because it more easily translates to actual clinical practice. We defined *no improvement* as a CGI score of 4 or greater, *partial improvement* as a CGI score of 3, and a *positive outcome* as a CGI score of 2 (much improved) or 1 (very much improved). *Response* rather than *remission* was the outcome of interest because, intuitively, response seems to best correlate with this decision point of interest—whether to continue an antidepressant trial.

In order to compare our findings with previous research, we focused on end point outcomes from weeks 6, 8, and 12. Prior work has clearly shown that subjects who demonstrate a partial response at any time—even in a single prior week—clearly have a better prognosis than those who had never shown any improvement.[2–5] We therefore sought to determine the proportion of subjects who ultimately responded at one of our chosen end points (week 6, 8, or 12) for each prior week in the subset of subjects who had never demonstrated either a partial (CGI score = 3) or full (CGI score = 1 or 2) response in any prior week. Subjects who dropped out of the study for any reason had their last observation carried forward. Subjects who

Table 1. Studies That Have Examined Conversion Rates to Positive Response in Subjects Who Were Unimproved in Prior Weeks

Study	n	Antidepressant(s) Used	Population	Trial Duration	Trial Format	Dosage Schedule	Definition of Unimprovement	Definition of Response
Quitkin et al,[1] 1984	92	Desipramine, mianserin, imipramine, phenelzine	Adult	6 wk	Double blind	Mixed	CGI score of 4 or higher	CGI score of 1 or 2
Nierenberg et al,[2] 1995	143	Fluoxetine	Adult	8 wk	Open label	Fixed: 20 mg/d	HDRS score decrease of < 20%	HDRS score decrease of ≥ 50%
Quitkin et al,[3] 1996	392	MAOIs, TCAs, and mianserin	Adult	6 wk	Double blind	Mixed	CGI score of 4 or higher	CGI score of 1 or 2
Quitkin et al,[4] 2003	840	Fluoxetine	Adult	12 wk	Open label	Fixed: 20 mg/d	< 25% decrease in HDRS score	HDRS score ≤ 7
Mulsant et al,[5] 2006	472	Nortriptyline and paroxetine	Geriatric	12 wk	Open label	Flexible	HDRS score ≥ 15	HDRS score ≤ 10 plus decrease of > 50%
Posternak et al (current study)	488	Fluoxetine	Adult	12 wk	Open label	Flexible	CGI score of 4 or higher	CGI score of 1 or 2

Abbreviations: CGI = Clinical Global Impressions scale, HDRS = Hamilton Depression Rating Scale, MAOI = monoamine oxidase inhibitor, TCA = tricyclic antidepressant.

missed a visit could subsequently be included with the data for the missed week being censored.

RESULTS

Open-Label Treatment

Of the 627 subjects who consented to screening for the study, 34 (5.4%) were excluded for medical reasons, 18 (2.9%) did not return to begin treatment, and 5 (0.8%) improved significantly during the washout period and did not begin treatment. Of the 570 participants who began open-label treatment, 488 were deemed nonresponders at week 1 and were included in our analyses. This cohort consisted of 262 (53.7%) women; the majority (77.9%) were white, 8.3% were African American, 8.6% were Hispanic, and the remainder were of other ethnicities. The participants' mean age was 37.6 years (SD = 11.1), and they had a mean of 14.8 years of education (SD = 2.6); 72.2% were employed, students, or homemakers; and 18.5% were married. The mean HDRS-17 score at baseline was 17.6 (SD = 4.6) (range, 7–35).

The mean dose of fluoxetine taken by participants during the open-label phase was 45.8 mg/d (SD = 15.1), and they took the medication for a mean of 9.7 weeks (SD = 3.8). Of 371 participants who completed the 12-week, open-label phase (65% of those who entered it), 295 (80%) were considered responders by CGI criteria at week 12; the intention-to-treat response rates at weeks 6, 8, and 12 were 45% (258/570), 48% (276/570), and 57% (325/570), respectively. In the cohort of subjects who were unimproved at end point (ie, CGI score ≥ 4), the mean percentage improvement in HDRS-17 scores was 0.9% (SD = 28.0; range, 145% worse to 54% improved).

Outcomes at Week 6

The likelihood of responding at week 6 for subjects who had never demonstrated any prior improvement was 36% at week 1, 29% at week 2, 18% at week 3, 17% at week 4, and 9% at week 5 (Table 2).

Outcomes at Week 8

The likelihood of responding at week 8 for subjects who had never demonstrated any prior improvement was 39% at week 1, 33% at week 2, 25% at week 3, 23% at week 4, 17% at week 5, and 10% at week 6 (Table 3).

Table 2. Proportion of Unimproved Subjects at Weeks 1, 2, 3, 4, and 5 Who Ultimately Responded at Week 6

	Week 1		Week 2		Week 3		Week 4		Week 5	
Study	n	%	n	%	n	%	n	%	n	%
Quitkin et al,[1] 1984							92	27		
Quitkin et al,[3] 1996	175	51	113	44	59	32	39	13	29	3
Mulsant et al,[5] 2006							168	14	125	5
Posternak et al	302	36	208	29	151	18	120	17	91	9

Table 3. Proportion of Unimproved Subjects at Weeks 4 and 6 Who Ultimately Responded at Week 8

	Week 4		Week 6	
Study	n	%	n	%
Nierenberg et al,[2] 1995	37	19	31	6
Mulsant et al,[5] 2006	168	31	107	9
Posternak et al	118	23	61	10

Table 4. Proportion of Unimproved Subjects at Weeks, 4, 6, and 8 Who Ultimately Responded at Week 12

	Week 4		Week 6		Week 8	
Study	n	%	n	%	n	%
Quitkin et al,[4] 2003	177	38	120	33	95	17
Mulsant et al,[5] 2006	168	30	107	20	86	10
Posternak et al	117	50	60	33	46	30

Outcomes at Week 12

The likelihood of responding at week 12 for subjects who had never demonstrated any improvement was 60% at week 1, 58% at week 2, 55% at week 3, 50% at week 4, 45% at week 5, 33% at week 6, 30% at week 8, and 20% at week 10 (Table 4).

DISCUSSION

Knowledge regarding what constitutes an adequate antidepressant trial is one of the most basic principles of antidepressant pharmacotherapy, and yet remarkably few data have been published on this topic. The present article

focused on the not uncommon scenario where little or no improvement has yet been observed. The multiple end point analyses we used allowed us to compare our findings with each prior study published on the topic. Our results were generally consistent with prior research, giving us increased confidence to offer prognostic guidelines at a variety of time frames.

With week 6 as the end point of interest, we found that 17% of subjects (about 1 in 6) who had demonstrated no improvement through the first 4 weeks of treatment converted to a positive response when the trial was extended 2 more weeks. This figure is very consistent with the results of Quitkin et al[3] and Mulsant et al,[5] who reported conversion rates of 13% and 14%, respectively. Of note, the 27% response rate reported by Quitkin and colleagues[1] in their seminal 1984 study, which historically was instrumental in extending the standard antidepressant trial duration from 4 to 6 weeks, now looks more like an aberration (Table 2).

With week 8 as the end point, we found that 23% of subjects who had demonstrated no improvement through the first 4 weeks of treatment converted to a positive response when the trial was extended 4 more weeks. This figure approximately splits the difference of what had been reported previously by Nierenberg et al[2] (19%) and Mulsant et al[5] (31%). If 6 weeks have transpired without any signs of improvement, only 10% or fewer respond when the trial is extended for 2 more weeks (Table 3).

The present study is now the third report to examine conditional probabilities of response for unimproved subjects for trials continued as long as 12 weeks (Table 4). At week 4, 50% of unimproved subjects converted to a positive response with 8 more weeks of treatment—a higher percentage than that reported by Quitkin et al[4] (38%) and Mulsant et al[5] (30%). For subjects who were unimproved after 6 weeks of treatment, one-third (33%) converted to a positive response with 6 additional weeks of treatment. Even after 8 weeks of treatment, we found that as many as 30% of unimproved subjects converted to a positive response with 4 additional weeks of treatment.

Tables 2–4 each suggest that the longer subjects go without improvement, the less likely they are to ultimately respond. This, of course, is hardly surprising. However, a second variable exists that could also account for these diminishing response rates: how much time is afforded to subjects subsequently to respond? For example, from Table 2 we see that the likelihood of responding at week 6 decreases with each successive week that subjects have failed to improve. But unimproved subjects at week 1 have 5 full weeks to convert to a positive response, whereas unimproved subjects at week 5 have only a single week to convert. Clearly, this is not a fair comparison. What would happen if the time afforded to convert to a positive response were held constant?

Our methodology allowed us to examine this question at 5 separate data points by posing the following question: for subjects who were unimproved through 2, 4, 6, 8, and 10 weeks, respectively, what was the likelihood of converting to a positive response *with exactly 2 more weeks of treatment?* To our surprise, both in ours and in Mulsant and colleagues'[5] study, there did not seem to be any decrement in response rates once the time allowed to convert to a positive response was held constant (Table 5). This counterintuitive finding raises the possibility that the diminishing returns associated with continued antidepressant therapy seen in Tables 2–4 may be more a function of how much longer a trial is continued than how long subjects have already gone without improvement.

Table 5. Proportion of Unimproved Subjects at Weeks 2, 4, 6, 8, and 10 Who Responded With Exactly 2 More Weeks of Treatment

	Week 2		Week 4		Week 6		Week 8		Week 10	
Study	n	%	n	%	n	%	n	%	n	%
Mulsant et al[5]	NM	13	168	14	107	9	86	17	67	10
Posternak et al	208	16	117	17	60	10	46	15	20	20

Abbreviation: NM = not mentioned.

If this finding proves to be correct, how might it be explained? Antidepressants are generally conceptualized as having a dichotomous response: either they work or they do not work. In a dichotomous model, a window of time is presumed to exist for a response to occur, and, beyond this window, responding is believed to be less and less likely. The present study, as well as the collection of studies reviewed here, was conducted with the aim of uncovering a natural drop-off in conversion rates, which would then establish an optimal trial duration "carved out of nature." In an alternative model, antidepressants could be conceptualized as offering continuous real or potential benefit, for example, by helping to facilitate the natural process of recovery from depression. In this model, no natural window of opportunity to respond may exist, making the search for one a potentially futile endeavor. The findings presented herein are too preliminary to discern which model is more valid, but Table 5 is more consistent with a continuous model. Clearly, this intriguing finding, along with its implications, warrants further investigation.

On the basis of these results, can a particular optimal trial duration be recommended? Tables 2–5 indicate that a substantial minority of subjects respond to continued treatment, even after many weeks without improvement. This provides some justification for extending antidepressant trials beyond the traditional 4 to 6 weeks. However, the question treaters face in these situations is not whether some subjects might respond to continued treatment, but whether extending an antidepressant trial is the *best* course of action. Tables 2–5, unfortunately, are unable to address this question. To do this, a direct comparison study would need to be conducted in which extending an antidepressant trial is compared against the main pharmacologic alternatives of switching antidepressants or augmentation. We are aware of only 2 such studies that have been conducted to date. In 1 study by Shelton et al,[11] subjects who had failed to respond to 7 weeks of treatment with nortriptyline were randomized to switch to fluoxetine, olanzapine, fluoxetine plus olanzapine,

or to remain on nortriptyline for 8 additional weeks. At end point, there were no statistically significant differences in response rates between these groups. In another study by Licht and Qvitzau,[12] 295 subjects who had not responded to 6 weeks of open-label treatment with sertraline titrated up to 100 mg were randomized in a double-blind manner for 5 additional weeks to 1 of 3 treatments: continued treatment with sertraline 100 mg, increased dosage of sertraline to 200 mg, or augmentation with the heterocyclic antidepressant mianserin. Continued treatment with sertraline 100 mg was just as effective as mianserin augmentation—and both yielded significantly higher response rates than sertraline 200 mg. In sum, we know at this point that (1) a substantial minority of nonresponding subjects respond to continued treatment with an antidepressant, and (2) no other intervention, such as dosage increase, switching antidepressants, or augmentation, has yet to demonstrate superior outcomes. Because the optimal trial duration remains unknown, clinicians, for now, will need to rely on their collective experience while perhaps incorporating the prognostic markers published herein to gauge the best course of action in each particular situation.

Several limitations to the present study should be noted. First, this was an open-label trial that lacked a placebo control group. Therefore, we cannot make any assertions regarding what is a true drug effect as compared to nonspecific improvement.

Second, because the study allowed for flexible dosing, it is possible that our reported response rates may be higher than what would have occurred had we kept the dosage constant. Since clinicians in the real world adjust dosing based on clinical circumstances, this again could be seen as a strength in that the methodology more closely resembles standard clinical practice.

Third, as had been done in most prior research, we used conditional probability analyses to gauge the likelihood of converting to positive response. A recent study by Sackeim et al,[13] however, suggests that the use of signal detection methodology may be superior in determining the optimal trial duration.

These limitations notwithstanding, our findings combined with the results of prior research suggest that approximately 1 in 6 patients who have derived no observable benefit through 4 weeks of treatment will respond if the trial is continued for 2 more weeks. If a patient has remained unimproved through 6 continuous weeks of treatment, there is a 10% or less likelihood of responding by week 8. When trials are extended as long as 12 weeks, a significant minority of unimproved patients will ultimately convert to a positive response, even when no improvement has been observed through the first 6–8 weeks of treatment. These results may allow clinicians to more accurately judge the likelihood of benefit from continued antidepressant therapy.

Drug names: desipramine (Norpramin and others), fluoxetine (Prozac and others), fluoxetine/olanzapine (Symbyax), imipramine (Tofranil and others), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil and others), sertraline (Zoloft and others).

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