# Initial Rate of Improvement in Relation to Remission of Major Depressive Disorder in Primary Care

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***Objective:*** In depression treatment, switching treatment after lack of initial improvement, e.g., after 6 weeks, may result in a better outcome. The extent of the lack of initial improvement, as well as the timing of its assessment on the basis of which treatment change may be considered, remains unclear. This study compared the relationships of several grades of symptom improvement after 2 and 6 weeks with remission after 10 weeks in depressed patients treated with antidepressants in primary care.

***Method:*** This was a prospective cohort study, conducted between January 1999 and September 2001 in primary care practices in the Netherlands, of 172 patients starting selective serotonin reuptake inhibitor (SSRI) treatment for major depressive disorder, diagnosed according to DSM-IV criteria. At weeks 2 and 6, patients were classified as unimproved, partially improved, or improved. For each category, we calculated the proportion of remission at week 10. The primary outcome measure was the Beck Depression Inventory.

***Results:*** Of the unimproved or partially improved patients at week 6, 29% (95% CI = 18 to 43) and 27% (95% CI = 17 to 40) attained remission at week 10, respectively.

***Conclusion:*** These data suggest that, in primary care, depression treatment with an SSRI should be reconsidered in depressed patients who are unimproved or partially improved by week 6.

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Selective serotonin reuptake inhibitors (SSRIs) form the mainstay of depression treatment in primary care. Yet, in some patients these medications are ineffective. In these patients, timely switching to another treatment may result in a better outcome.[1,2] Current evidence suggests that substantial improvement occurs within the first 2 weeks, which challenges the notion that the onset of action of antidepressants takes more than 2 weeks.[3] As a consequence, it may be pertinent to reexamine a commonly quoted recommendation, that an antidepressant trial must last at least 6 weeks before considering a change in treatment.[4] Another reason to reexamine the relation between initial symptom change and outcome is that earlier studies[5–8] recommended treatment change based on analyses in which the treatment objective was defined as response, i.e., a reduction of at least 50% from pretreatment depression severity. The ultimate treatment goal, however, is remission.[9] Since remission represents a greater degree of improvement in comparison with response, it will, on average, take longer to reach remission than to attain response.[10] Only 1 study,[11] performed in specialty care, investigated the relation between initial symptom change and remission over a sufficiently long period, i.e., 10 to 12 weeks.[12] To date, this relation has not been investigated in primary care.

In the present study, we investigated to what extent the rate of improvement after 2 or 6 weeks of SSRI administration relates to remission of depression by week 10 in patients suffering from a major depressive episode and who are treated with SSRIs in primary care settings.

## METHOD

We obtained data from a cluster randomized controlled trial performed in 30 primary care practices in the Netherlands. The study design and flow of patients through the trial are described in detail elsewhere.[13] In short, we compared the influence on medication adherence and treatment result of either a depression care program or a systematic follow-up program in SSRI-treated patients with a major depressive episode, according to DSM-IV. We found no differences in outcome at week 10 and week 26 between these 2 programs. In both treatment arms, 47% of patients attained remission by week 10.

**Table 1. Baseline Demographic and Clinical Characteristics of the Study Sample[a]**

| Characteristic | Study Patients (N = 172) |
|---|---|
| Demographic | |
| Age, y | 44.2 (13.6) |
| Female, % | 68.4 |
| Employed, % | 62.7 |
| Unfit for work, % | 10.1 |
| Clinical | |
| Beck Depression Inventory score | 22.2 (9.0) |
| Symptom Checklist-90-Revised global severity index | 1.3 (0.6) |
| Clinical Global Impressions-Severity of Illness score | 4.4 (0.7) |

[a]Data are shown as mean (SD) except where noted otherwise.

**Table 2. Relation of Rate of Improvement at Week 2 and Week 6 to Remission at Week 10**

| | Proportion of Patients Attaining Remission by Week 10[a] | | | | | |
|---|---|---|---|---|---|---|
| | Week 2 | | | Week 6 | | |
| Category | N/N | % | 95% CI | N/N | % | 95% CI |
| Unimproved | 37/93 | 40 | 30 to 50 | 13/45 | 29 | 18 to 43 |
| Partially improved | 25/49 | 51 | 38 to 64 | 14/52 | 27 | 17 to 40 |
| Improved | 16/24 | 67 | 47 to 82 | 52/73 | 71 | 60 to 80 |
| Total | 78/166 | 47 | 40 to 55 | 79/170 | 47 | 39 to 54 |

[a]Week 2 and week 6 analyses are based on 166 and 170 patients, respectively, because of missing data.

### Data Analysis

In this study, we examined the rate of improvement at weeks 2 and 6 after starting SSRI treatment in relation to remission by week 10. The time points at which depression severity was measured after baseline, i.e., weeks 2, 6, and 10, were chosen to be compatible with treatment guidelines[14] and daily practice in primary care settings in the Netherlands. Patients were categorized according to commonly accepted criteria[12,15] as unimproved, i.e., less than 25% improvement on the Beck Depression Inventory (BDI)[16] score; partially improved (25%–49% improvement on the BDI score); and improved (50% or greater improvement on the BDI score). The criterion for remission was a BDI score of less than or equal to 8 at week 10.[17] We calculated the proportion of remission at week 10 for each category and provided exact binomial 95% confidence intervals.

## RESULTS

In total, 211 patients were included in the randomized controlled trial. After selection of subjects with BDI scores available at week ten, 172 patients (82%) remained for the present analysis.

Reasons for dropout were adverse events, referral to a psychologist, and no-show. Between the intervention groups, no relevant differences in reasons for dropout were observed. Baseline characteristics of the patients included in this study are reported in Table 1. These characteristics were similar to those of the 39 patients not included except for baseline BDI score (mean [SD], 22.2 [9.0] vs. 25.6 [9.9], respectively).

The relation between rate of improvement at weeks 2 and 6 with remission at week 10 is shown in Table 2. Within the categories "unimproved" and "partially improved," the proportion of patients attaining remission at week 10 decreased from week 2 to week 6. The lowest proportions of patients attaining remission by week 10 were observed for patients who were unimproved or partially improved after 6 weeks of treatment (29% [95% CI = 18 to 43] and 27% [95% CI = 17 to 40], respectively).

## DISCUSSION

Depressed patients who were unimproved or partially improved after 6 weeks of SSRI treatment had the lowest chance to reach remission by week 10. An important presupposition for changing treatment after lack of initial improvement is that the chance of remission will increase by doing so. Therefore, a criterion by which to decide which probability of reaching remission by week 10 is low enough to justify treatment change should be available. Based on an extensive review[1] examining strategies for patients unimproved after 4 to 6 weeks of drug treatment, the remission rate after the switch to a second drug was estimated at 30%,[11] while unimproved patients who continued placebo after 6 weeks had negligible remission rates between weeks 6 and 12, i.e., < 10%.[18,19] Consequently, it is justified for treatment change to be considered if the chance of remission is less than 30%.

If we apply the aforementioned criterion of 30% to our results, the point estimates and their 95% confidence intervals for all patients at week 2, as well as for patients improved at week 6, do not give cause for reconsidering treatment. On the basis of our results, treatment with an SSRI could be reconsidered in depressed patients who are unimproved or partially improved by week 6, however.

To our knowledge, this is the first study in primary care of the relation between initial symptom improvement and remission from depression. Our results provide evidence for the already established practice of reconsidering antidepressant treatment after 6 weeks.

There are limitations to the study that may have bearing on its generalizability. First, the analysis is based on patients who completed the treatment period of 10 weeks. However, those patients who dropped out were not different except for a slightly higher BDI score at baseline. Severity of initial depressive symptoms is a predictor of persistence of depression.[20,21] Consequently, it is reasonable to assume that the proportions of unimproved and partially improved patients attaining remission by week 10 in

the patients who dropped out would have been lower than the proportions demonstrated in the completer analysis. Second, the results may not be generalizable to specific SSRIs. In our study, all SSRIs available in the Netherlands at the time were prescribed, i.e., paroxetine (71%), fluoxetine (5%), citalopram (7%), sertraline (13%), and fluvoxamine (4%). For instance, it was suggested that fluoxetine has a slower onset of action compared with the other SSRIs,[22] which may entail a different relation between initial rate of improvement and remission.

There is some discrepancy between our results and those of the only available comparator study by Quitkin et al.[11] In the latter study, it was observed that 41% (95% CI = 31 to 52) of unimproved patients and 48% (95% CI = 40 to 57) of patients partially improved by week 6 still attained remission. However, differences in design hamper comparison between the studies. For instance, Quitkin et al.[11] recruited patients partly by advertising and treated them in specialty care. Therefore, the characteristics of patients differed between the studies. In addition, all patients were treated with fluoxetine, which may have a slower onset of action.[22] Also, Quitkin et al.[11] assessed remission at week 12 instead of week 10. The longer duration of treatment might partly explain the higher rate of remission,[23] i.e., 70% of the completers.[11] The differences between these studies demonstrate that application of their results to practice is not straightforward. First, one has to ascertain at which time points symptom change should be assessed and, second, how long a trial of SSRIs should be, taking into account that patients will not endure a nonefficacious treatment for a period much longer than 10 weeks.[12]

Our results may help primary care physicians who are considering when to change treatment. Changing treatment includes the options of raising the dose, augmentation with other medications or psychotherapy, and switching to another antidepressant.[1,2] Discussion of which strategy to follow is beyond the scope of this article.

At the start of treatment, primary care physicians should inform the patient of how long a trial with an SSRI takes. If the rationale of the trial length is made clear, adherence may improve.

We suggest that future research aim at direct comparison of strategies by conducting randomized clinical trials in which 1 arm includes patients who switch medication if unimproved at 6 weeks, and the other arm includes patients who do not switch. Results from such studies will add substantially to the evidence on which switch guidelines can be based.

In summary, the results of the present study suggest that treatment with SSRIs may be reconsidered when patients are unimproved or partially improved after a treatment duration of 6 weeks.

*Drug names:* citalopram (Celexa and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

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