# Limitations in Efficacy of Antidepressant Monotherapy

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Treatment for major depressive disorder does not achieve remission in about 50% of patients following 2 treatment trials. Researchers conducted the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study to compare various treatments for efficacy and tolerability. This article will focus on the efficacy of antidepressant monotherapy as determined by the STAR*D trial. Patients in the first treatment step of STAR*D received citalopram monotherapy and, depending on their response, moved either to follow-up or through a series of up to 4 additional treatment steps, each comprising different monotherapies, combinations, or augmentation treatment options. Only 1 of 3 patients remitted with the initial monotherapy. Rates of remission for each consecutive monotherapy were increasingly lower, suggesting that a series of monotherapy options may not be the best treatment strategy for patients who are nonresponsive to an initial monotherapy.

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Major depressive disorder (MDD) is a heterogeneous disorder associated with high mortality and a lifetime risk of 10% to 25% for women and 5% to 12% for men.[1] Current treatments, including selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, may produce partial improvement of symptoms but too frequently do not lead to remission.[2] In fact, the majority of patients with MDD never achieve symptom remission with the first medication treatment.[3] This article summarizes data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[4] to determine the efficacy of monotherapy, and specifically, monotherapy used in sequences, in the treatment of depression.

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## AN OVERVIEW OF STAR*D

### Population

The STAR*D trial was a 7-year, multicenter study that enrolled over 4000 patients, from both primary care settings and psychiatric practices, with nonpsychotic MDD. Participants were 18 to 75 years old and had at least moderate levels of depression, with scores on the 17-item Hamilton Rating Scale for Depression (HAM-D-17) of at least 14.[5] Patients were representative of a clinical population, many with concurrent psychiatric and/or general medical conditions, in order to enhance generalizability. Patients with previous suicide attempts were included, as were individuals who were actively abusing substances, as long as outpatient treatment was acceptable.

### Treatment Levels

The trial consisted of multiple treatment steps, each lasting up to 14 weeks.[5] To mimic routine practice and to ensure adequate dosing, both clinicians and patients knew what treatments patients were receiving. At the first step, patients were given the SSRI citalopram. If their depression remitted, they were encouraged to enter follow-up. Patients who responded to the citalopram monotherapy but who fell short of remission were given the option of going into follow-up or continuing to the second step (level 2), which was encouraged.

Level 2 comprised 7 treatments divided into 2 categories, monotherapy switch and augmentation. Patients at this treatment level were able to choose their treatment strategy and then were randomly assigned to a specific treatment. Monotherapy options were the SSRI sertraline, the extended-release formulations of bupropion or ven-

  

lafaxine, or cognitive therapy. Patients were allowed to reject the cognitive therapy option. The augmentation options were citalopram augmented with bupropion sustained release, buspirone, or cognitive therapy. Patients in level 1 who responded to citalopram but who did not remit tended to choose to have their treatment augmented, while patients who did not respond well to citalopram or experienced intolerable adverse events usually preferred the switch option.[6]

Patients entering the third level of treatment were again allowed to choose between the switch or the augmentation strategies or both. Switch options were mirtazapine and nortriptyline. The augmentation therapy, lithium or triiodothyronine, was used in combination with the primary drug that the patient was taking at level 2. For instance, if a patient had been taking citalopram augmented with bupropion, bupropion was discontinued and lithium or triiodothyronine was added.

Patients reaching the fourth treatment level, having not reached remission with, or been intolerant to, treatment in the previous 3 levels, were randomly assigned to either tranylcypromine or treatment with a combination of venlafaxine extended release and mirtazapine.

## RESPONSE AND REMISSION IN STAR*D

Remission was chosen as the primary endpoint because remission has the most important clinical implications. Patients whose episodes of depression do not remit function more poorly, have a worse prognosis,[7] and use more health care services than those whose depression remits. Growing evidence suggests that even modest levels of depression can contribute to or worsen the outcome of medical comorbidities,[8] and continued depressive symptomatology also carries a continued risk of suicide.[7]

Response and remission were measured using the HAM-D-17 or the 16-item Quick Inventory of Depressive Symptoms–Self Report (QIDS-SR-16). Results obtained from both the HAM-D-17 and the QIDS-SR-16 can be used together to form an overall picture of remission rates because these 2 rating scales are comparable.[9]

## STAR*D OUTCOMES

Patients in the first treatment level received citalopram at a mean dose of 41.8 mg/day at level exit, with an average treatment duration of 10 weeks.[10] Nearly half of the participants at this level responded to citalopram, and approximately one third did so after 6 weeks of treatment. Ultimately, of the patients who remitted, about half did so after 6 weeks.[10] Patients continued to achieve response or remission at 8 weeks or later. These results highlight the need for longer studies of remission, as a meaningful number of patients can be expected to respond or remit even after 8 weeks of treatment.

In level 2, monotherapy patients received mean daily doses of 282.7 mg of bupropion, 135.5 mg of sertraline, or 193.6 mg of venlafaxine at level exit.[11] Outcomes did not differ significantly among the 3 medications, contradicting the expectation that a dual-action antidepressant would provide much better outcomes. The overall finding was that about 1 in 4 patients whose depression had not remitted at level 1 achieved remission after a monotherapy switch in level 2.[11] Thus, after 2 sequential monotherapies, the remission rate was slightly less than 50%. About 1 in 3 patients who received augmentation medication at level 2 achieved remission.[12]

Level 3 monotherapy participants received mean doses of 42.1 mg of mirtazapine or 96.8 mg of nortriptyline per day.[13] These options did not have a significant difference in time to remission, and remission rates were very low. Only about 10% of patients at this level achieved remission when outcome was measured using the QIDS-SR-16.[13] The results were not significantly different (16.1%) when the HAM-D-17 was used.[13] Averaging the 2 scores resulted in an overall approximate remission rate of 13%.

At level 4, patients receiving monotherapy treatment were dosed at a mean 36.9 mg/day of tranylcypromine at level exit, which was adequate but not aggressive.[14] This treatment produced an overall approximate remission rate of 10% compared to approximately 15% for the level 4 combination treatment.[14] The difference in outcomes was not statistically significant, but the sample size was small. The combination treatment was better tolerated than the monotherapy with these agents.

## CURRENT UNDERSTANDING

In analyzing the results of STAR*D with regard to efficacy across all levels, it is apparent that the overall acute remission rates for consecutive monotherapies were modest at best. Two thirds of patients eventually remitted after 4 treatment steps, but this outcome still left a third of patients unremitted despite multiple treatments. While these results are not unsatisfactory, there are a significant number of patients who do not benefit from the monotherapy treatment strategy. Earlier use of augmentation or combination treatments may help more patients reach remission than the exclusive reliance on multiple monotherapy treatment steps.

*Drug names:* bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), nortriptyline (Pamelor and others), sertraline (Zoloft and others), tranylcypromine (Parnate and others), venlafaxine (Effexor).

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, buspirone and lithium are not approved by the U.S. Food and Drug Administration for use as augmentation for depression treatment, and triiodothyronine is not approved for the treatment of depression.

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