



Harvard Mental Health Letter

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Finding the right depression medication

*STAR*D and other studies provide guidance, but the research continues.*

In spite of the variety of medication options now available, major depression remains a challenging disease to treat. Only about half of adult patients respond to the first antidepressant prescribed, with only one-third achieving remission.

When symptoms are not adequately relieved by the first antidepressant, patients and their clinicians face a difficult decision. Although two broad strategies exist—switching to a new drug or augmenting the first drug with a second—it hasn't been clear which strategy is best. Most of the research has been on initial treatment, pitting a new drug against an old one. Studies evaluating medication augmentation or switching strategies have usually been short-term and compared a drug to a placebo, rather than to another drug.

Over the past few years, two separate streams of research in adults have helped fill this gap in knowledge. One is the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the largest prospective study of successive treatment options ever conducted. The study enrolled 3,671 patients at 41 sites nationwide (23 psychiatric clinics and 18 primary care clinics). The design was intended to mimic real-world practice, where nearly half of patients with major depression receive their care from primary care physicians, and where the first treatment offered may not work.

STAR*D results indicate that—with persistent trial and error to find the right medication—nearly seven in 10 adult pa-

tients with major depression will eventually find a treatment that works (see table, page 3). However, the study also made clear what many clinicians and patients know from experience: remission becomes much harder to achieve after two medication trials have failed.

Although new antidepressants are in development, the drug testing process takes years. A second and quite active area of research, therefore, is aimed at identifying new ways to augment medications already available to make them more effective.

- Most adults will try two or more medications before finding one that alleviates their depression.
- STAR*D suggests taking a medication for at least eight weeks before trying another.
- If the first medication fails, switching medications or augmenting the first drug with another is equally effective.

atric disorders. A common challenge, for instance, is distinguishing major depression from bipolar disorder, yet this distinction significantly influences treatment choices. Patients with bipolar disorder typically don't respond to antidepressants alone, and instead require a mood stabilizer to alleviate symptoms. In addition, major depression frequently occurs in conjunction with other disorders, such as anxiety, which can also affect medication choice and response.

Give it more time. Although the standard advice is for patients to take a medication for six weeks to see if symptoms improve,

Initial considerations

When patients do not benefit adequately from a first medication, taken as prescribed, it's wise to do the following before deciding on the next treatment.

Review symptoms and diagnosis. Major depression can be difficult to diagnose because symptoms vary and may also overlap with those of other psychi-

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Depression medication *continued*

the STAR*D trial suggests that many patients need more time to respond. All patients in the study initially received citalopram (Celexa), a selective serotonin reuptake inhibitor (SSRI). Half of the patients who reached remission did so after six weeks; some needed as long as 12 or 14 weeks. As a result, the investigators recommended that patients take an initial drug for at least eight weeks. They also recommended that patients complete self-report instruments such as the 16-item Quick Inventory of Depressive Symptomatology (available free, along with other instruments for clinicians, at www.ids-qids.org) to monitor progress and side effects.

Consider options. Many choices are available if a depression treatment fails to relieve symptoms. In STAR*D, none of the options was a clear winner. And patients could choose to switch drugs or augment them at critical junctures, so it remains unknown whether it's better to augment antidepressants that are providing only partial relief or switch to new ones. Even so, the study provides new information about how likely it is that a patient will achieve remission after a previous drug fails.

Switching medications

One option is to switch to another drug in the same class, such as from one SSRI to another. The rationale is that although drugs in the same class share the same primary target in the brain—the neurotransmitters serotonin, dopamine, or norepinephrine—they affect other brain chemicals in different ways.

Another option is to switch to a different class of medication, such as switching from an SSRI to a dual-action serotonin and norepinephrine reuptake inhibitor (SNRI), or to a tricyclic antidepressant. The rationale in this case is that changing the primary target may be necessary to alleviate symptoms.

STAR*D investigators found that about one in four patients achieved remission after switching to a second drug, whether they switched within class or to

When to consider psychotherapy

Another option to consider—at least after the first antidepressant doesn't work—is psychotherapy. While the sample sizes were small, STAR*D suggests that patients with depression who did not respond initially to citalopram were about equally likely to achieve remission whether they chose another medication or cognitive therapy as the next step.

another class. In level two of the study, patients who chose to switch to a new drug after taking the SSRI citalopram were randomized either to another SSRI, sertraline (Zoloft); to the SNRI venlafaxine (Effexor); or to another dual-action drug, the norepinephrine and dopamine reuptake inhibitor (NDRI) bupropion (Wellbutrin). Remission rates were about the same for all three drugs: 27% of patients reached remission with sertraline, 25% with venlafaxine, and 26% with bupropion.

Switching within drug class or to another class was also about equally effective in level three of the study, when patients who did not respond to two previous drugs could choose to switch medications again. At this stage, they were randomized either to the SNRI mirtazapine (Remeron), or to the tricyclic antidepressant nortriptyline (Pamelor). Remission rates were lower than before, but they were similar regardless of which drug was chosen: 8% of patients responded to mirtazapine and 12% to nortriptyline. The difference was not statistically significant.

Traditional augmentation options

Augmentation involves supplementing an antidepressant with another drug. If a second antidepressant is added, this is sometimes called combination therapy. Other augmentation strategies involve different categories of drugs, supplements, and hormones. The rationale for augmentation is to target multiple brain functions at once.

STAR*D results indicate that all of these augmentation practices work equally well after one unsuccessful antidepressant trial—about one in three patients achieved remission in level two of the study. If, however, a patient's symptoms do not respond adequately after two drug trials, STAR*D suggests that augmenting with T₃ thyroid hormone (Cytomel) may be slightly more effective and tolerable than using lithium.

Bupropion or bupirone. A common tactic is to combine an SSRI with the NDRI bupropion or the anxiety medication bupirone (BuSpar). STAR*D investigators found that, after failing to adequately respond to citalopram alone, 39% of patients achieved remission after being randomized to combination therapy with bupropion, while 33% attained remission after augmentation with bupirone. However, the difference was not statistically significant.

Lithium. This mood stabilizer is one of the best-studied augmenting agents in depression treatment. Although earlier studies suggested that augmentation with lithium, which increases serotonin levels, boosts response to antidepressants, a recent review concluded that it may not be as effective when taken with newer antidepressants. During level three of STAR*D, 13% of patients who had not responded to two previous treatments achieved remission after being randomized to lithium augmentation.

T₃ thyroid hormone. In level three of STAR*D, 25% of patients who had failed to respond to two previous treatments achieved remission after being randomized to augmentation with T₃ thyroid hormone—representing a slight but not statistically significant advantage over lithium augmentation.

Mirtazapine. In level four of STAR*D, patients who had failed to respond to three previous treatments were randomized either to receive a combination of venlafaxine plus mirtazapine, or to receive tranylcypromine (Parnate), an MAO inhibitor. Although

remission rates were similar, investigators concluded the combination was slightly better: 16% of patients achieved remission with the combination, compared with 14% on tranylcypromine alone. An advantage of adding mirtazapine to an SSRI is not only that the two drugs should act synergistically in the brain to boost antidepressant effects, but also that mirtazapine may counter the anxiety and sexual dysfunction that are common SSRI effects. A disadvantage of adding mirtazapine is that it may cause weight gain and sedation.

Newer augmentation options

Although most studies so far are preliminary, several new augmentation strategies show promise.

Second-generation antipsychotics. In November 2007, the FDA approved the antipsychotic aripiprazole (Abilify) for use as an augmentation agent in major depression. Studies suggest that other second-generation antipsychotics, such as risperidone (Risperdal), olanzapine (Zyprexa), ziprasidone (Geodon), and quetiapine (Seroquel), may also be helpful as augmentation agents. It's not clear why, but in some people the drugs act synergistically with antidepressants. They may also help by

alleviating anxiety and agitation. Side effects can be significant, particularly weight gain and the development of metabolic syndrome (which increases the risk of heart disease).

Other agents. Researchers are also investigating many other augmentation agents, including hormones such as estrogen and testosterone; dietary supplements such as methylfolate, S-adenosyl-L-methionine (SAME), and omega-3 fatty acids; and a variety of other drugs, such as anticonvulsants and benzodiazepines.

Clearly, there is no one-size-fits-all solution when a first antidepressant fails to alleviate symptoms, because individuals vary so greatly in their response to medications. But as researchers identify and test additional treatment options, they hope to improve the odds of achieving remission. ♥

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For more references, please see www.health.harvard.edu/mentalextra.

STAR*D design and outcomes

Patients progressed from one level to the next if their symptoms were not adequately relieved after 14 weeks of a particular treatment.

Study arm	Treatment options	Cumulative remission rates
Level 1	Citalopram (Celexa)	33%
Level 2	Switch to bupropion (Wellbutrin), sertraline (Zoloft), venlafaxine (Effexor), or cognitive therapy	57%
Level 3	Stop current therapy and switch to mirtazapine (Remeron) or nortriptyline (Pamelor)	63%
Level 4	Stop current therapy and receive tranylcypromine (Parnate) or mirtazapine plus venlafaxine	67%

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