First Antidepressant Fails 70% of Time

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Jan. 4, 2006 - Antidepressant medication, all by itself, puts depression into remission for 30% of patients, a government-funded study shows.

What about the other 70% of people with depression? And how long must the lucky 30% stay on medication? Stay tuned. The study is just starting to get interesting.

Unlike nearly every other study of antidepressant medications, this one is funded by the National Institute of Mental Health (NIMH) -- not by the drug industry. It doesn't just measure small improvements in carefully selected people with depression. This study looks at real patients seeking help from real-world psychiatrists and primary-care doctors. And it plans to continue until nearly every patient fully recovers from depression.

"We have to increase our expectations from depression treatments," study co-leader Madhukar H. Trivedi, MD, tells WebMD. "We have to push for full remission as an outcome, because falling short leads to less quality of life, with worsening of symptoms over time."

The first results from the 4,000-patient study -- the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study -- appear in the January issue of the *American Journal of Psychiatry*.

NIMH Director Thomas R. Insel, MD, hails STAR*D as a landmark for depression research.

"Too many research studies have little immediate relevance to practice, and too little practice is based on research evidence," Insel writes in an editorial accompanying the study. "STAR*D [is] studying patients in real-world settings and asking questions with practical relevance."

Married Patients Get Better Faster

In this first report, Trivedi and colleagues report on some 3,000 patients who completed the first phase of the study. All patients first get 12 weeks of treatment with Celexa, an SSRI antidepressant.

Why Celexa? Trivedi says it's not because they think Celexa is more effective than other antidepressants. The researchers chose to start with Celexa because SSRI antidepressants

are the first choice of most U.S. doctors and because of Celexa's chemistry. The drug stays in the body long enough to avoid withdrawal symptoms if a patient misses a few doses, but it goes away fast enough so that its effects won't be confused with those of the next drug doctors may try.

In fact, Trivedi says, he thinks the results seen with Celexa should apply to other modern antidepressant drugs.

Overall, about 30% of patients got full remission with Celexa treatment. But it didn't happen overnight. Nearly all patients needed at least eight weeks of treatment -- and a relatively high dose of Celexa -- before they got better.

"We find there is a time point in the first few weeks of depression treatment when doctors and patients lose patience and the patient drops out of treatment. The drop-out rate is huge," Trivedi says. "But if you go on long enough, remission rates are higher. You may need more doctor visits than people generally have when getting treated for their depression."

The patients who got better tended to be white, female, better educated, with higher pay, and married. Being married seemed to be particularly helpful.

"Being in a marital relationship seems to produce better outcomes," Trivedi says. "It is hard to separate out better marital status from other factors such as being in a better socioeconomic group. But the finding is very interesting. It sounds like a meaningful marital relationship makes depression treatment work better."

Why?

"Maybe it is because the spouse offers the patient support," Trivedi suggests. "Maybe the spouse is encouraging the patient to stay with the treatment. Maybe the spouse is identifying things for the patient that the patient brought back to us and that let us tailor that individual's treatment much better. And there is the potential that these positive relationships may make the stressors in the patients' day-to-day lives a little shorter."

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Because the patients are being seen in busy psychiatric clinics or primary-care centers, STAR*D patients first get antidepressant medication without psychotherapy. That may be part of the explanation for the 70% failure rate, says depression expert Andrew Elmore, PhD, a private-practice psychotherapist and assistant clinical professor at Mt. Sinai School of Medicine in New York.

"If you are running a race, you need food *and* training. Most people need drugs *and* therapy to treat their depression," Elmore tells WebMD. "In all the studies, the group that

gets both goal-oriented psychotherapy and an effective drug does better than the group that gets either one alone."

But the bigger question, Insel notes, is what treatment do those 70% of depressed patients need now?

Finding Out What It Takes to Beat Depression

There's no answer to Insel's question -- today. That may change this summer, when findings from the second part of the STAR*D trial will be announced.

Part two of the study is much more complicated. Patients who don't get full remission of their depression will be offered the chance to switch to one or more different antidepressant drugs, add a new antidepressant drug, or switch to psychotherapy (with or without drug treatment).

"If you get to full remission with the first medication, you are better off because you don't have to go to the expense and time of trying more things," Trivedi says. "For those who don't get full remission, it is the same thing as with diabetes and arthritis and hypertension and other things -- you keep looking for something that works. But for those who finally get full remission, I think there is a profound payoff. Your symptoms are all gone, and you return to your previous level of function, and your long-term outcome is profoundly better than if you didn't get to remission."

When patients do get full remission, they enter a 12-month follow-up period. During this time, drug treatment continues.

Elmore argues that while these patients are getting successful treatment, it's too soon to say they are in full remission.

"Is it remission when they still have to take a drug?" Elmore asks. "My epilepsy is under control when I take phenobarbital every day. But if I still need the drug, my epilepsy is not in remission."

But Elmore praises the STAR*D trial for providing desperately needed real-world information. And whether it's called remission or successful treatment, Trivedi notes that patients badly need to get their depression under control.

"If patient symptoms have reduced to levels where they are virtually gone, that is remission," he says. "There may be some minor symptoms left, but their functioning is the same as you and I. And if you do achieve remission, your longer-term outcome is better than if we stop treatment before remission. A person not in remission is three times more likely to have a relapse in three to nine months."

Measuring Depression

Trivedi says one of the most important parts of the STAR*D trial is that all patients get evaluated for depression symptoms at every doctor visit.

"If you have high blood pressure, and nobody measures your blood pressure, how would you know to do anything different if your medication isn't working?" Trivedi says. "You have to measure symptoms on a regular basis. Patients can do this themselves. I personally would say psychotherapy patients should measure, too. Any treatment that actually is likely to be used for depression, we should regularly be measuring patient symptoms."

Doctors who aren't trained in psychotherapy may need to measure. But Elmore says trained therapists are capable of more sophisticated evaluations than multiple-choice questionnaires can provide.

"We measure progress by getting to know a patient well enough to know whether that person's situation has improved," he says. "I would think that the judicious therapist measures patient progress via means far more robust than paper-and-pencil tests. Therapy is not just giving advice. It is trying to understand whether the advice is helping the patient, and making the patient comfortable enough to know whether the therapy is helping or not. This can be done without subjecting a patient to a written exam."

SOURCES: Trivedi, M.H. *American Journal of Psychiatry*, January 2006; vol 163: pp 1-13. Insel, T.R. *American Journal of Psychiatry*, January 2006; vol 163. STAR*D web site. Madhukar Hariprasad Trivedi, MD, professor and director, mood disorders research program and clinic, University of Texas Southwestern Medical Center at Dallas. Andrew Elmore, PhD, psychotherapist; assistant clinical professor, Mt. Sinai School of Medicine, New York.