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Post by Former NIMH Director Thomas Insel: Antidepressants: A complicated picture

By Thomas Insel on December 6, 2011

A new report tracking antidepressant use among Americans from 2005-2008 found that more than 1 in 10 Americans ages 12 and older report taking an antidepressant medication.[i] These new data, from the Center for Disease Control and Prevention's (CDC's) National Health and Nutrition Examination Survey (NHANES), comes in the wake of a lively debate in the media about whether antidepressants are effective in treating depression, or if they are just expensive, overused placebos.

The issue is more complicated than that. Treating depression involves many moving parts, only one of which is antidepressants. And a person's response to them is dependent on many factors. It's worth taking a few moments to review the multiple issues surrounding antidepressant use and efficacy.

Who is taking antidepressants and why?

As these new CDC data show, 11 percent of Americans aged 12 and older (3.7 percent of youth between 12 and 17) report taking antidepressants. Last year, antidepressants were the second most commonly prescribed medications, right after drugs to lower cholesterol. About 254 million prescriptions were written for them, resulting in nearly $10 billion in costs.[ii]

Antidepressants are approved for the treatment of certain mood and anxiety disorders. These disorders are common. Depression affected 6.4 percent of adults in the U.S. in 2008,[iii] and about 4 percent of 8-15 -year-olds.[iv] Anxiety disorders (including obsessive compulsive disorder, post traumatic stress disorder, generalized anxiety disorder and phobias) affect about 18 percent of the adult population in a given year.[v] Although depression and anxiety disorders are the primary indications for prescribing antidepressants, doctors have prescribed these medications, generally "off-label," to treat chronic pain, menstrual symptoms, low energy, and other maladies, with or without accompanying depressive or anxiety symptoms. However, we do not know how many of these prescriptions are actually taken after they are prescribed.

Are antidepressants overused?

Depression continues to be the leading cause of medical disability in the United States and Canada, accounting for nearly 10 percent of all medical disability.[vi] Depression is also associated with increased mortality. In severe major depressive disorder, some reports have estimated a risk of suicide beyond 6 percent.[vii] Depression after heart attack confers a three-fold increase in cardiovascular mortality. The persistence of such high morbidity and mortality in the face of widespread use of antidepressants suggests either that the medications are ineffective, or they are not being used by those who need them the most. Indeed, there are data suggesting both underuse and overuse of psychiatric medications. Certainly it is clear that there are high proportions of persons with mental disorders who receive no treatment whatsoever. In the case of depression, recent findings indicate

that only about half those with major depressive disorder receive care.[viii]

Who is prescribing antidepressants?

Much of the growth of antidepressant use has been driven by a substantial increase in antidepressant prescriptions by non-psychiatrists.[ix] One study found that nearly 80 percent of antidepressant prescriptions are written by medical professionals other than psychiatrists.[x] Many of these prescriptions are written without a specific psychiatric diagnosis. However, we do not know whether this is because of inadequate assessment, or if it is due to disincentives for using psychiatric diagnoses in billing records, or for other reasons.

How do antidepressants compare to placebos?

In general, the efficacy of a drug is defined by how it differs from placebo. More than two dozen antidepressants have been approved by the Food and Drug Administration (FDA) based on trials in which the drug is better than placebo. Sometimes the differences are small. Sometimes only positive results have been selected for submission to FDA. And sometimes the placebo effects are profound. For reasons that are not entirely clear, placebo effects have increased markedly over the past two decades in trials of psychiatric medications.

Mild depression tends to improve on placebo so that the difference between antidepressant use and placebo effect is very small, or at times, absent. In more severe forms of depression, antidepressants show greater efficacy. It is important to note that these clinical studies have primarily focused on reducing the symptoms of depression and not on a broader range of potential outcomes (such as changes in everyday functions, cognitive abilities, quality of life, etc.). In addition, because clinical trials are conducted in a controlled environment, they do not necessarily reflect the way actual clinical practice operates. And even under research conditions, clinical trials for antidepressants use rating scales that may be weak or imprecise indicators of efficacy.

What does research tell us about the long-term efficacy and effectiveness of antidepressants among real-world patients and how best to use them?

Prior to the past decade, nearly all studies of antidepressants looked at outcome after 6 or 8 weeks, and could only address whether patients had a reduction in some symptoms. And in most clinical trials of treatment for depression, the measure of success is simply "response" to treatment, which means that the person's symptoms have decreased by at least half of what they were at the start of the trial.

Some meta-analyses (studies that combine the results from many different trials) have shown that antidepressants can certainly be efficacious for some people. For instance, meta-analyses have demonstrated that antidepressants are efficacious in depressed patients with heart disease or other chronic medical illness.[xi] [xii]

But what about long-term effectiveness and true remission of symptoms? In the NIMH-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study (www.nimh.nih.gov//funding/clinical-research/practical/stard/index.shtml), the outcome measure was remission of depressive symptoms, e.g., becoming symptom-free. This outcome was selected because people who reach this goal generally function better socially

and at work, and have a better chance of staying well than do people who only achieve a response but not a remission. STAR*D reported remission rates of 31 percent after 14 weeks and 65 percent at six months. These results may seem modest (placebo response rates are often over 30 percent in antidepressant trials). But STAR*D was not a good test of efficacy or effectiveness because it did not have a placebo comparison. While STAR*D was helpful for comparing antidepressants, in the absence of placebo, one does not know how many people would have been in remission without active medication.

Perhaps the best evidence for efficacy comes from patients who have been treated successfully with antidepressants and are switched in a blinded fashion to placebo. In a meta-analysis of 31 withdrawal studies among more than 4,000 patients, Geddes and colleagues found that 41 percent of patients who were switched to placebo relapsed, compared to 18 percent who remained on an antidepressant.[xiii] These studies provide compelling evidence that antidepressants are effective for some people.

Other research, especially among teens with depression, has found that while antidepressants can be helpful for some, it is the combination of medication and cognitive behavioral therapy that is most effective in achieving remission sooner.[xiv] Still, relapse is a concern, especially if an antidepressant is not continued. And drop-out rates during these trials are relatively high.

Combination treatment continues to show the most promise among older adults with depression as well. In a sample of older adults with depression, the combination of medication and interpersonal psychotherapy was more effective than either alone or than a placebo. When compared to placebo, Reynolds and colleagues also found that maintenance antidepressant use was more efficacious in preventing relapse during three years of follow-up.[xv] [xvi] [xvii]

The bottom line is that these medications appear to have a relatively small effect in patients broadly classified as having depression. In some patients, perhaps those with more severe clinical conditions, they appear to be essential for remission. Clearly we need to know more about who will and will not benefit. And we need better, faster, more effective medications for depression that will help more people.

What do we know about treating depression?

We know that depression is a very heterogeneous syndrome. Major depressive disorder is defined by having at least five of nine criteria described in the Diagnostic and Statistical Manual (DSM). These signs and symptoms must persist over time (at least two weeks) and cause distress or dysfunction. This means two people who share as few as one of the nine criteria could receive the same diagnosis. Depression can also vary widely in other characteristics, ranging from the length and pattern of depressive episodes, to the presence of other physical and mental disorders and medications, to family history. It is not surprising, therefore, that different people respond differently to different treatments. At a biological level, depression likely comprises scores of different disorders. A true understanding of the nature of these different forms of depression and the ability to predict who will benefit from the various treatments available depends on a better understanding of the biology of depression, either directly or indirectly through the use of "biomarkers."

NIMH is funding the Establishing Moderators/Mediators for a Biosignature of Antidepressant Response in Clinical Care (EMBARC) study, a first step in discovering biosignatures for the personalized treatment of depression. EMBARC aims to identify a standard set of biomarkers and other measures that can be used to predict which interventions will produce the best treatment outcomes for an individual. And to better sort out

the heterogeneity of depression and other mental disorders, the NIMH Research Domain Criteria (RDoC) project will organize mental disorder diagnoses according to what we have learned from neuroscience and genomics in addition to clinical features, complementing the traditional "DSM" approach to psychiatric diagnosis.

In the meantime, there is promising research into fast-acting antidepressant agents that dramatically cut the response-to-treatment time. The drug ketamine has been found to lift depression in hours, rather than weeks. Although the use of ketamine— administered intravenously—is only experimental, it does provide us with a "proof of concept" that rapidly acting antidepressants can be developed. An NIMH initiative, Rapidly Acting Treatments for Treatment-resistant Depression (RAPID) , will be following up on this lead to create newer, faster acting interventions.

As we engage ourselves in efforts to gain a deeper understanding of the biology of depression, it is important to remember that optimal treatment for depression does not begin or end with medication. Treating depression is an art that requires many tools. We will not save lives by dismissing any of the tools we currently have available, even as we endeavor to develop better ones. A quality treatment plan for depression includes a thorough assessment, a comprehensive treatment plan that includes choices tailored to and guided by the individual—whether that be medication, psychotherapy or both—and careful, frequent follow-up.

[i] Pratt L, Brody DJ, Gu Q. Antidepressant Use in Persons Aged 12 and Over: United States, 2005-2008. NCHS Data Brief. No 76. October 2011.

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[iii] SAMHSA, National Survey on Drug Use and Health

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[v] Kessler RC, et al.. Archives of General Psychiatry, 2005 Jun;62(6):617-27.

[vi] The World Health Organization. *The global burden of disease: 2004 update*, Table A2: Burden of disease in DALYs by cause, sex and income group in WHO regions, estimates for 2004. Geneva, Switzerland: WHO, 2008. http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_AnnexA.pdf

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[x] Mark T et al., Psychiatric Svcs, 2009 Sept. 60:1167

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[xii] Pizzi C et al.,Am J Cardiology, 2011 Apr. 107(7):972-979.

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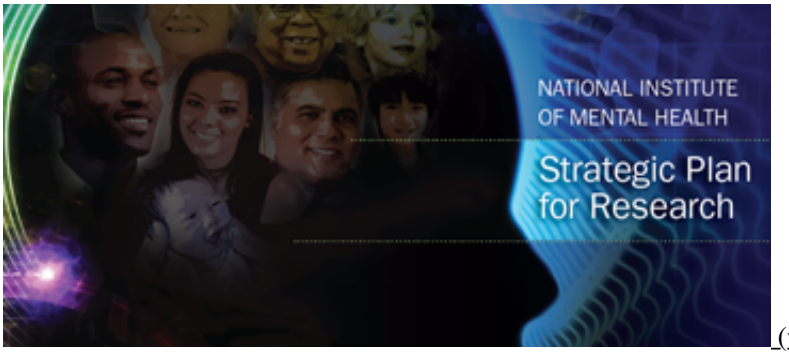
[xv] Reynolds, et al, JAMA, Jan. 6, 1999. 281(1): 39-45

[xvi] Reynolds, et al, Arch Gen Psychiatry.2011 Jan. 68 (1): 51-60

[xvii] Reynolds, et al., NEJM 354(1): 1130- 11381

NIMH Strategic Plan



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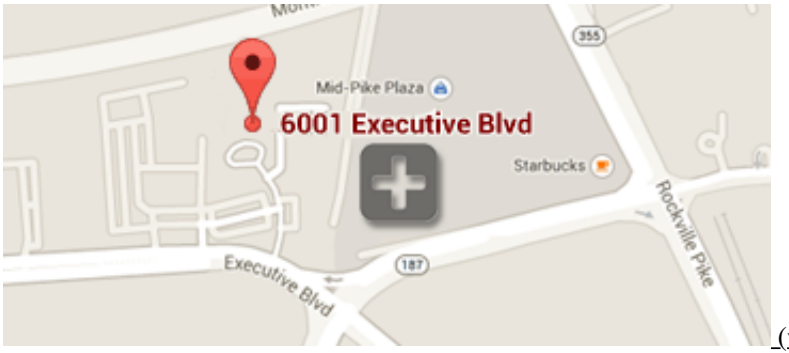

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