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## Treating depression

# Antidepressant drug trials turn away most of the depressed population

Studies establishing the effectiveness of antidepressants are based on highly selective samples of depressed patients. New research by Brown University psychiatrists found as many as 85 percent of depressed patients treated in an outpatient setting would be excluded from the typical study to determine whether an antidepressant works.

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PROVIDENCE, R.I. —While antidepressants are among the most frequently prescribed medications, most patients treated for major depression in a typical outpatient psychiatric practice would not qualify to take part in a clinical trial for a new antidepressant drug, according to a new Brown University study.

Trials to determine the effectiveness of antidepressants have historically evaluated only a small subset of depressed individuals with a very specific clinical profile. People diagnosed with other psychiatric problems and people with mild depression are among those excluded, says the study, which

appears in the March 2002 *American Journal of Psychiatry*.

“When you take any medicine you assume it’s been found to be effective for your condition,” said Mark Zimmerman, associate professor of psychiatry and human behavior, director of outpatient psychiatry at Rhode Island Hospital, and the study’s lead researcher. “No one knows for sure whether antidepressants are effective for most of the patients we treat.”

As few as 15 percent of 346 depressed patients evaluated in the Rhode Island Hospital Department of Psychiatry outpatient clinic would have met the eligibility requirements of a standard drug trial, depending on the criteria.

To determine whether the clinic patients would qualify for the drug studies, the researchers reviewed inclusion and exclusion criteria used in 31 antidepressant trials published from 1994 to 1998 in five leading psychiatric journals. Many of the studies excluded patients who had psychotic features, a history of manic episodes, suicide risk, unstable medical illnesses, or a history of drug or alcohol abuse. Several also excluded subjects with eating disorders, obsessive-compulsive disorder or panic disorder.

Nearly all of the studies excluded patients who fell below a cutoff score on a measure of symptom severity, even though they were diagnosed with major depression. “We are not aware of any other medical condition in which individuals with the disorder are routinely excluded because they are not sick enough,” said Zimmerman.

“Drug companies are concerned that individuals with mild depression will respond just as well to a placebo as they will to antidepressant medication,” said Zimmerman. “However, this

represents a sizable number of individuals who are prescribed these medicines, especially by primary care physicians.”

The researchers conducted diagnostic evaluations of patients at the Rhode Island Hospital Department of Psychiatry outpatient practice, a group ranging in age from 16 to 65. Excluding patients with any of the features commonly used in efficacy trials eliminated two-thirds of the patients. If patients with an anxiety disorder were also excluded, then more than 85 percent of the patients would not have qualified for a drug study of antidepressants – yet more than 90 percent of the patients in the study for whom prescribing information was available were being treated with antidepressants at the time of the evaluation.

Some extrapolation of antidepressant studies by clinicians will always be necessary, Zimmerman said. It would be impossible to establish the effectiveness of antidepressant medications in every conceivable population of depressed patients. But the current practice of limiting studies to only “pure” moderate-to-severely ill depressives may skew the findings of drug trials, he added. If antidepressants are, in fact, not effective for some of these large subgroups of depressed individuals, their prescription incurs an unjustifiable exposure of risks and side effects, and alternative treatments need to be considered.

Opening antidepressant trials to patients with a wider range of symptoms would allow researchers to learn whether any specific subsets respond or do not respond to a drug. The question now is whether government mandates are necessary to make trials more inclusive, Zimmerman said. There is little motivation for drug companies – whose primary aim is to show that their medication is safe and that it works for some patients – to do this.

“Drug companies have been correct in assuming that if they show their medicine works for a highly select group of depressed patients, physicians will use it for all patients,” said Zimmerman.

This study was supported by grants from the National Institutes of Mental Health. Zimmerman worked with Jill I. Mattia, clinical assistant professor, and Michael A. Posternak, research fellow, in the Department of Psychiatry and Human Behavior at Brown University.

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■ [top of file](#)

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