

St. John's wort has undergone more human testing than most synthetic antidepressants at the time of their approval for marketing. The vast majority show an advantage for SJW over placebo and equivalence with synthetic antidepressants. Since they were done primarily in Germany, which doesn't use the American diagnostic system (DSM-IV), most of them were not classified as "major depression" - a DSM term. The severity of their depression, however, would surely have qualified most of these patients as "major depression" by the DSM standard.

For many reasons, a significant proportion of clinical trials with antidepressants as well as other psychotherapeutic drugs fail to produce a significant advantage over placebo. Because of this, no single trial can be considered "definitive." Proof of efficacy is relative, and must take into account the weight of all available evidence - this includes basic pharmacology as well as human clinical trials.

The "true" mechanism of action is not known for any antidepressant. For example, the relationship between serotonin uptake inhibition and antidepressant effect is not understood today any more than it was in the early 60's when we first figured out what the first (accidentally discovered) antidepressant, imipramine, was doing in the brain of rats. Likewise, the mechanism of action of hypericum, despite reports in the literature of serotonin uptake inhibition, is unknown. Recent studies suggest that this reported uptake inhibition is just an artifact of the particular test-tube assay.

The recent study in the JAMA, designed and sponsored by Pfizer, was a very unusual trial for several reasons. The primary one, as already stated by Dr. Rosenthal, is that the patients were so chronic and severe that they were unlikely to have responded to any antidepressant. Unfortunately, the other design flaw was the lack of a comparison drug, otherwise known as a positive control. In this way, one can determine whether the drug really failed to work or the trial simply lacked sensitivity. When drug companies test their own products, they never use patients like the ones in the Shelton study. The risk of failure is too great. But then, failure to show an effect over placebo doesn't count against them at the FDA *if* there is no positive control.

I initiated the hypericum trial conducted by the NIH when I was with the National Institute of Mental Health. I originally designed the study in 1995 to include patients with Hamilton depression scores (HAMD) of 16 or greater, since I wanted to capture the "mild to moderate" range of depression. This was later changed to 17, which was, and is, considered to be the industry "standard" for depression trials. After I left the project, this entry criterion was changed again to 20 or greater on the HAMD. This is the same as for the JAMA study, and would be considered in the "moderate to severe" range of depression. Fortunately, this study included a positive control, sertraline, which is the Pfizer drug, Zoloft. This design prompted the initiation of the hypericum study by Pfizer.

The NIH study is currently under analysis, and the results are not yet known. However, there is some indication that the overall response rate was low - not unexpected for this "moderate to severe" category of patients. A number of additional studies with hypericum are ongoing. One in comparison to Prozac is ongoing at Massachusetts General Hospital in Boston; another at McLean Hospital in Boston. Perhaps these results will help to clarify the role for hypericum in "major depression."

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