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Suggestion in the Treatment of Depression

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Meta-analyses consistently reveal that most of the response to antidepressant treatment can be obtained by placebo, and the difference between response to the drug and the response to any treatment is not clinically significant for most individuals diagnosed with major depressive disorder. Furthermore, the best predictor of antidepressant efficacy is the response to placebo during the so-called placebo run-in period. It can also be shown that a significant portion of the placebo effect is expectancy. These data thus indicate that suggestion is a central factor in treating depression. Therefore, the use of hypnosis, which is based on suggestion, as a treatment adjunct can be expected to enhance treatment outcome.

Keywords: antidepressants, depression, suggestion

The meta-analyses reviewed in this article were initiated not because of any interest in evaluating the effects of antidepressants, but because of the first author’s long-standing interest in the effects of suggestion and expectancy (Kirsch, 1985). Response expectancies are anticipations of automatic subjective reactions, such as changes in depression, anxiety, pain, etc. Kirsch has argued that response expectancies are self-confirming. The world in which we live is ambiguous, and one of the functions of the brain is to disambiguate it rapidly enough to respond quickly. We do this, in part, by forming expectations. So what we experience at any given time is a joint function of the stimuli to which we are exposed and our beliefs and expectations about those stimuli (Kirsch, 1999; Michael, Garry, & Kirsch, 2012).

The response expectancy hypothesis has been the focus of most of the first author’s research. The particular topic areas (hypnosis, psychotherapy, placebo effects, etc.) were chosen merely because they provided a convenient opportunity for examining expectancy effects. It seemed that depression ought to be particularly responsive to expectancy effects because hopelessness is a central feature of depression (Abramson,
Seligman, & Teasdale, 1978), and hopelessness is an expectancy. Specifically, it is the expectancy that a negative state of affairs will not get better, no matter what one does to alleviate it.

If you ask people diagnosed with major depressive disorder (MDD) what the worst thing in their lives is, many will tell you that it is their depression. They believe that their depression will continue, no matter what they do—a very depressing thought indeed. As John Teasdale (1985) noted, such people are depressed about their depression. Does it therefore follow that the belief that one will improve, the opposite of the hopelessness that may be maintaining the depression or at the very least is an important component of it, can become a significant factor in treatment? Yapko (2010) indeed notes that developing “realistic hopefulness” is a variable in alleviating depression. Rutherford, Wager, and Roose (2010) looked at expectancy in the treatment of depression. Successful pharmacological treatment of depression seems always to involve expectancy as a significant component. Thus, there appears to be a substantial effect of positive expectancy associated with the treatment of depression.

The connection between placebo responding and expectancy is a much-researched phenomenon. Stewart-Williams and Podd (2004) define a placebo as “a substance or procedure that has no inherent power to produce an effect that is sought or expected” (p. 326), and the placebo effect as:

a genuine psychological or physiological effect, in a human or another animal, which is attributable to receiving a substance or undergoing a procedure, but is not due to the inherent powers of that substance or procedure. (p. 326)

The placebo effect can be created and enhanced via classical conditioning, a result clearly demonstrated in studies on pain and immunosuppression (Ader, 1997; Voudouris, Peck, & Coleman 1990), but cognition, particularly in humans, is a significant factor in placebo responding, and the effects of conditioning are often mediated by expectancy. For example, a placebo cream created a greater analgesic effect in subjects unaware that the pain stimulus had been reduced during conditioning trials, but not in those who were aware (Montgomery & Kirsch, 1997). Additionally, the direction of a placebo response can be shaped by cognition, as seen in studies in which groups receive the same placebo with opposing expectations, and report different effects (Stewart-Williams & Podd, 2004). Thus placebo responding can be strongly mediated by expectancy.

### Antidepressant Medications and Placebo Effects

In 1998, Sapirstein and Kirsch undertook a meta-analysis, the purpose of which was to evaluate the placebo effect in depression (Kirsch & Sapirstein, 1998). They searched the literature for studies in which patients diagnosed with MDD had been randomized to receive antidepressant medication, an inert placebo, psychotherapy, or no treatment at all. They included studies of psychotherapy, because those were the only ones in which
patients had been randomized to a no-treatment control condition, and they needed that condition to evaluate the placebo effect.

The response to a placebo is not the same as the effect of the placebo. The placebo response (as opposed to the placebo effect) may, at least in part, be due to the passage of time, spontaneous remission, the natural history of the disorder, and regression to the mean. Just as the difference between the drug response and the placebo response is deemed to be the drug effect, so the difference between the placebo response and improvement in a no-treatment control group can be interpreted as the placebo effect.

This meta-analysis proved to be quite controversial. Its publication led to heated exchanges. The response from critics was that these data could not be accurate. Perhaps the search had led the authors to analyze an unrepresentative subset of clinical trials. Antidepressants had been evaluated in numerous trials, and their effectiveness had been well established.

In an effort to respond to these critics, Kirsch and others decided to replicate their study with a different set of clinical trials (Kirsch, Moore, Scoboria, & Nicholls, 2002), using the Freedom of Information Act to request that the Food and Drug Administration (FDA) provide the data that pharmaceutical companies had sent to it in the process of obtaining approval for six new generation antidepressants that accounted for the bulk of antidepressant prescriptions being written at the time. There are a number of advantages to the FDA data set. First, the FDA requires that the pharmaceutical companies provide information on all of the clinical trials that they have sponsored. Thus, the researchers had data on unpublished trials as well as published trials. Second, the same primary outcome measure—the Hamilton depression scale (HAM-D)—was used in all of the trials. That made it easy to understand the clinical significance of the drug–placebo differences. Third, these were the data on the basis of which the medications were approved. In that sense, they have a privileged status. If there is anything wrong with them, the decision to approve the medications in the first place can be called into question.

In the data sent by the FDA, only 43% of the trials showed a statistically significant benefit of drug over placebo. The remaining 57% were failed or negative trials. The results of the analysis indicated that the placebo response was 82% of the response to these antidepressants. Subsequently, Kirsch and colleagues replicated their meta-analysis on a larger number of trials that had been submitted to the FDA (Kirsch et al., 2008). With this expanded data set, they found once again that 82% of the drug response was duplicated by placebo. More important, in both analyses, the mean difference between drug and placebo was less than two points on the HAM-D, and the standardized mean difference (SMD) was 0.32. The National Institute for Clinical Excellence (NICE), which drafts treatment guidelines for the National Health Service in the United Kingdom, has established a 3 point difference between drug and placebo on the HAM-D or an SMD of 0.50 as the criteria of clinical significance (NICE, 2004). Thus, when published and unpublished data are combined, they fail to show a clinically significant advantage for antidepressant medication over inert placebo. These analyses have since been replicated repeatedly, and despite differences in the way the data are presented,
the numbers are remarkably consistent. SMDs range between 0.30 and 0.34, and the raw score differences on the HAM-D are always below 3 points (Fournier et al., 2010; NICE, 2004; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008).

Severity of Depression and Antidepressant Effectiveness

Critics have argued that the meta-analysis results were based on clinical trials conducted on subjects who were not very depressed. In individuals with more severe depression, they argued, a more substantial difference would certainly be found. In fact, it was this criticism that led Kirsch and colleagues to re-analyze the FDA data (Kirsch et al., 2008). They categorized the clinical trials in the FDA database according to the severity of the patients’ depression at the beginning of the trial, using conventional categories of depression (American Psychiatric Association, 2000; NICE, 2004). However, only one of the trials was conducted on individuals with moderate depression scores, and that trial failed to show any significant difference between drug and placebo. Indeed, the difference was virtually nil (0.07 points on the HAM-D, SMD = 0.03). All of the rest of the trials were conducted on patients whose mean baseline scores put them in the “very severe” category of depression, and even among these patients, the drug-placebo difference was below the level of clinical significance (2.36 HAM-D points, SMD = 0.33).

Still, severity did make a difference. Patients with scores at the very extreme end of depression severity, those scoring at least 28 on the HAM-D, showed an average drug-placebo difference of 4.36 points. To find out how many patients fell within this extremely depressed group, Mark Zimmerman from the Brown University School of Medicine was asked for the raw data from a study in which he and his colleagues assessed HAM-D scores of patients who had been diagnosed with unipolar MDD after presenting for an intake at a psychiatric outpatient practice (Zimmerman, Chelminski, & Posternak, 2005). Patients with HAM-D scores of 28 or above represented 11% of these patients. This suggests that 89% of patients diagnosed with MDD are not receiving a clinically significant benefit from the antidepressants that are prescribed for them.

Predicting Response to Treatment

Severity of depression is one of the few predictors of response to treatment. Type of antidepressant has little if any impact on treatment response. As summarized in a 2011 meta-analysis of studies comparing one antidepressant to another:

On the basis of 234 studies, no clinically relevant differences in efficacy or effectiveness were detected for the treatment of acute, continuation, and maintenance phases of MDD. No differences in efficacy were seen in patients with accompanying symptoms or in subgroups based on age, sex, ethnicity, or comorbid conditions . . . . Current evidence does not warrant recommending a particular second-generation antidepressant on the basis of differences in efficacy. (Gartlehner et al., 2011)
Although type of medication does not make a clinically significant difference in outcome, response to placebo does. Almost all antidepressant trials include a placebo run-in phase. Before the trial begins, all of the patients are given a placebo for a week or two. After this run-in period, the patients are reassessed, and anyone who has improved substantially is excluded from the trial. That leaves patients who have not benefitted at all from placebo and those who have benefited only a little bit. These are the patients who are randomized to be given the drug or kept on a placebo. In examining the data, it is evident that the patients who show at least a little improvement during the run-in period are the ones most likely to respond to the real drug, as shown not only by physician ratings, but also by changes in brain function (Hunter, Leuchter, Morgan, & Cook, 2006; Quitkin et al., 1998).

**How Did These Drugs Get Approved?**

How is it that medications with such weak efficacy data were approved by the FDA? The answer lies in an understanding of the approval criteria used by the FDA. The FDA requires two adequately conducted clinical trials showing a significant difference between drug and placebo. But there is a loophole: There is no limit to the number of trials that can be conducted in search of these two significant trials. Trials showing negative results simply do not count. Furthermore, the clinical significance of the findings is not considered. All that matters is that the results are statistically significant.

The most egregious example of the implementation of this criterion is provided by the FDA’s approval of Viibryd in 2011 (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails). Seven controlled efficacy trials were conducted. The first five failed to show any significant differences on any measure of depression, and the mean drug–placebo difference in these studies was less than \(\frac{1}{2}\) point on the HAM-D. The company ran two more studies and managed to obtain small but significant drug–placebo differences (1.70 points). The mean drug–placebo difference across the seven studies was 1.01 HAM-D points. This was sufficient for the FDA to grant approval.

**Clinical Conclusions**

In summary, there is a strong therapeutic response to antidepressant medication. But the response to placebo is almost as strong. This presents a therapeutic dilemma. The drug effect of antidepressants is not clinically significant, but the placebo effect is. What should be done clinically in light of these findings?

One possibility would be to prescribe placebos, but this represents an unacceptable deception. Besides being ethically questionable, it runs the risk of undermining trust, which may be one of the most important clinical tools that clinicians have at
Another possibility that has been proposed is to use antidepressants as active placebos (Hollon, DeRubeis, Shelton, & Weiss, 2002; Moerman, 2002). However, this alternative is precluded by the presence of side effects and health risks (including increased risk of stroke, gastrointestinal bleeding, overall mortality, and congenital malformations in the offspring of women taking antidepressants while pregnant) associated with antidepressant use (Andrews, Thomson, Amstadter, & Neale, 2012). In addition, Andrews and colleagues have reported convincing evidence that the use of antidepressants increases the risk of relapse following recovery from depression.

A better alternative is the use of non-drug treatments. Kirsch and colleagues have conducted a meta-analysis of various treatments for depression, including antidepressants, psychotherapy, the combination of psychotherapy and antidepressants, and “alternative” treatments, which included acupuncture and physical exercise (Khan, Faucett, Lichtenberg, Kirsch, & Brown, 2012). They found no significant differences between these treatments or within different types of psychotherapy. When all treatments are equally effective, choice should be based on side effects and risks of harm.

Although psychotherapy is no better (or worse) than antidepressants in the short term, it seems to have a particular advantage in the long term. Specifically, short-term, cognitive-behavioral psychotherapy (CBT) seems to decrease relapse rates for as long as 6 years following discontinuation of drug treatment (Fava et al., 2004). Furthermore, the effect seems specific to the skills that are taught as part of the treatment. The control group in this clinical trial received the same amount of supportive care from the same psychiatrist, with only the components specific to CBT missing.

Although CBT may be more than a placebo, its effectiveness might be increased by enhancing its placebo components. The placebo effect is a component of all treatments for any condition that can be influenced by expectancy or suggestion. The effect of a medical treatment is generally an additive combination of the specific drug effect plus what is added by the placebo components of the treatment. For example, the pain reducing effect of morphine is cut in half when patients are administered morphine without knowing it (Benedetti et al., 2003).

Additionally, given the data that expectancy plays a significant role in both placebo and active treatment responding in individuals diagnosed with MDD (Rutherford et al., 2010), altering negative expectancy—that is, hopelessness—in individuals who are depressed, would essentially enhance the placebo component of treatment. So how can the placebo component of CBT be boosted? One possibility is the addition of hypnosis as a non-deceptive placebo (Kirsch, 1994). Like CBT, hypnosis may be more than a placebo, but like any treatment, it has placebo components, and the placebo components seem to be very strong. A meta-analysis comparing CBT plus hypnosis to CBT alone showed a substantial benefit for adding hypnosis to treatment (Kirsch, Montgomery, & Sapirstein, 1995). Yapko (2010) also notes that hypnosis has been demonstrated to be helpful in the treatment of depression, and as an adjunct to various aspects of CBT. In addition, hypnosis and placebo share a number of common characteristics:
They are effective for the same clinical conditions,
They can be used to boost the effectiveness of other treatments,
They are both based on suggestion, and
They are both linked to expectation.

The formation of realistic, non-hopeless expectations is one of the most powerful components of any effective treatment for depression, be it medical or psychological. In this context, suggestion represents a means of presenting alternative expectations, and hypnosis is the most effective and best-elaborated set of procedures for administering suggestions effectively and without deception. Using the disputing techniques of CBT as a basis for developing a hypnotic suggestion for a more realistic belief may significantly enhance the effectiveness of CBT alone. A specific hypnotic technique that utilizes this concept is age progression; allowing the clinician to guide the patient to develop an image of a brighter future (Torem, 2006).

In further exploring the potential for hypnosis as a means to capitalize on the responsiveness of depression to suggestion, Yapko (2006) points out that individuals diagnosed with MDD are narrowly focused on negative percepts such as hopelessness, and hypnosis utilizes narrowing of focus as a step in enhancing the intensity of the experience. This might indeed indicate another means by which the natural characteristics of depression to respond particularly well to hypnosis.

While there have been few clinical trials of hypnosis in the treatment of depression (see however Alladin & Alibhai, 2007; and Dobbin, Maxwell, & Elton, 2009), a growing body of clinical evidence points to the huge potential of hypnosis to improve treatment outcomes and reduce human suffering. In addition to the alteration of negative expectancies via simple suggestion, skill building, ego strengthening, and enhancing motivation for action are among the areas of hypnotic intervention that have shown potential clinically to alleviate depression. The authors hope that the dearth of evidence for the use of this promising and powerful technique for treating depression will be remedied in the near future.

References


