Published in final edited form as:

Psychother Psychosom. 2012 ; 81(5): . doi:10.1159/000337053.

Open-Label Placebo for Major Depressive Disorder: A Pilot Randomized Controlled Trial

John M. Kelley, PhD^{1,2,3}, Ted J. Kaptchuk², Cristina Cusin, MD³, Samuel Lipkin, BA³, and Maurizio Fava, MD³

¹Psychology Department, Endicott College

²Program in Placebo Studies, Beth Israel Deaconess Medical Center and Harvard Medical School

³Depression Clinical and Research Program, Massachusetts General Hospital and Harvard Medical School

Keywords

Randomized Controlled Trial; Major Depressive Disorder; Placebo

In randomized controlled trials (RCTs), major depressive disorder (MDD) patients treated with double-blind placebos often show substantial improvement. Indeed, two meta-analyses have estimated that the double-blind placebo response is 80% as large as the double-blind antidepressant response [1,2]. This strong placebo response combined with the absence of side effects has prompted suggestions to use open-label placebo as a first-line treatment for depression [3]. Here we report a pilot study investigating this intriguing question for MDD.

We conducted an RCT of open-label placebo in adult outpatients with a primary diagnosis of non-psychotic MDD as diagnosed by the Structured Clinical Interview for DSM-IV [4]. For the first two weeks, patients were randomized to either open-label placebo or waitlist control. After two weeks, participants originally randomized to open-label placebo continued for an additional two weeks on open-label placebo; and participants originally assigned to waitlist control were switched to open-label placebo for an additional four weeks, so long as they continued to meet eligibility requirements after two weeks on the waitlist. Patients were instructed to take two placebo pills, twice daily. The placebos were blue capsules containing microcrystalline cellulose.

Blinded clinicians assessed patients at baseline and every two weeks thereafter. The primary outcome was the clinician-rated 17-item Hamilton Scale for Depression (HAM-D-17) [5]. Secondary, self-report, outcomes were the Quick Inventory of Depressive Symptoms (QIDS) [6] and the Symptoms of Depression Questionnaire (SDQ) [7]. The primary test of efficacy was at two weeks. The entire sample was used to examine pre-post improvement after four weeks of open-label placebo treatment.

Prior to randomization, the treating psychiatrists provided all participants with a rationale explaining why open-label placebos might be effective. The rationale included four points: (a) in RCTs placebos are roughly 80% as effective as antidepressants; (b) classical conditioning is a possible mechanism for automatic self-healing; (c) placebo-treated patients

who are more compliant have better outcomes, therefore the placebos should be taken faithfully; and (d) positive expectations increase placebo effects, but it is OK to have doubts. Although the rationale was scripted, treating psychiatrists were encouraged to deliver the rationale in a natural and supportive manner that allowed for questions and answers. All participants provided written informed consent. Patients were paid \$20 for each completed assessment, and all patients were offered three months of free psychiatric treatment after the trial.

Our principal goal was to examine the feasibility of conducting trials of open-label placebo for MDD. Recruitment for this study was the fastest of the ten most recently conducted MDD studies in the Depression Clinic at Massachusetts General Hospital. Mean number of patients screened per month was 4.13 as compared to only 2.55 for the other nine trials. In addition, 75 percent of patients completed the trial. We recruited a total of 20 patients, primarily women (70%) of middle age (38.8 ± 12.6) with moderately severe depression at baseline (mean HAM-D-17 = 18.0 ± 4.9). There were no significant differences between the open-label placebo (N=11) and waitlist control (N=9) groups on demographics or baseline severity.

At the two-week endpoint, there were no statistically significant differences between open-label placebo and waitlist; and the observed symptom improvement was relatively small compared with typical MDD RCTs (Table 1A). On the other hand, the effect size for the main outcome measure (HAM-D-17) was medium ($d = .54$), which is larger than typical effect sizes for the drug-placebo difference in MDD RCTs [1] and above the criterion for a clinically significant improvement set by the National Institute for Clinical Excellence (NICE) in the UK [8]. In addition, there were statistically significant pre-post improvements on all three outcome measures after four weeks of open-label placebo treatment, with moderate to large effect sizes (Table 1B). However, improvement on the HAM-D-17 was relatively small as compared to the improvement typically in MDD RCTs.

To our knowledge, this is the first RCT to test the efficacy of open-label placebo for MDD. Despite the fact that we observed a medium-sized effect for the main outcome measure, our findings do not support the hypothesis that open-label placebo is effective for MDD. However, the results were in the predicted direction, and this pilot study was limited by small sample size, low statistical power, and short duration.

An important question that might be raised is whether this study tests open-label placebo or the power of suggestion of the rationale. Critics might contend that a true test of open-label placebo should provide no rationale for effectiveness. However, this eliminates positive expectancy, which is as important to the placebo effect as the placebo pill itself. Moreover, in clinical practice, treatment is always accompanied by a rationale for effectiveness. If placebo antidepressants were to be used in clinical practice, they too would need to be delivered with a rationale for effectiveness.

Another possible criticism of this study is that it only generalizes to patients willing to try open-label placebo for MDD. We agree that this limits generalizability, but the same limit applies to any treatment (e.g., antidepressant trials only generalize to patients willing to take antidepressants). Moreover, the only population to which we would seek to generalize is patients who are willing to try open-label placebo as a first-line treatment for depression.

In summary, this pilot study demonstrated that trials of open-label placebo for depression are feasible. Patients were readily recruited, and 75 percent completed a four week trial. However, our results are insufficient to support the hypothesis that open-label placebo is an effective treatment for depression. We did, however, see small, but statistically significant

pre-post improvement at four weeks for the entire sample. Given the small sample size of this pilot study, larger trials of open-label placebo for MDD are warranted.

Acknowledgments

Funding: JK and TK partially funded by NCCAM grant # 2K24 AT004095.

References

1. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: A meta-analysis of data submitted to the food and drug administration. *PLoS Med*. 2008; 5:e45. [PubMed: 18303940]
2. Kirsch I, Moore TJ, Scoboria A, Nicholls SS. The Emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. *Prevention and Treatment*. 2002; 5:Article 23.
3. Brown WA. Placebo as a treatment for depression. *Neuropsychopharmacology*. 1994; 10:265–269. [PubMed: 7945737]
4. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured clinical interview for Axis-DSM-IV disorders. New York: Biometrics Research Department, New York State Psychiatric Institute; 1995.
5. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960; 23:56–62. [PubMed: 14399272]
6. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB. The 16-item quick inventory of depressive symptomatology (QIDS): A psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003; 54:573–583. [PubMed: 12946886]
7. Pedrelli, P.; Blais, MA.; Alpert, A.; Shelton, RC.; Fava, M. Reliability and validity of the symptoms of depression questionnaire (SDQ). Under review
8. National Institute for Clinical Excellence. Depression: Management of depression in primary and secondary care. London, England: 2004.
9. Cohen J. A power primer. *Psychol Bull*. 1992; 112:155–159. [PubMed: 19565683]

Table 1

Improvement in Depressive Symptoms after Treatment with Open-Label Placebo

A. Symptom Improvement by Treatment Group at 2 Weeks						
Measure	Waitlist (N=9)	Open-Label (N=11)	Difference	95% CI	d	p
HAM-D-17	-0.67±4.00	1.64±4.52	2.30	-1.76 – 6.36	.54	.26
QIDS	-0.22±2.44	2.27±3.88	2.50	-.64 – 5.63	.77	.13
SDQ	1.38±10.77	3.70±18.98	2.33	-13.68 – 18.33	.15	.75

B. Pre-Post Symptom Levels and Improvement after 4 Weeks of Placebo Treatment						
Measure	Pre (N=20)	Post (N=20)	Difference	95% CI	d	p
HAM-D-17	18.00±4.94	14.75±6.61	3.25	.44 – 6.06	.56	.03
QIDS	14.85±2.68	12.10±4.34	2.75	.95 – 4.55	.76	.005
SDQ	146.94±19.71	137.06±27.50	9.89	2.08 – 17.70	.41	.02

Note: All values are means ± standard deviations. Positive scores indicate improvement. HAM-D-17=17-item Hamilton Depression Scale (physician-rated). QIDS=Quick Inventory of Depressive Symptomatology (patient-reported). SDQ=Symptoms of Depression Questionnaire (patient-reported). CI=Confidence Interval. d=Cohen's standardized mean difference effect size. For Cohen's d: small=.20, medium=.50, large=.80 [9]. Between-groups differences (Table 1A) were tested with analysis of covariance, controlling for baseline severity. Pre-post differences (Table 1B) were tested with paired-samples t-tests. All analyses were intent-to-treat, and missing values were replaced using the Last Observation Carried Forward (LOCF) method. All tests were two-tailed, with alpha set at 5%.