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Commentary: Is the Placebo Effect Actually Increasing Over Time?:

(Commentary for the article "Variation in placebo effect sizes in clinical trials of oral interventions for management of the behavioral and psychological symptoms of dementia (BPSD): a systematic review and meta-analysis" by Hyde AJ, et al.)

Dilip V. Jeste, M.D.[1,2,3] and **Ellen E. Lee, M.D.**[1,2]

[1]Department of Psychiatry, University of California, San Diego, La Jolla, CA, US

[2]Sam and Rose Stein Institute for Research on Aging, University of California, San Diego, La Jolla, CA, United States

[3]Department of Neurosciences, University of California, San Diego

Placebo effect has long been a topic of considerable clinical, scientific, and public interest (1). The word 'placebo' is derived from Latin for "I will please". Two centuries ago, a medical dictionary defined placebo as any medicine adapted to please rather than benefit the patient. However, it was not until the 1960s that the placebo effect became widely recognized and placebo-controlled trials became the norm in the approval of new medications (2).

Placebo effect means that the subject receiving it experiences an improvement in his or her condition that is primarily attributable to the subject's personal expectations, rather than to any biological or other proposed mechanisms related to the treatment itself. Thus a placebo "medicine" is often called a sugar pill that does not contain an active substance intended to affect health. Of course, placebos are not restricted to substances but include sham treatments that superficially mimic the actual treatment (e.g., sham dialysis or sham group therapy). Contrary to popular belief, placebo response does not have to be positive, but can be negative. A person may experience worsening of original symptoms or develop new side effects due to negative expectations about the "treatment" (3). This is sometimes referred to as "nocebo effect" (from Latin, meaning "I shall harm").

Biological explanations of placebo effect, based on empirical, though limited, data, include alterations in levels of inflammatory markers, endocannabinoids, endogenous opioids, or dopamine metabolism (4). Other explanations include expectancy effects and

Corresponding Author: Dilip V. Jeste, M.D.,Senior Associate Dean for Healthy Aging and Senior Care, Estelle and Edgar Levi Chair in Aging, Director, Sam and Rose Stein Institute for Research on Aging, Distinguished Professor of Psychiatry and Neurosciences, University of California San Diego, 9500 Gilman Drive, #0664, La Jolla, CA 92093 Tel: +1 858 534 4020; Fax: +1 858 543 5475; djeste@ucsd.edu.

Contributors

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Ellen E. Lee was involved in manuscript preparation.

Conflicts of Interest

The authors declare no relevant conflicts of interest.

methodological issues. While several studies have investigated personality traits of placebo responders, no clear relationship between particular personality patterns and placebo effect have been established (5).

The holy grail of effective treatments is demonstration of significantly better response to the treatment compared to placebo in a randomized controlled trial (RCT). The usual assumption is that placebo response in a serious condition would be relatively small and stable. One potentially serious and difficult-to-treat condition is severe behavior problems in persons with advanced dementia. There are no FDA-approved pharmacotherapies for these symptoms, medications commonly used off-label are associated with adverse effects and risks, and effective behavioral interventions are often unavailable or difficult to implement (6). Yet, in FDA-approved RCTs of antipsychotics in nursing homes, for older persons with dementia complicated by psychosis or severe agitation, the placebo response rate ranged between 35% and 50% (6). The probable reason for this unexpectedly high placebo response is the “tender loving care” that is associated with participation in a research trial. For individuals with severe dementia receiving suboptimal care in understaffed nursing homes, research participation includes markedly enhanced attention and care – with complete physical examinations, treatment for pain and other frequently ignored problems, and overall improved healthcare. It is no wonder then that these patients’ behavior problems improve. The placebo response thus reflects response to (unplanned) psychosocial treatment that is involved in a clinical trial.

In an interesting paper published in the present issue of this journal, Hyde and colleagues describe the results of a meta-analysis of placebo effect sizes over time in intervention trials for behavioral and psychological symptoms of dementia (7). Noting trends of increasing placebo effect sizes with a variety of treatments (including antidepressants, antipsychotics, cognitive enhancers, and psychosocial interventions), the authors examined 25 RCTs published between 2000–2015, using the Neuropsychiatric Inventory (NPI) as the primary outcome measure. Comparison of the first 12 studies (published in 2000–2008) with the second 13 studies (published in 2009–2015) showed that placebo effect sizes have increased significantly over time.

The authors investigated a number of possible explanations (methodological issues, societal changes in expectations and clinical care, regression to the mean, funding sources, patient and investigator expectations, and clinical characteristics), but the analysis did not reveal a clear cause for the increased placebo effect sizes. Certain clinical characteristics were associated with increased placebo effect sizes over time: Alzheimer’s dementia type, baseline agitation, *Ginkgo biloba*, and duration of treatment. However, the number of studies was relatively small and the interventions varied widely, hampering comparison of the different interventions. Independent of the year of the study, longer duration interventions had lower placebo effect sizes compared to shorter duration interventions. Surprisingly, active treatment groups also had increased improvements in NPI scores with time, supporting the possibility that a systematic process was concomitantly improving placebo effect sizes. Participant and investigator expectations were not assessed.

As the authors note, the findings of this meta-analysis are limited in some ways. Only RCTs of oral pharmacological agents were included, but it is noteworthy that no antipsychotic trials were included. This limitation is likely due to the study selection criteria used by the authors, however it also decreases the generalizability of the study's findings as antipsychotics are a commonly used treatment for agitation and psychosis associated with dementia. Nonetheless, we agree with the authors' suggestion for basing sample size calculations (power analyses) for future RCTs on the larger placebo effect sizes seen in recent trials, thus increasing the sample sizes in future studies. There is a clear need to run adequately powered RCTs of adequate duration of treatment (at least 20–26 weeks), and also a need to look more closely at behavioral interventions.

From a broader perspective, one wonders about the reasons for an overall trend in trials of various psychiatric treatments (especially antidepressants) suggesting greater placebo response in recent years. These findings have been attributed to a number of methodological changes over the years including longer trial lengths, inclusion of persons with higher baseline illness severity, confounding with benzodiazepine "rescue" medications, longer duration of illness, less qualified symptom raters, as well as changing recruitment strategies (8). It is well known that specific subgroups of individuals (minorities, non-English speaking or literate, low socioeconomic status) are less likely to qualify for or consent to research participation (9). Additionally, the "professional" research participant is a growing phenomenon, mainly in the United States. Perhaps the type of people who participate in clinical trials has changed during recent years? A related question is whether there is a change in the nocebo response rate too. Such questions are of clinical/medical as well as social significance and deserve to be evaluated with systematic meta-analyses.

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References

1. de Craen AJ, Kaptchuk TJ, Tijssen JG, et al.: Placebos and placebo effects in medicine: historical overview. J R Soc Med 1999; 92:511–515 [PubMed: 10692902]
2. Beecher HK: The powerful placebo. Journal of the American Medical Association 1955; 159:1602–1606 [PubMed: 13271123]
3. Hahn RA: The nocebo phenomenon: concept, evidence, and implications for public health. Prev Med 1997; 26:607–611 [PubMed: 9327466]
4. Dodd S, Dean OM, Vian J, et al.: A Review of the Theoretical and Biological Understanding of the Nocebo and Placebo Phenomena. Clin Ther 2017; 39:469–476 [PubMed: 28161116]
5. Doongaji DR, Vahia VN,Bharucha MP: On placebos, placebo responses and placebo responders. (A review of psychological, psychopharmacological and psychophysiological factors). I. Psychological factors. Journal of postgraduate medicine 1978; 24:91–97 [PubMed: 364041]
6. Jeste DV, Blazer D, Casey D, et al.: ACNP White Paper: update on use of antipsychotic drugs in elderly persons with dementia. Neuropsychopharmacology 2008; 33:957–970 [PubMed: 17637610]
7. Hyde AJ, May BH, Xue CC, et al.: Variation in placebo effect sizes in clinical trials of oral interventions for management of the behavioral and psychological symptoms of dementia (BPSD): a systematic review and meta-analysis. American Journal of Geriatric Psychiatry 2017;

8. Walsh BT, Seidman SN, Sysko R, et al.: Placebo response in studies of major depression: variable, substantial, and growing. Jama 2002; 287:1840–1847 [PubMed: 11939870]

9. Schneider LS: Drug development, clinical trials, cultural heterogeneity in Alzheimer disease: the need for pro-active recruitment. Alzheimer disease and associated disorders 2005; 19:279–283 [PubMed: 16327360]