BRAIN. Broad Research in Artificial Intelligence and Neuroscience
e-ISSN: 2067-3957 | p-ISSN: 2068-0473
Covered in: Web of Science (ESCI); EBSCO; JERIH PLUS (hkdir.no); IndexCopernicus; Google Scholar; SHERPA/RoMEO; ArticleReach Direct; WorldCat; CrossRef; Peeref; Bridge of Knowledge (mostwiedzy.pl); abcdindex.com; Editage; Ingenta Connect Publication; OALib; scite.ai; Scholar9; Scientific and Technical Information Portal; FID Move; ADVANCED SCIENCES INDEX (European Science Evaluation Center, neredataltics.org); ivySCI; exaly.com; Journal Selector Tool (letpub.com); Citefactor.org; fatcat!; ZDB catalogue; Catalogue SUDOC (abes.fr); OpenAlex; Wikidata; The ISSN Portal; Socolar; KVK-Volltitel (kit.edu)
2024, Volume 15, Issue 4, pages: 7-10.
Submitted: October 6th, 2024 | *Accepted for publication:* November 9th, 2024

EXPERT COMMENTARY: Communication between Psychiatrists and Patients Regarding Placebo and Nocebo

Michael Davidson
Department of Basic and Clinical Sciences,
Professor of Psychiatry and Chair of Psychiatry,
University of Nicosia Medical School, Nicosia, Cyprus
mdavidson6@gmail.com,
davidson.m@unic.ac.cy
Tel +972 524446520, +357 22 471900

In this insightful commentary, Prof. Dr. Michael Davidson delves into the nuanced dynamics of placebo and nocebo effects in psychiatric treatments, with a focus on communication strategies between psychiatrists and patients. He explores the balance required in presenting the benefits and potential adverse effects of psychotropic drugs while enhancing therapeutic outcomes and minimizing nocebo risks. The commentary highlights the critical role of non-specific factors such as physician communication, patient conditioning, and natural disease progression in amplifying treatment efficacy. Prof. Davidson also underscores the ethical and practical dilemmas faced by psychiatrists in daily practice, such as the fine line between full disclosure and mitigating nocebo effects, especially in conditions like Major Depressive Disorder (MDD), where placebo response can significantly influence outcomes. By examining established and emerging treatments, including SSRIs, ECT, and psychedelics, Prof. Davidson offers a comprehensive perspective on the evolving clinical skills required to manage placebo and nocebo effects effectively, ensuring both adherence to ethical standards and the best possible patient care.

Keywords: *psychotropic drugs; placebo effect; nocebo effect; major depressive disorder (MDD); selective serotonin reuptake inhibitors (SSRIs); ethical disclosure.*

How to cite: Davidson, M. (2024).Communication between psychiatrists and patients regarding placebo and nocebo. *BRAIN. Broad Research in Artificial Intelligence and Neuroscience*, *15*(4), 7-10. https://doi.org/10.70594/brain/15.4/1

The therapeutic response to most psychotropic drugs is the sum of the drug's pharmacologic effects plus circumstantial effects including the placebo effect and the placebo response. Also, many psychotropic drugs produce non-therapeutic, yet perceivable effects which are generally called adverse effects.

The specific pharmacologic effects of psychotropic drugs are not very large as expressed by a small to medium difference between the active drug and placebo called effect size (ES) (Chirita et al., 2012). The ES in most Randomized Controlled Trials (RCT) in psychiatry ranges between 0.2 to 0.6. Therefore, in daily clinical practice, any additional, non-specific circumstances associated with the treatment that can enhance the drug's pharmacologic effects are desirable, as they can benefit the patient. Many of these non-specific effects are grouped under the umbrella of placebo response. Communicating a sense of competence, optimism, and assurances by the prescribing physician, the patient's conditioning by a previous positive experience with the same or a similar drug, and improvements related to regression to the means and to the natural course of the disease, all enhance the effectiveness of the treatment. Prescribing physicians are expected by professional organization ethical codes to present to patients only the benefits supported by scientific evidence as well as all the adverse effects. While in research this is a well define process described in the trial consent form, in daily clinical practice prescribing physicians often face a difficult balancing dilemma between the duty to truth and full disclosure and the patients' therapeutic benefits.

Often, in an attempt to obtain the best therapeutic results, it is tempting to exaggerate the benefits attributed to the psychotropic drug. However, this approach has it is own drawbacks. If the benefits do not materialize as promised and expected, the patient might lose faith in science in general, in the drug in particular, and in the treating team, and may drop out from treatment prematurely.

Like the communication of the benefits, communication of the potential adverse effects of the prescribed drug poses a dilemma. Along with the duty to truly and fully disclose all the potential adverse effects of the drug, the prescriber might consider the risk of the nocebo effects which are true perceived adverse effects not directly caused by the pharmacologic effect of the drug but related to the circumstances of the treatment. Overemphasizing such effects might increase the nocebo effects, and inconvenience the patient who might eventually drop out of treatment.

While all psychiatric disorders and many somatic afflictions respond to placebo, Major Depressive Disorder has one of the largest responses to placebo. It is estimated that placebo response may account for well over 50% of treatment response in RCTs of antidepressants. Much of the placebo response is determined by the treatment setup and the personnel administering the treatment. In a study in which several psychiatrists prescribed different antidepressants, it turned out that the prescribing psychiatrist rather than the specific antidepressant explained most of the variance in the antidepressant therapeutic effect (Mc Kay et al 2006)

Antidepressant SSRIs affecting synaptic catecholamines are the effective, recommended treatment for MDD. However, the placebo response in MDD is high and for some patients, MDD may remit even in the absence of treatment hence in the individuals patient treated in clinical practice it is not possible to distinguish between the pharmacological effect of the drug and the placebo response. Furthermore, for the therapeutic benefits to fully manifest it might take up to 6 weeks, with vegetative symptoms improvements such as sleep, appetite, and slow movements preceding improvement in mood by 1-3 weeks. Therefore, circumstances enhancing the placebo

response might not only speed the relief of suffering but also bridge the gap until the full pharmacological effect of the antidepressant kicks in, so that the patient does not drop out of treatment prematurely.

Likewise, the nocebo effect might affect the treatment of MDD. Anxiety, insomnia, poor appetite, and low sexual desire are widespread manifestations of MDD. Feeling giddiness, difficulties falling asleep, nausea and erectile dysfunction are mild and transient adverse effects during the first days and treatment with SSRIs (Izzat et al, 2021). Overemphasizing such AE might enhance the nocebo effects superimposed on the illness manifestations which are not yet relieved by the treatment and cause patients to drop out of treatment before the treatment benefits have a chance to manifest.

About 1/4 to 1/3 of the patients affected by MDD do not improve at all or only enhance partially with SSRI treatment. In daily clinical practice patients who do not improve under SSRI treatment are treated with an SSRI augmented by an antipsychotic a practice supported by RCT evidence, or treated with Electro Convulsive therapy (ECT) a practice supported only by poor quality evidence. Like most treatments in psychiatry, the pathophysiologic mechanism by which ECT produces the presumed therapeutic effect is not understood. However, it is plausible that ECT produces a considerable placebo response as well as a nocebo response. Although it is conducted under very short general anesthesia it has all the elements of a medical procedure which might enhance the placebo effect. Also, it might induce brief well-perceived amnesia which might further enhance the placebo effect.

Over the last decade, psychedelic drugs with or without psychotherapy have been proposed as a treatment for MDD and the FDA/EMA have recently approved intranasal ketamine as a treatment for MDD. However, because of the very powerful perceived dissociative effect of psychedelics, it is not possible to blind RCT. Attempts to perform remote assessment so that the raters remain blind or to use an active placebo so that the patient is not aware if she got the experimental drug or the control drug, have only partially addressed the issue of functional unblinding. A recent study that administered ketamine to depressed patients under general anesthesia did not separate from placebo (Lii et al., 2024).

Often patients insist on being treated with prescription or over-the-counter medications that are supported by debatable evidence or not supported at all by evidence, such as inositol, folic acid, niacin, omega-3, ago-puncture, and Trans-Magnetic Stimulation. This in turn further complicates the decision of the treating psychiatrist who should not deny the patient the benefit of a placebo yet should not encourage the patient to use treatments not supported by valid evidence.

In summary, the prescribing psychiatrists should keep in mind that the patient approached you to achieve relief from mental anguish and not to get a lecture in neuropharmacology, statistics, and research methodology. Hence, presenting and manipulating the placebo/nocebo aspect of treatment for the benefit of the patients while adhering to the local ethical code is an important and evolving clinical skill.

References

Chirita, R., Sacuiu, I., Burlea, A., & Chirita, V. (2012, June). The role of nitric oxide inhibitors in treatment on symptom severity and cognitive deficits in schizophrenia. In *International Journal of Neuropsychopharmacology* (Vol. 15, p. 113). Cambridge University Press.

Izzat, A. A. H., Anghel, L., Stefanescu, B., Kantor, C., & Ciubara, A. (2021). Prevention of psychoactive substance use. *Archiv Euromedica, 11*(5), 59-61. https://doi.org/10.35630/2199-885X/2021/11/5.16

McKay, K. M., Imel, Z. E., & Wampold, B. E. (2006). Psychiatrist effects in the psychopharmacological treatment of depression. *Journal of affective disorders*, *92*(2-3), 287–290. https://doi.org/10.1016/j.jad.2006.01.020

Lii, T. R., Smith, A. E., Flohr, J. R., Okada, R. L., Nyongesa, C. A., Cianfichi, L. J., Hack, L. M., Schatzberg, A. F., & Heifets, B. D. (2023). Randomized Trial of Ketamine Masked by Surgical Anesthesia in Depressed Patients. *medRxiv : the preprint server for health sciences*, 2023.04.28.23289210. https://doi.org/10.1101/2023.04.28.23289210