Psychiatria Danubina, 2014; Vol. 26, No. 2, pp 92-95 *Editorial*

THE PLACEBO-NOCEBO RESPONSE IN PATIENTS WITH DEPRESSION: DO WE NEED TO RECONSIDER OUR TREATMENT APPROACH AND CLINICAL TRIAL DESIGNS?

Miro Jakovljević

University Hospital Centre Zagreb, Department of Psychiatry, Zagreb, Croatia

* * * * *

Conflicting data and misunderstanding of placebo and nocebo phenomena are essential components of the great scandal related to the treatment of depressive disorders. This scandal has two opposite aspects: glorification and vilification, contradictory estimates about under-prescription and over-prescription of antidepressant drugs. More than twenty years ago, Cassano (1992) cautioned that "depression is one of the great scandals of medicine" because "it is an underdiagnosed and undertreated disorder. Only a small percentage of depression is recognized, appropriately defined and studied. In addition, a limited number of patients receive treatment, and many of those who are treated receive inadequate dosages of antidepressant drugs. Furthermore, despite evidence showing that depression recurs and recommendation advocating the benefits of long-term maintenance treatment to prevent recurrence, only a few patients receive long-term treatment for depression". Recently, Stahl (2013) also cautioned that "the true scandal lies in the treatment of the depressive disorders. A third of patients in a real life never fill their first antidepressant prescription, and for those who do, perhaps less than half get a second month of treatment and maybe less than a quarter get an adequate trial of 3 months or longer". Despite the overall increase in number of depressed people seeking help, only half of them receive any form of treatment, and only about half of these receive adequate treatment (Kessler et al. 2003, Wancata & Friedrich 2011, Yapko 2013).

From the opposite and vilifying view antidepressants reflect one of the major medicalization of living problems in modern society (Ioannidis 2008). Antidepressants are among the most widely prescribed medications all over the world although they are "little more than a deceptive product of greedy, lying pharmaceutical companies that sell hope to the hopeless" (see Yapko 2013). Selective and distorted reporting of RCTs results has been claimed to be a major problem. According to the critics antidepressants are not effective and their side-effects and costs do not justify their use in clinical practice. Antidepressants are depicted as placebos with side-effects. Unfortunately, patients are affected by these attitudes through public media in different harmful ways.

Depression, antidepressants and placebo-nocebo response

Understanding non-pharmacological factors that positively or negatively influence drug treatment response is fundamental. According to the "Dodo bird verdict" in psychotherapy 40 percent of change comes from patients' personal resources, both psychological and environmental, 30 percent from common features of therapists such as empathy, warmth, acceptance, and encouragement of risk taking, 15 percent from patients' trust and expectation, sometimes called placebo, and 15 percent from the therapist's specific techniques and theoretical models (Lewis 2011). Placebo and nocebo reactions are particularly important components of the treatment and clinical research of depression. It seems that is more and more difficult to prove that the efficacy of novel antidepressants and even well established antidepressant is not more than a placebo response to fake treatment. Placebo response in clinical trials has inflated so much over recent time that there is no difference between investigated antidepressants and compared inactive substances in some trials and even antidepressant were less effective than fake treatment in other trials. It's notthatantidepressants don't work, it's that everything works, including antidepressants.

Depression is a disorder that has been proved to be highly responsive to placebo treatments. In antidepressant trials for adults, the placebo rate is 30-50%, compared with a medication response rate of 45-70%, and it has risen at a rate of 7% per decade over the past 30 years (Mora et al. 2011, Rutherford & Roose 2012). Increased placebo response is associated with more study sites, poor rater blinding, multiple active treatment arms, lower probability of receiving placebo, single baseline rating, briefer duration of illness in current episode, more study visits, sample of symptomatic and optimistic/enthusiastic clinicians (Rutherford & Roose 2012). Some authors, on the basis of meta-analyses, claimed that 50 percent of clinical improvement in patients with depression is an effect of placebo, 25 percent is due to pharmacodynamic effects and 25 percent to spontaneous remission (Kirsch et al. 1998, 2008, Benedetti 2011). Some aspects of depression like distress, irritable mood, demoralization, somatization, disease phobia or hypochondriasis, pain, fear,

doubt, anger, death desire and loneliness increase susceptibility to the placebo and nocebo responses.

Nocebo responses are common in clinical trials and practice and can result in discontinuation of trial participation, alteration of treatment schedules and lack of adherence. Recently Mitsikostas et al. (2013) reported "that almost one out of 20 placebo treated patients (4.5%) discontinued treatment due to adverse events (AEs) indicating a significant nocebo response in trials for depression treatment adversely affecting adherence and efficacy of current treatments in clinical practice, with additional implications for trial designing". Furthermore, of 3255 placebo-treated patients from 21 RCTs, almost half (44.7%) reported at least one AE. It is interesting that "the more AEs recorded in the active drug arm the more AEs were observed in the placebo arm" (Mitsikostas et al. 2013). For depressed patients, the prescription of antidepressants may have different meanings and result in feelings of punishment, confirmation of self-blaming beliefs, reinforcement of masochist trends, or ambivalence and resignation regarding the painful feeling of loneliness and isolation, and imply as if the medications could replace the human relationship (Frey et al. 2004). The neurobiological and psychobiological understanding of placebo and nocebo responses in antidepressant trials has important implications on clinical practice (see Jakšić et al. 2013, Eknoyan et al. 2013).

Depression as a nocebo response to stressful life events

Causal factors of depression are linked to adverse life experiences and negative beliefs, views and expectations. As depression may be provoked by negative expectations it can be described in some way as a nocebo response to stressful and important life events. Depressed patients are characteristically engaged in a negative view of themselves, in a negative view of the world and in a negative view of their future. Negativistic, pessimistic and fatalistic thinking may be the cause of nocebo response and essential features of depression. According to the model of learned helplessness and hopelessness repeated exposure to uncontrollable events with faulty learning due to negative attribution style leads to negative affectivity (low mood, loss of pleasure, feelings of guilt, irritability, anxiety), negative cognitions (negative view of the self, the world and the future, indecisiveness, self-devaluation, self-blame, hopelessness), negative motivations (loss of interest, suicidal drive, social withdrawal, and neglect of appearance and hygiene), behavioral changes (agitation, hypoactivity, psychomotor retardation) and vegetative changes (reduced libido, loss of appetite and weight, vague aches and pains). The concept of depression as a nocebo reaction to life events may explain high rates of placebo reaction in patients with depression. Depression is an vicious circle in which pessimistic thinking, negative expectations and negative emotions feed on each other. Placebo response is related to positive expectations which can set in motion a positive cycle, in which positive fluctuations in mood and well-being are interpreted as evidence of treatment effect instilling a sense of hope.

Hypnosis may be thought of as a nondeceptive form of placebo (Kirsch 1994) and hypnotherapy may be very helpful in breaking depressive episode, developing antidepressive pathways and experience, promoting self-confidence, establishing positive expectancy and relapse prevention (Alladin 2007, 2012). Placebo response can be conceptualized as a positive and nocebo response as a negative self-hypnosis (Sliwinski & Elkins 2013, Alladin 2007). Individuals with predisposition to depression not only focus on negative thoughts but also on negative imagery (Alladin 2007).

According to the evolutionary model depression serves the triple purpose: 1. to signal submission to dominant figures in a hierarchy conflict and internally communicate defeat, 2. to signal helplessness and communicate a need for help to potential care givers and 3. to disengage from commitments to futile or dangerous goals (Nesse 2000, Bruene 2008). Viewed from this perspective, depression is expected to respond to interpersonal relationships and caring as well as to placebo psychological treatment. The way in which negative thinking, negative beliefs and negative expectations produce their negative effects in the form of nocebo response and depression, provides some clues as to how they can be reversed by drug treatment and psychotherapy. Non-specific psychological interventions that include discussion of the patient's problem and manipulation of the patient's belief about treatment may also produce a significant effect (McQueen et al. 2013).

Novel study designs for drug testing: How to resolve placebo problem?

With the standard randomized controlled trial design, it seems difficult to estimate the impact of the non-pharmacological treatment response. A crucial question is how pharmacological effects of a drug (true drug response - TDR) can be separated from psychosocial (placebo pattern - PPR) responses (Sonawalla & Rosenbaum 2002). There is a need for more creative designs capable of disentangling the nonspecific treatment response including both placebo and nocebo reactions.

Kirsch & Weixel (1988) proposed the "balanced placebo design" (BPD). Subjects receive either drug or placebo, and half of each group is receiving false information about treatment. Thus, the group that is receiving the active medication but believes to receive inactive substance serves to estimate 'true' drug effect. The group that is receiving false (inactive) medication but believes to be receiving real (active) medication, serves to estimate psychological, placebo and nocebo response.

Enck et al. (2011) proposed a number of alternative trial designs including the 'balanced cross-over design' (BCD) and the 'delayed response design (DRD). In the BCD subjects are divided into four groups, and all are told they are participating in a conventional randomized double-blinded and placebo-controlled cross-over trial, in which they will receive both the drug and the placebo at two different occasions in a randomized and double-blinded order. Group 1 will receive the active drug twice, group 2 will receive false drug (inactive substance) twice, group 3 will receive the real drug first and the false drug at the second occasion, and group 4 will receive first the false drug and then the real drug.

Some authors have proposed only CER (comparative effectiveness research) trials without placebo arm in which novel compounds are compared to approved drugs or standard therapy. According to Enck et al. (2013) two variants of a good study design are appropriate: one involves testing novel drug during Phase II and III with minimizing the placebo-response and optimizing drug-placebo differences, and the second involves testing approved drugs during Phase IV under routine clinical practice with maximizing placebo response.

Minimizing or maximizing placebo responses in clinical trials?

Minimizing placebo responses and/or optimizing drug effect-placebo response differences are scientific, ethical and regulatory requirements when testing new drugs (Enck et al. 2013). Placebo response in depression is usually regarded as a bane of research and a nuisance to be eliminated or minimized. Technical, impersonal or neutral clinician-patient relationship is commonly recommended for minimizing placebo response in RCTs, which is in contradiction with the efficacy paradox phenomenon (Walach 2001). However, the opposite strategy could be more fruitful. According to the concept of depression as a nocebo response to stressful life, placebo response, instead of being minimized, should be maximized in order to optimize patients' response to both real and fake medication. This could be provided by creating an optimal treatment context (see Jakovljević 2013), "pleasing the patients", paying them appropriate sum of money for participation in RCT and inducing alliance effect with narrative and relational concordance (see also Verhulst et al. 2013), activating natural healing processes, creating rapport with feelings of mutual respect, trust, confidence and hope in order to establish and maintain positive therapeutic physician-patient relationship (see Jakovljević 2013), recontextualizing patients' reality and improving their satisfaction, teaching them an optimistic explanatory style through the ABCDE model (Seligman 2006). However, the medical profession in general including psychiatry in particular tends to resist the idea of deliberately maximizing placebo response and medical program that specifically attempts to teach this are missing or very scarce (Verhulst et al. 2013). Creative psychopharmacotherapy is a conceptual framework that integrates placebo healing into clinical practice. It is placebo-response maximizing and nocebo-response minimizing practice (Jakovljević 2013). There have been some interesting proposals for preventing the nocebo impact in RCTs. Informed consents for the tested drugs might be modified to reduce possible fear or anxiety induction, the likely nocebo response should be carefully discussed with the participants, investigators should be blind to the analysis of the recorded AEs (Mitsikostas et al. 2013). Personalized approach with placebo-response maximizing and nocebo-response minimizing practice could help to increase scientific insights into depression and its treatment.

Conclusion

Nocebo and placebo phenomena in the treatment of depression deserve a new approach in the context of clinical trial design as well as in everyday clinical practice. Placebo response is associated with positive modulators and nocebo response with negative modulators of treatment outcome. Therapeutic clinician-patient relationship stimulates placebo responses and prevent nocebo reactions, while anti-therapeutic relationship stimulates nocebo responses and prevent placebo reactions. A challenge in antidepressant clinical trials is to differentiate true drug response from placebo pattern response so many strategies are suggested to lower placebo reactions. Personalized placebo-maximizing and nocebo-minimizing strategy could help to increase transdisciplinary scientific insights into depression and its treatment.

Acknowledgements: None.

Conflict of interest: None to declare.

References

1. *Alladin A: Handbook of Cognitive Hypnotherapy for Depression – An Evidence-Based Approach. Walter Kluwer/ Lippincott Williams & Wilkins, 2007.*
2. *Alladin A: Cognitive hypnotherapy for major depressive disorder. American Journal of Clinical Hypnosis 2012; 54:275-293.*
3. *Benedetti F, Carlino E & Pollo A: How placebo changes the patient's brain. Neuropsychopharmacology 2011; 36:339-354.*
4. *Bruene M: Textbook of Evolutionary Psychiatry – The Origins of Psychopathology. Oxford University Press, 2008.*
5. *Cassano GB: Introduction at a Symposim: The Serotonin Reuptake Inhibitors: Are They Changing Clinical Practice? International Clinical Psychopharmacology 1992; 7(suppl 2):3.*
6. *Eknoyan D, Hurley RA & Taber KH: The neutobiology of placebo and nocebo: How expectations influence treatment*

outcomes. The Journal of Neuropsychiatry and Clinical Neurosciences 2013; 25:vi-254. doi:10.1176/ašši.neuropsych.13090207

7. *Enck P, Klosterhalfen S, Weimer K, Horing B & Zipfel S: The placebo response in clinical trials: more questions than answers. Phil. Trans. R. Soc. B 2011; 366:1889-1895. doi:10.1098/rstb.2010.0384*
8. *Enck P, Bingel U, Schedlowski M & Rief W: The placebo response in medicine: minimize, maximize or personalize? Nature Reviews/Drug Discovery 2013; 12:191-204.*
9. *Ioannidis JPA: Effectivenes of antidepressants: an evidence myth constructed from a thousand randomized trials? Philosophy, Ethics, and Humanities in Medicine 2008; 3:14 doi:10.1186/1747-5341-3-14*
10. *Jakovljević M: How to increase treatment effectiveness and efficiency in psychiatry: Creative psychopharmacotherapy – Part 1: Definition, fundamental principles and higher effectiveness polipharmacy. Psychiatr Danub 2013; 25:269-273.*
11. *Jakovljević M: How to increase treatment effectiveness and efficiency in psychiatry: Creative psychopharmacotherapy – Part 2: Creating favorable treatment context and fostering patients' creativity. Psychiatr Danub 2013; 25:274-279.*
12. *Jakovljević M: The placebo-nocebo response: Controversies and challenges from clinical and research perspective. European Neuropsychopharmacology 2014; 24:333-341.*
13. *Jakšić N, Aukst-Margetić B & Jakovljević M: Does personality play a relevant role in the placebo effect? Psychiatr Danub 2013; 25:17-23.*
14. *Kessler R, Berglund P, Demler D, et al: The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). Journal of the American Medical association 2003; 289:3095-3105.*
15. *Kirsch I: Clinical hypnosis as a nondeceptive placebo: Empirically derived techniques. American Journal of Clinical Hypnosis 1994; 37:95-106.*
16. *McQueen D, Cohen S, St John-Smith P & Rampes H: Rethinking placebo in psychiatry: how and why placebo effects occur. Advances in Psychiatric Treatment 2013; 19:171-180.*
17. *Mitsikostas DS, Mantonakis L & Chalarakis N: Nocebo in clinical trials for depression: A meta-analysis. Psychiatry Research 2014; 215:82-86.*
18. *Lewis B: Narrative Psychiatry – HowS tories Can Shape Clinical Practice. The Johns Hopkins University Press, Baltimore, 2011.*
19. *Mora MS, Nestorius Y & Rief W: Lessons learned from placebo groups in antidepressant trials. Phil. Trans. R. Soc. B 2011; 366:1879-1888. doi:10.1098/rstb.2010.0394*
20. *Rutherford BR & Roose SP: A model of placebo response in antidepressant clinical trials. Am J Psychiatry 2012; ajp.psychiatryonline.org*
21. *Seligman MEP: Learned Optimism: How to Change Your Mind and Your Life. Vintage Books, New York, NY, 2006.*
22. *Sliwinski J & Elkins GR: Enhancing placebo effects: Insights from social psychology. American Journal of Clinical Hypnosis 2913; 55:236-248.*
23. *Sonawalla SB & Rosenbaum JF: Placebo response in depression. Dialogues in Clinical Neuroscience 2002; 4:105-113.*
24. *Stahl SM: Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Fourth Edition. Cambridge University Press, 2013.*
25. *Verhulst J, Kramer D, Swann AC, Hale-Richlen B & Beahrs J: The medical alliance – From placebo response to alliance effect. The Journal of Nervous and Mental Disease 2013; 201:546-552.*
26. *Walach H: The efficacy paradox in randomized controlled trials of CAM and elsewhere: beware of placebo trap. Journal of Alternative and Complementary Medicine 2001; 7:213-218.*
27. *Wancata J & Friedrich F: Depression: a diagnosis aptly used? Psychiatr Danub 2011; 23:406-411.*
28. *Yapko M: Treating depression with antidepressants: Drug-placebo efficacy debates limit broader consideration. American Journal of Clinical Hypnosis 2013; 55:272-290.*

Correspondence:

Professor Miro Jakovljević, MD, PhD
University Hospital Centre Zagreb, Department of Psychiatry
Kišpatićeva 12, 10000 Zagreb, Croatia
E-mail: psychiatry@kbc-zagreb.hr