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PLACEBO AND NOCEBO EFFECT: A MINI-REVIEW

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SUMMARY

It is well-known that placebo is a substance without medical effects, which benefits the health status because of the patient's belief that the substance is effective and that the nocebo is defined as a substance without medical effects but which worsenes the health status of the person taking it by the negative beliefs and expectations of the patient. Starting with the history of the placebo effect and giving a review of the most significant studies reporting about the placebo effect from 1939-2013 it was our intention to give the all-around look on this phenomena discussing the neurobiological and other theories of its origin and concentrating especially on the field of psychiatry and finally coming to conclusions regarding the conductance of clinical trials and ethics. Regarding psychiatry, the placebo effect has a substantial role in most of psychiatric conditions including depression, anxiety, addictions, and contrary to what may have been expected, schizophrenia. Likewise, the nocebo effect is not to be neglected as the studies are being conducted to identify the factors causing it so it could be prevented.

Key words: *placebo effect - nocebo effect – schizophrenia - history of medicine*

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Introduction

According to definition, placebo is a substance without medical effects, which benefits the health status because of the patient's belief that the substance is effective. In scientific studies placebo is defined as a substance without medical effects taken by control group of patients in the study, in order to eliminate effects of the process of taking substance (Wolman 1989).

On the other side, nocebo is defined as a substance without medical effects but which worsenes the health status of the person taking it by the negative beliefs and expectations of the patient (Colloca & Miller 2011).

The term has it roots in the latin word placebo, placere, which means „I will please“, or „I will do good“, and nocebo, nocere, which means „I will harm“. The concept of placebo and nocebo is in many cases linked to a number of myths and misapprehensions of which the most popular are the ones saying that placebo is helpful only in psychogenic disorders, that it is “a treatment for neurotic patients when the clinician has nothing better to offer” and that placebo is a catch-all for non-pharmacological effects in RCTs, a device for eliminating bias in trials and establishing the ‘true’ biochemical effect of drug treatments (Jopling 2008).

History and well known studies of placebo effects

Some historians think that the history of medicine is in a good part history of placebo, but it is not only a conundrum, it is a big puzzle wrapped into the great mystery of human body, brain and mind relationships (Jubb & Bensing 2013, Jakovljevic 2014). We must remember different official therapies in history of mainstream medicine such as release of the blood, putting arsen on the wounds or using the snake oil. It is considered that many patients got well on these therapies and that it was actually placebo effect (Lipton 2007), but the history of placebo is tied to the name of the medical doctor from New England Elisha Perkins (1741-1799) who claimed that many diseases can be healed by touching the body with metal sticks, later called Perkins' sticks. Healing effects of his sticks Perkins described as their magnetic effects. He belived in the healing effects of his sticks and went to New York in the time of the yellow fever epidemic where he got ill and died. Other medical doctor, John Haygarth made an experiment with Perkins' sticks painting the wooden sticks and making them look like metal sticks and then treated the patients with rheumatic disorders. He observed that the same patients gained equal benefit whether treated with metal or wooden sticks. That was the first experiment in history which showed the power of the placebo effect (Jacobs 2000).

In the 18th century placebo was used in medicine as a substance without therapeutic value, but in the 19th century placebo was treated as a medication, more as a manner of pleasing the patient than treating him.

It was long considered that there is no place for placebo in surgery. But in 1939 Italian surgeon Davide Fieschi tried a new technique for treatment of patients with angina pectoris. He considered that higher blood flow in the hearth would lower the pain in patients with angina pectoris so he made short cuts on the chest and suspended two inner chest arteries. There was improvement in three quarters of patients and one quarter was considered cured. In the year 1959 L. Cobb tested this procedure in the way that one group of patients was treated in the Fiesci technique and other

group of patients was just cut with short cuts on the chest imitating real procedure. There was no difference in the final result in these two groups (Cobb et al. 1959).

Similar study was conducted by B. Moseley who wanted to assess which part of the operation that he conducted on arthtritic knees was the most helpful for the patients. He divided patients in three groups. In the first group he peeled off the damaged cartilage, in the second group he washed the knee and in that way removed the possible causes of the inflammation and in the third group he made a „false operation". All patients had the same postoperative treatment. Results showed that there was no difference in the therapeutic success of the groups. Although the first surgical study was done in 1959 and Moseley's in 2002 and published in the New England Journal of Medicine (Moseley et al. 2002), from today's point of view there were lots of ethical resents in both of these studies.

The example of an unethical study is the study conducted by the American Public Health Association in 1932 when they recruited 399 young Afro Americans to test what happens if sifilis is not treated. Study was conducted continuosly and without change in the construct of the study until 1972 although there was an effective treatment with penicilin from 1940's. American president Bill Clinton apologized to the participants of the study as well as their families in 1997.

Importance of ethical issues was also shown in the Suede study conducted in the late 1990's with the aim to explore effectivenes of the pacemaker. In one group of patients pacemaker was implanted and turned on, while in the other group of patients pacemaker was implanted but not turned on. It is interesting that there were improvements in the group with turned off pacemakers but it is also interesting that this study didn't stimulate any ethical dilemmas (Linde et al. 1999).

The importance of the „right diagnosis" and the placebo effect in that context was shown in the study conducted by Thomas in 1987 with 200 participans who had undefined health problems. They were divided in two groups, first group was told by their doctor that he is not certain what is wrong with them, and the other group was told the real diagnosis with the strong positive attitude that they will get well after the treatment. Both groups had the same therapeutic procedures. After 2 weeks 39% of the participants in the first group got well and in the other group the percentage of the participants who got well was 64% (Thomas 1987).

Moerman meta-analysis included 117 studies about the treatment of the ulcus disease and showed the losing of faith in the medication. Results of the study showed that cimetidin was a new drug in the 1975, and it showed positive results in 80% of the patients, and as time passed the results have fallen to 50%. Similar results repeated later with ranitidin. Results of these meta-analysis showed that placebo effects are higher if patients take three instead of two tablets (Moerman 1981).

Possible action mechanisms of placebo and nocebo

Action mechanism of placebo has not yet been explained despite of its long-term presence in medicine. Etiologically there are several possible mechanisms of placebo effect: the expectation model, the reflex/Pavlovian conditioning and the opioid model as the three that are best-known (Moerman 1981). From the group of psychological explanations there are also positive or negative thinking, autosuggestion, self-deception or self-fulfilling prophecy, optimism- and pessimism-related personality traits, interpersonal expectation effects and unique interpersonal dynamics (therapeutic, neutral or anti-therapeutic doctor-patient relationship), pharmacophylic and pharmacophobic personality traits while neurobiological explanations also include salutogenesis- or pathogenesis-related mind-body mechanisms activation, reward-punishment system activation (dopamine-mediated pathways are involved in reward, motivation and expectancy of reward), sensitization or habituation mechanisms (placebo analgesia and nocebo hyperalgesia are mediated by cholecystokinin and nitrous oxide), trustworthiness or untrustworthiness activation (the higher the amigdala activity, the more untrustworthiness; oxitocyn increases trust and placebo response by binding to its receptors in amigdala), self-regulation and self-stabilization vs. self-defeating thoughts and mechanisms, personal mastery and hope, learned helplessness and hopelessness, related to serotonergic and noradrenergic mechanisms, self-healing energy or process (vismedicatrix nature – the tendency of nature to heal), immune and hormonal responses are associated with placebo and nocebo reactions, genetic predisposition to placebo or nocebo response (different genetic polimorphisms affect placebo vs. nocebo responding) and unidentified parallel interventions (Jopling 2008, Jubb & Bensing 2013, Bootzin & Bailey 2005, Enck et al. 2013, Murray & Stoessl 2013, Benedetti 2013).

Expectation model explains how thoughts and beliefs can have strong influence on the health state and on the neurochemical reactions in the body and can lead to hormonal and immunological response of the patient, what seems to be the placebo reaction but is actually a true therapeutic response. On the other side, negative beliefs and expectations can lead to worsening of the health state or the nocebo effect (Moerman 1981, Guess et al. 2002, Manchikanti et al. 2011). The main role in this phenomena has our „belief system", an important part of our mental model and of our healing process, including feeling sick, seeking relief, meeting the therapist and receiving the therapy (Jopling 2008, Benedetti 2013).

Reflex conditioning explains the placebo effect as a learned response to medical intervention by the principals of Pavlov's conditioned reflex. Experience of an earlier improvement acts as a conditioned stimulus originated by the previous positive experience with a doctor or medication.

Although these two models were at first seen as conforonted, the predominant opinion today is that they coexist and have complementary roles in the occurrence of the placebo response. In the case of placebo analgesia studies suggest that this answer is modulated primarily by the expectation model, but it can include conditioning model which represents the integration of previous experience (Moerman 1981, Guess et al. 2002, Manchikanti et al. 2011). Gender is a proven predictor of the placebo response and also exerts some influence on the nocebo response, in one conducted study on the aggravation of symptoms of nausea, women were more susceptible to conditioning and men to generated expectations (Hauser et al. 2012). There are also evidence that suggest that behavior can be triggered by stimuli presented outside of conscious awareness what was shown in the study where significant placebo and nocebo effects were found in both first group (using clearly visible stimuli) and second group (using nonconscious stimuli), indicating that the mechanisms responsible for placebo and nocebo effects can operate without conscious awareness of the triggering cues (Jensen et al. 2012).

According to the opioid model, the endorphins are released as a response to the placebo stimulus and have an important role in the placebo response. Proofs of this model are the changes in the brain activity in opioid-rich brain areas when applicating the placebo, the similar brain answers to placebo and to the active substance and the direct opioid releasing proven with sensitive molecular imaging technics (Finniss & Benedetti 2007, Amanzio & Benedetti 1999).

The opioid model is also tested in the placebo induced analgesia. Neurobiological studies have shown that placebo analgesia, achieved with expectation mechanisms and conditioning can be unmade with application of the opioid antagonist naloxon what proves the participation of the opioid system in psychological mechanisms of expectation and conditioning (Price 1999).

While the placebo effect is probably partially conditioned with the opioid system, nocebo effect is an opposite phenomenon and according to some studies could be modulated by cholecystokinine (CCK). There are evidence that CCK induces nocebo hyperalgesia transforming anxiety into pain. Nocebo effects by the negative expectations model induce and mobilise the hypothalamic-pituitary-adrenal axis (HPA axis) which increases the plasma concentrations of the adrenocorticotropic hormone (ACTH) and cortisol. Nocebo hyperalgesia and higher activity of HPA axis can be antagonised with diazepam what also indicates that anxiety has a big role in these processes. Further studies showed that for the treatment of pain better results are achieved when the patient is completely aware of the administration of the medication compared to applying the pain medication without the patient's awareness. This proves that total effectiveness of the applied medication is achieved combining its pharmacological effect with the psychosocial context of the treatment (Finniss & Benedetti 2007, Bausell et al. 2005).

Other considered explanations of the placebo and nocebo mechanisms are the spontaneous recovery, fluctuation of symptoms, improvement with other parallel therapies, the mistakes in measurement of subjective effects and finally the wish of the patients to please their therapist by saying they are better while they are not. It is also important to consider the wishes and motivation of the therapist to achieve „improvement“ of the health status of the subject and in that way his objectivity in the assessement of his subject's health status (Lipton 2007). The doctor-patient relationship can be therapeutic, anti-therapeutic and neutral and this physician as a placebo or nocebo inductor phenomena is quite controversial and interesting. There are well-known sayings and metaphors such as „homo homini medicamentum est“, „the doctor as the drug“ and „the doctor as a walking placebo“, but we must not neglect the opposite, toxic effect as well (Jubb & Bensing 2013).

In everyday clinical practice we should be aware that nocebo can be equally strong as placebo. With their attitude and especially verbally doctors can send a message to their patients which lowers their hope for improvement. Patients sometimes demand their doctors to tell them „how long are they going to live“ after getting a serious diagnosis. The potential power of the statement „you have six months to live“ is well-known. In his book „Biology of belief“ B. Lipton describes the case of Clifton Meador, a doctor from Nashville who in 1974 had a patient Sam Londe with an esophageal carcinoma, illness then considered fatal. Londe was under treatment, but everyone in the medical community „knew“ that the cancer will be back and suggested so to the patient. Big surprise came after Londe died when authopsy discovered very small cancer in his body, certainly not big enough to kill him. There was no trace of esophagus cancer for which everyone thought it was fatal. The question is what was the cause of death of mr.Londe if it was not the cancer? Did he die because he believed he will die? Years afer that his doctor wondered if he has ruined his patient's hope? Lipton says that „disturbing cases of nocebo worn us that doctors, parents, teachers, etc. can destroye one's hope by programming the person to believe in it's helplessness“ (Lipton 2007).

Modern psychiatry and medicine in general tend to disregard the idea of deliberately maximizing the placebo response linking it with prescientific medicine and with unethical and deceitful practices. There is a lack of conceptual frameworks that integrate placebo healing into standard clinical practice as well as medical education programs that specifically teach this (Jakovljevic 2014, Verhulst et al. 2013). It has been well known from ancient times that drugs without therapeutic rituals are less effective and new concepts from the recent insights into physiology of placebos

and pathophyisiology of nocebos are emerging, like creating placebo responders in the laboratory. However, placebo must not become a justification for bizarre therapies, quackery and malpractice. Conceptual framework of creative psychopharmacotherapy involves personalization and maximization of the placebo response and minimization of the nocebo response in order to increase treatment effectiveness and treatment efficiency (Jakovljevic 2014, 2013a, 2013b, Benedetti 2013).

Treatment outcome depends on a complex interaction of the four groups of factors: 1. pharmacodynamic and pharmacokinetic factors via impact on disease mechanisms; 2. vulnerability factors which enhance the likelihood of disease/illness relapse or recurrence; 3. resilience and protective factors that enhance the likelihood of recovery from the mental disorder; 4. generative or creativity factors which increase reveletary learning, resource acquisition and development accentuating personal growth. Placebo or nocebo responses can be triggered by many various interrelated factors associated with vulnerability, resilience and potentials for personal growth (Jakovljevic 2014, Enck et al. 2013).

Besides, it is well-known that a depressive and anxious person reacts worse to the treatment than a person in a better mood and that psychically labile persons feel the side-effects of the medications more often. Furthermore, traits such as neuroticism, pessimism and type A personalities may predispose individuals to the nocebo effect phenomenon. (Data-Franco & Berk 2013, Liccardi et al. 2004). Information about the difficulties which may occur during the treatment can make a person more prone to develop that difficulties, what was shown in the study about the side-effects of the aspirine conducted in three American clinics. In the first two clinics the researchers warned the participants about the possible gastrointestinal side-effects caused by the aspirine, and in the third clinic there was no such warning. Among the participants warned about the possibility of such side-effects, there was three times more of those with side-effects compared to the third group that didn't get such unfavourable information which obviously stressed participants and made the first two groups inducible for such side-effects. Similar study which confirms the egzistence of nocebo is a study from the early 80's in which 34 students participated in the experiment in which they were told that low electricity will be released through their head which will cause them a mild headache. Although they didn't get any electricity at all, 67 of them got a headache (Podnar 2009). Recent meta-analyses show a considerable prevalence, ranging from 18% in the symptomatic treatment of migraine, to more than 74% in multiple sclerosis (Data-Franco & Berk 2013). Genetic predisposition to placebo response has been demonstrated only for depression and social anxiety by now and such a predisposition to nocebo response has so far not been shown (Hauser et al. 2012). In the placebo or nocebo response mystery equation we should not neglect personal life stories, background, culture, patient's life script and relationships between clinicians and their patients (Jakovljevic 2014, Mommaerts & Devroe 2012, McQueen et al. 2013).

Placebo and psychiatric disorders

Psychiatry is a field where placebo effects have been researched the most, especially in treating depression. In some studies placebo effect was so emphasized that this formed the opinions that it should be used independently in the treatment of depressive patients with mild and moderate depression, Kirsch (2002) consideres that 80% of the depression treatment effectiveness should be encountered to placebo. Author of that study even had to citate the Law of the freedom of informing to bring out the informations about clinical studies of the common antidepressants because the FDA didn't want to publish the results of his studies (Kirsch & Moore 2002, Leuchter et al. 2002, Hrobjartsson & Goetzsche 2004). Some think that the amount and the effect of the commercials for antidepressants is in proportion with the effects of these medications. It is interesting that in years as the efficacy of antidepressants grew so did the reaction to the placebo which is explained with higher expectations and faith in new medications appearing in the market. Nevertheless, studies have shown that the effects of the placebo are manifested earlier in the treatment of the depression, before the effects of the antidepressants and have a tendention for quicker interuption and are poorly maintained through a longer period of time (Quitkin et al. 1991). On the other side, frequent absence of a therapeutic response to the psychopharmacs can be connected to the prejudices towards the psychiatric disorders as something abstract and unmaterial on which the medications can not influence. Neuroimaging studies comparing the effect of antidepressants and placebos by means of PET revealed that both placebo and fluoxetine treatment induced regional metabolic increases in the prefrontal and posterior cingulate, and metabolic decreases in the subgenual and thalamus (Kato 2013). Other studies have reported a significant role of nucleus accumbens following the placebo administration in depression, Parkinson's disease and pain (Fuente Fernandez et al. 2001, Mayberg et al. 2002, Scott et al. 2007). A very interesting conclusion was made about the prefrontal cortex, which we know is related to many functions such as expectation generation, cognitive appraisal, memory retrieval and emotional modulation, when there has been shown that the loss of prefrontal control is associated with a loss of placebo response (Benedetti 2013).

Psychopharmacotherapy is a context dependent practice because different treatment contexts may affect the meaning of biological variables in different ways. Patients are not just neurobiological objects who respond only neurochemically to medications, but also

subjects who respond to the meaning that prescribed medications have for them and their psychiatrists (Jakovljevic 2014, Mintz 2005).

When it comes to psychiatric disorders like addiction the role of placebo is quite obvious. Various studies have reported that expecting a drug of abuse makes it more pleasurable, resulting from a complex interaction between pharmacological effects, psychological factors and conditioned responses (Volkow et al. 2003, 2006, Duvauchelle et al. 2000). In alcohol abuse, contrary to what should be expected there is no definitive role for placebo and placebo-related effects (Testa et al. 2006) but when it comes to tobacco smoking and nicotine intake there are studies that suggest that the placebo and expectation effects have a crucial role although there has been suprisingly little research performed in this field (Dar et al. 2005, Perkins et al. 2004, Juliano & Brandon 2002).

If there is a mental disorder in which there shouldn't be expectations of a placebo effect, it is schizophrenia. Other psychiatric disorders include cognition, beliefs, expectations, feelings in greater amount – all of them can be improved when the patient believes in the therapeutic procedure. Schizophrenia is different from those disorders, it is characterised with reality distorsion, damaged thought processes, unability to differ outside world from the inner thoughts, and often accompanied with bizarre sensory phenomenon which can appear just from aberrant kindling of schizophrenic neurons. The question is, how can these symptoms which obviously originate from disturbed neurochemistry and neurobiology answer to a placebo? Regardless of causes, it happens. Not only does the placebo effect exist in the teratment of the patients with schizophrenia, but there is also an increase in the placebo effects in the last twenty years (Kinon et al. 2011). In some studies the placebo response in schizophrenia is growing up to 30%. One study was conducted in order to identify potential contributors to placebo response in randomized controlled trials of antipsychotic treatment in schizophrenia and the results were that younger age, shorter duration of illness, greater baseline symptom severity, and shorter trial duration were significantly associated with greater placebo response (Agid et al. 2013).

There are even some opinions that the placebo effect has a role in electroconvulsive therapy (ECT) and that the ECT may work by harnessing placebo effects and thereby is even more controversial because it has serious side effects and provides results marginally better than administrating placebo (Blease 2013).

Placebo and nocebo in the investigations

In investigations of the new medications the aim is to show that the experimental medication is more effective than the placebo. During the last few years, in addition to the high placebo response, there are attempts of identifying the factors that are increasing the placebo response. The increased placebo response over the years is partly explained by unidentified parallel interventions, patient factors, issues with trial designs, and regional variability or demographic differences (Pilla Reddy et al. 2013). There are reports that exploration and better understanding of placebo-related personality would facilitate the use of placebo in clinical practice and improve the methodology of clinical trials (Jaksic et al. 2013). Special strategies are developed to predict the placebo responders before entering the study in order to eliminate more expressive placebo effects and covering possible differences between the experimental medication and the placebo. For this purpose the careful application of diagnostic rating scales is recommended to prevent the inclusion of the false positive diagnosed patients in the studies. It is interesting that there are studies that introduced the "efficacy paradox" which means that placebo treatments can have larger effects than "evidence-based treatments" (McQueen et al. 2013). This phenomenon has become a problem in for example clinical trials for discovering new antidepressant medications, placebo response in these trials is substantial and has been increasing. High placebo response rates hamper efforts to detect signals of efficacy for new medications, contributing to trial failures and delaying the delivery of new treatments to market. It is associated with more study sites, poor rater blinding, multiple active treatment arms, lower probability of receiving inactive control, single baseline rating, shorter duration of symptoms in current episode, more study visits and optimistic and enthusiastic clinicians (Rutherford & Roose 2013). The solution is to minimize the placebo response in clinical trials and maximize it in clinical practice (Rutherford & Roose 2013, Waber et al. 2008). The desired goal should be just the opposite to those proclaimed in clinical trials (Enck et al. 2013). This is why the placebo effect is the source of disagreement between three discrete perspectives: the clinical trial researcher, the placebo researcher and the clinician (Huculak 2013). Also there are opinions that placebo is an ambiguous, redundant term and that the so-called placebo effect conceals far more interesting effects that are attributed to the patient's expectation and that this term should be abandoned focusing instead on a deeper understanding of the expectation variable, including its causes, effects, and effect modifiers (Shahar & Shahar 2013).

Nocebo on the other hand may affect the trials in a different way, two recent systemic meta-analyses searched for nocebo in trials for prevention of migraine and tension-type headache and revealed that 1 out of 20 patients treated with placebo withdraw treatment due to adverse effects, as that were the adverse effects expected from the active medication it confirmed that pretrial suggestions induce the adverse events in placebo-treated patients and the conclusion was that nocebo reduces the study population by 10% and limits the treatment outcomes in randomized controlled trials for primary headache (Mitsikostas 2012, Weissenfeld et al. 2010).

Placebo controlled studies are demanded at least in initial phases of determining efficacy and safety of the new medication and its superiority compared to placebo, placebo controlled double blind studies represent the golden standard in clinical investigations. Lately, these kind of studies were criticised more because of ethical than methodological issues. The proposition is that studies are conducted with two active substances so that the control group receives the actual therapy as well. On the other side, sometimes there is more danger in conducting a study with a bad experimental medication than with a placebo. If the experiment with two active substanes is conducted, there are no ethical dilemmas if there is an honest wish to determine which drug is more efficacious. Critics think that it is unethical to give placebo when there exists approved medication, even in a case of a clean informed consent because of the threatening of the principles of well being – patient is asked to sacrifice for the well being of others. In the Declaration of Helsinki it is written that in every study all patients should be ensured with the best diagnostic and therapeutic method. New directions are pointing out the usage of placebo in studies – if there is an efficacious treatment for any state, the usage of the placebo group of medication is unethical. It is considered that the future of placebo in studies is uncertain – placebo will be allowed in little number of studies, most of the researches will be conducted with active medications. It will be especially taken into account that placebo is not used in more severe medical conditions for which there is an efficacious treatment. For now, these points of view are also divided – one think that in the future it is important to use placebo in studies of medication with vital importance, while the other think that with development of medical science the creation of the studies with placebo will be less important. From the ethical point of view, problems can occur not just in studies but also in placebo-using therapy. In both cases the well being and the autonomy of the patient can be damaged. Basic duty of every clinican is still to act in order with the best interests of the patient and to have in mind in every moment that the therapeutic role of a medical doctor is more important than the role of the researcher (Rich 2003, Benedetti 2009, De Roy 2004, Macklin 2009).

Conclusions

Placebo and nocebo are the phenomena recognised through all of the history of medicine, but not earlier than the 19th century, when placebo got the meaning of the medication, more attention was paid to placebo as a therapeutic option.

Examples of the placebo effects can be found in every field of medicine. Mechanism of action of this phenomenon is yet unknown although researches focused on the expectation model, the model of conditioned reflexes and the opioid model which are probably complementary. Lots of researches in this field show that thoughts and beliefs can have important influence on the human neurobiology and create therapeutic process in that way. It is important to continuously develop consciousness, especially through educational processes during the medical education, about the importance of placebo and nocebo phenomenon and then in clinical practise to keep in mind not to send messages that lower the patient's hope.

Psychiatry is the field of medicine where placebo and nocebo effects are mostly expressed and in concordance with that researched the most, especially in the treatment of depression, although placebo effect is impressive even in some studies on patients with schizophrenia.

Today, placebo controlled studies of new medications are a question of ethical dilemmas so in the future the application of new medications compared to placebo may probably be limited only on initial phases of the study.

> *Henry Ford: „Whether you belive that you can or can not do something.... you are right“*

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