Coll. Antropol. **35** (2011) Suppl. 2: 319–323
Review

Placebo in the Treatment of Pain

Renata Dobrila-Dintinjana[1] and Antica Načinović-Duletić[2]

[1] Clinic for Radiotherapy and Oncology, Rijeka University Hospital, Rijeka, Croatia
[2] Department of Hematology and Clinical Immunology, Rijeka University Hospital Center, Rijeka, Croatia

A B S T R A C T

Placebo is the use of the substance or procedure without specific activity for the condition that is trying to be healed. In medicine, benefits of placebo effect are used since 1985 and 1978 placebo effect was first scientifically confirmed. It was found that placebo induced analgesia depends on the release of endogenous opiates in the brain and that the placebo effect can be undone using the opiates antagonist naloxone. Functional magnetic resonance imaging of the brain showed that placebo analgesia was obtained regarding the activation and increased functional relationship between ant. cingulate, prefrontal, orbitofrontal, and insular cortex, nucleus accumlens, amygdala, periaqueduktalne gray matter and spinal cord. Placebo also facilitates descending inhibition of nociceptive reflexes through periacvaeductal gray substance. Placebo effect can be achieved in several ways: by using pharmacological preparations or simulation of operating or other procedures. This phenomenon is associated with perception and expectation of the patient. To achieve the effect of placebo it is essential degree of the suggestions of the person who prescribe a placebo, and the degree of belief of the person receiving the placebo. Expected effect of placebo is to achieve the same effect as the right remedy. Achieved placebo effect depends on the way of presentation. If a substance is presented as harmful, it may cause harmful effects, called »nocebo« effect. Placebo effect is not equal in all patients, same as the real effect of the drug is not always equal in all patients. Application of placebo in terms of analgesia will cause a positive response in 35% of patients. Almost the same percentage (36%) of patients will respond to treatment with morphine in medium doses (6–8 mg). Therefore, one should remember that response to placebo does not mean that a person simulates the pain and then it is unethical to withhold the correct treatment especially in light of findings that the prefrontal cortex is activated expecting liberation of pain and how this action reduce activities in brain regions responsible for sensation of pain (thalamus, somatosensory cortex and other parts of the cortex). However, the use of placebos is ethically, legally and morally very dubious. The basis for the placebo effect is deception. It undermines honest relationship and trust between doctor and patient which is extremely important for successful treatment. Consciously giving placebos to patients for a condition that can be adequately treated, with prejudice the right of patients to the best care possible, opens up many bioethical issues. Despite all the current knowledge level, placebo effect remains still a scientific mystery.

***Key words**: analgesia, pain, placebo effect, placebo analgesia, nocebo, neuroimaging studies*

Introduction and Historical Aspects

Placebo is a drug or treatment which produces no specific biologic effects on the medical condition or symptom which ought to be cured[1]. Placebo effect is also universal phenomenon which is present in practice of medicine from its very beginnings[1,2]. The word placebo is the initial world of psalm 116:6 »placebo Domino in regione vivorum« (I will please the Lord in the land of living beings). This psalm was spoken by paid people above the graves of wealthy individuals[2]. During centuries there was no many knowledge about real mechanism for treatment of diseases. We have to assume that many of treatments used in pre-scientific era were based on placebo effect.

In 1811 Robert Hooper in »Quincy' s Lexicon-Medicum« described placebo as »an epithet given to any medicine adapted more to please than benefit to the patient«. Although Richard Cabot in 1903 says that »I have not yet found any case in which a lie does not do more harm than good«, in 1955 surgeon Henry Beecher discover that patients treated by enthusiastic surgeons have better outcome than those one treated by skeptic surgeons[3,4]. He

Received for publication May 30, 2011

published in JAMA paper named »The powerful placebo« and opened new era on placebo use. Austin Bradford Hill designed the first randomized trial and use of placebo started in clinical trials under the assumption that placebos has no efficacy in specific treatment effect. After many double-blind control randomized clinical trials were conducted over the world, investigators noticed that placebo sometimes has unexpected outcomes almost equally powerful as active substance with which placebo was compared. Although this observation was not confirmed by evaluation of 130 controlled trials and 52 randomized controlled trials, some investigators start to analyze placebo effect in healthy and sick people. These analytical results are substantial data about placebo effect; especially in the field of pain[5].

In modern medicine, placebo effect is defined »as the part of the therapeutic response that is not attributable to the properties of active ingredients«[6,7]. Placebo treatment refers to an inert agent or treatment and placebo effect refer to an outcome. While placebo is conducted to desirable consequences in the patients, nocebo (»I will harm«) is the phenomenon that is opposite to placebo[6,7]. Nocebo effect is present if negative effect occurs in expectations of negative occurrence. Both, placebo and nocebo effects are complex mechanisms and placebo effect was specially investigated in pain analgesia studies[7,8].

As we know, the pain is the oldest phenomenon for human life, an unpleasant emotional experience, multidimensional and fully personal experience that's under the influence of many cultural, ethnic and linguistic differences. Today we know very much about pathogenesis of pain and we have many analgesic drugs and therapeutic procedures for relieving a pain[7,8]. Placebo analgesia is the most investigated models of placebo response. But, still we can hear from medical stuff that »patient is exaggerate with his pain«, because placebo injection of glucose gave him pain relief and that kind of solving patients pain is used by significant number of clinical and generally practice doctors.

Aim of this article is to present the most recent findings in field of placebo induced analgesia and to devote attention of medical stuff on fact that pain relief after use of placebo doesn't mean that patient wasn't suffered from pain.

General Data about Placebo

The various forms of placebo effects were investigated. Despite the one or other situation, most of population can be placebo sensitive with different consistency of the placebo response[6,7]. Contextual factors (conditioning, expectancy and drug related instructions) predict placebo response. It seems that use of multiple pills, more colorful, bigger and more expensive drugs produce higher magnitude of placebo response. Also, intravenous injections are more powerful than intramuscular, and placebo analgesia can show somatotropic distribution[8,9].

Placebo effect is not the same in all patients, which is not surprising because even the effect of a real cure is not always the same for all patients. In contrast to these patients in whom we achieved a response after administration of placebo, in patients with Alzheimer disease we will not get a response to placebo due to nonfunctional prefrontal cortex which is responsible for realizing a sense of expectation[1,6,10,11].

The length of a placebo effect is different. For panic disorder placebo can be an effective over 8 weeks, 6 months for angina pectoris and even two and a half years in rheumatoid arthritis. In mild pain, after verbal suggestion, placebo effect may be much stronger and persist even after the tenth application[3,7,10–12].

Placebo and Analgesia

In terms of analgesia, placebo will cause a positive response in 39% of patients. Almost the same percentage (36%) of patients will respond to treatment with morphine. Placebo analgesia can be quick and powerful; if subject believe that its receiving potent pain killer, by for example intravenous injection, the pain intensity can drop out for 2–5 points (out of 10) on visual analogue scale (VAS). Measuring by efficacy index (pain decrease with placebo/pain decrease with morphine) is 0,56 which means that placebo is effective 56% as a standard dose of morphine![10,11,13].

The use of placebo in the treatment of pain has shown that the result is better if the pain is more intensive. Placebo also extend the period through which the patient can tolerate the pain[6,7,13].

Benedetti was comparing benefit in patients with postoperative pain due to the »open« and »hidden« administration of analgesics. It proved advantage of the »open« treatment administration[14]. Also, the placebo effect occurs only if the patient knows that he received it because action is based on the fact that the brain, expecting relief from pain, start to produce endogenous opiates. Except this path, placebo analgesia also includes opiate downward path for the pain control which inhibits pain by processing it the spinal cord and thus reduces the response to pain in the brain[14–16].

Common Principles of the Placebo Effect

Hróbjartsson and Peter Gotzsche examined the nature of the placebo effect. The research was published in 2001 and 2004 when they published a follow-up study. They concluded that in the group that received placebo there was no statistically significant improvement compared with group which did not receive therapy[17,18]. Also, there was no significant placebo effect in studies that measured objective outcomes (such as blood pressure). Placebo effect can only be proven in studies where the outcome (success or failure of therapy) was reported by the patient. Finally, considering that in clinical studies, patients do not know which treatment they receive, the authors concluded that testing of the placebo effect do not have great significance in clinical studies[17–19].

At 2010 Goffaux et al modeled the placebo effect[9]. As we mentioned above, in induction phase therapeutic message and method of administration have a great impact on placebo effect. Reassuring message has been shown to provide quick pain relief while message with uncertainty can induce hyperalgesia-nocebo effect. Patients convinced that they'll have better follow up and estimation of side effects has better placebo effect. If placebo is congruent with individual's beliefs and values, effect will be higher[7,9].

In next phase, psychological mechanisms (which include past experiences of patient) are activating neurochemical and neurophysiological mechanisms. Those are responsible for the emergence of placebo effect[9,16,19].

Imaging Approach to Placebo

For decades the main problem in pain analgesia was to notice and quantify the pain. The problem is bigger because there are not existing objective biological markers for pain. Many scales and questionnaires are developed to facilitate the pain measurement[9,20].

Today, several new imaging modalities are enhancing the pain research: Single Photon Emission Computed Tomography (SPECT), functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Those imaging modalities are opening objective approach for the pain and pain relief researches[21].

In 2002 Petrovic et al confirmed the increased activity in anterior cingulated cortex (by functional magnetic resonance imaging of brain) during placebo and opioid induced analgesia[22]. Anterior cingulated activity is also accompanied with activity in periaqueductal gray matter--mesencephalic region. When radioactive μ-opiate receptor traces were used, investigators found that opiate secretion increase significantly in the limbic circuit during expectations of pain relief[22–24]. Activation of endogenous opiate system does not fully explaining placebo analgesia due to fact that non steroidal anti-inflammatory drugs and others are mediated by other unknown mechanisms[24–26].

For placebo analgesia, together with opiate system is involved dopaminergic »reward system«; subjects in whom the activation of this system is stronger are better placebo responders. Placebo effect is increasing the activity of dopaminergic cells in the nucleus accumbens[27]. Therefore, nocebo effect can be tied to a deactivation of dopaminergic and opiate system; or nocebo suggestion is producing anxiety which activates the cholecystokinin (potent opiate antagonist) related pro-nociceptive system and also descending hypothalamus-pituitary gland axis[15,27,28].

Foundations of Placebo Effect

Psychophysiological mediators are conditioning, cognition, motivation and emotions; endorphins, dopamine and others neuromodulators and neurotransmiters are also involved[6,29]. Conditioning and expectations of relief can be connected to nocebo effect.

There are many examples how placebo works due to conditioning theory; theory based on Pavlovian stimulus substitution concept[30,31]. If placebo is described as muscle relaxant it will cause such relaxation, and if it is described as opposite, it will produce muscle tension. On the other side, patients which are frequently taking the same shape, color, taste and size of pill for some condition (headache, heart pain) if after several associations placebo is given to them for same condition, they will observe pain relief[30–32].

On those observations Goldstein (1962) developed expectance theory for placebo response which is connected to patient expectation[33]. Patient perception and expectations are enhanced trough patient-doctors relationship (placebo response was increased from 44% to 62% with doctors encouraging), differences in size (large pills better than smaller) and color of placebo pills (hot colored pills are working as stimulants pills and cold colored pills as depressants)[33–35]. But same supstance causes both the stimulation and depression, depending on the description that was used for supstance (conditioning!). Thus, conditioning and expectation are interwoven together with other factors (motivation, emotions, subjective experience, quality of life, ect); and some still unknown in enabling placebo effect[33–35]. If doctor who prescribe placebo medication/intervention has optimistic, warm and confidently approach to patient placebo showed higher magnitude of response[6,9,35,36].

Motivation (a patients desire for relief) can explain a large part of placebo effect, but motivation failed to produce placebo response in various kind of pain (for example burning pain)[37]. Although stress is increasing level of pain and distress, in some point can also produce stress--induced analgesia. So anxiety can produce stress-induced analgesia, but also can (through motivation and expectancy) produce higher level of placebo response. It is not clear whether anxiety is cause or consequence of placebo[36,37]. In studies of placebo analgesia, only subjective decrease of anxiety was predictor of placebo response[6,9,37].

Placebo analgesia can be viewed also as »meaning response«. Moerman define the physiological and psychological effects of meaning in the treatment of disease; when placebo is used the response is connected to inert treatment or drug[38]. Various factors can influent the »meaning of treatment«, especially doctors-patients relationship. Among other facts, this is why placebo has better outcome in open protocols versus blind randomized clinical trials[38,39]. Conditioning, expectance and meaning response are not part of patients emotions while receiving drug in blind randomized clinical trial; placebo response will be better if patient is encouraged by her/his doctor[6,9,12,39].

When we are discussing placebo analgesia we must not forget fact that culture is playing specific role in perceiving and interpreting pain; the description of pain vary among cultural different countries. When placebo analgesia response is studying, biopsychosocial model must be taken into consideration. It can be a point for understanding placebo on the different corners of view:

brain imaging, cognitive and emotional behavior together with interactions between different cultures[40].

Imaging studies provide us new data of how brain activity was related to cognitive inputs (expectations of pain relief). Some imaging studies confirmed that data from neuropharmacologic studies about influence of cognitive input on modulating physical and emotional states through endogenous opiate system[40,41]. This studies also showed how brain is able to use cognitive issues for activation of some functional areas[41,42].

Since last decade placebo was described in behavioral terms. Placebo response increase the chance of organism to respond positively for any external intervention and it is now clear that placebo must be the part of »embedded« endogenous physiological responses which are significant for self-preservation[6].

Placebo effect depends on genetic variation too. These findings are still in their early stages and more researches are necessary. So far, it was discovered that patients with social behavior disorders inherited variant of the gene for tryptophan-hydroxylase-2, which is associated with reduced activity in nucleus amigdala and causes greater sensitivity to placebo[43].

Placebo is under influence of many intrinsic and extrinsic factors, it is mediated by psychological and physiological mechanisms and its involving endogenous opiate system.

Clinical Practice and Ethical Consideration

Using placebos deeply affects the relationship between patient and doctor. If the patient discovers that placebo has been prescribed instead of the drug it can significantly impair their interoperability.

But in every day clinical practice sometimes we are forced to deal with decision of using placebo and many of clinicians use it. However, regardless of the seriousness of the situation that could happen, survey conducted in Denmark showed that 48% of family physicians, in certain situations will recourse to the use of placebos. Most often this is used when prescribing antibiotics, even though we know that this is a viral infection or when prescribing vitamin when patient complains of fatigue[44].

In United Kingdom law prohibits the use of placebo, but despite of that 24% of clinicians use it and another 18% of them use it depending on circumstances[45].

Therefore is not surprisingly that American Pain Society at 2005 published a paper on the use of placebo in clinical research and patient care. Their conclusions were that »the deceptive use of placebo and the misinterpretation of the placebo response to discredit the patients pan report is unethical and has to be forbidden« and that »when using placebos, doctors have an ethical obligation to ensure that placebos are not used to deception, punishment or under-treatment of patient with pain«[45].

Three years later, in USA a recent survey of 679 physicians, found that about half of them prescribed placebo treatments on a regular basis! Most (62%) said that such a practice is ethical; mostly of them are internists and rheumatologists[46]. They think that patients will benefit from positive expectations, not because the doctors think that treatment will have a physiological effect on the patient condition. They are using saline injections, sugar pills, but also over-the-counter analgesics (41%), vitamins (38%), antibiotics (13%) and sedatives (13%) as placebos. They describe to their patients that prescribed medicine is uncommon for their health condition, but might be beneficial[46]. Colleagues working in hospitals less frequently use placebo than general practice doctors[45,46].

Conclusion

In conclusion we can say that base of placebo is deception. It spoils honest relationship and trust between doctor and patient which is an extremely important link in the treatment. Administering a placebo instead of drug is unethical, and contrary to the Hippocratic Oath that all doctors swear[47].

Consciously providing placebos to patients for a condition that can be properly treated, raises the question about patient right on the best possible care, and open many bioethical issues. We must ask ourselves whether encouraging the patient, providing support and warm words in combination with placebo would be sufficient to administer the right medications at lower doses, and again on the other hand, if the same would be ethically correct, and how to deal with those who do not believe? What to do with patients who have objective obstacles (e.g. use of morphine for respiratory insufficiency in patient with burns) appropriate treatment cannot be provided – whether it's justified to administer a placebo?

The concept of placebo and its effectiveness is certainly one of the most widely used concepts in medicine and time will surely provide answer for at least some of these questions. Until then we should act according to our conscience and ethical principles.

REFERENCES

1. MARGO CE, Surv Ophthalmol, 44 (1999) 33. — 2. JACOBS B, J R Soc Med, 93 (2000) 213. — 3. BEECHER HK, J Am Med Assoc, 159 (1955) 1602. — 4. DE CRAEN AJ, KAPTCHUK TJ, TIJSSEN JG, KLEIJNEN J, J R Soc Med, 92 (1999) 511. — 5. KAPTCHUK TJ, Lancet, 351 (1998) 1722. — 6. GREENE CS, GODDARD G, MACALUSO GM, MAURO G, Journal of Orofacial Pain, 23 (2009) 221. — 7. MANCHIKANTI L, GIORDANO J, FELLOWS B, HIRSCH JA, Pain physician, 14 (2011) 155. — 8. TURNER JA, DEYO RA, LOESER JD, VON KORFF M, FORDYCE WE, JAMA, 271 (1994) 1609. — 9. GOFFAUX P, LÉONARD G, MARCHAND S, RAINVILLE P, Placebo analgesia. In: Beaulieu P, Lussier D, Porreca F, Dickenson AH (eds). Pharmacology of Pain. IASP Press, Seattle, 2010, pp 451. — 10. HOFFMAN GA, HARRINGTON A, FIELDS HL, Perspect

Biol Med, 48 (2005) 248. — 11. BENEDETTI F, ARDUINO C, COSTA S, VIGHETTI S, TARENZI L, RAINERO I, ASTEGGIANO G, Pain, 121 (2006) 133. — 12. PRICE DD, MILLING LS, KIRSCH I, MONTGOMERY GH, NICHOLLS SS, Pain, 83 (1999) 147. — 13. LEVINE JD, GORDON NC, SMITH R, FIELDS HL, Pain 10 (1981) 379. — 14. BENEDETTI F, Annu Rev Pharmacol Toxicol, 48 (2008) 33. — 15. BENEDETTI F, AMANZIO M, Prog Neurobio, 52 (1997) 109. — 16. BENEDETTI F, MAYBERG HS, WAGER TD, STOHLER CS, ZUBIETA JK, J. Neurosci, 45 (2005) 11390. — 17. HROBJARTSSON A, GOTZSCHE PC, N Engl J Med, 344 (2001) 1594. — 18. HROBJARTSSON A, GOTZSCHE PC, J Intern Med, 256 (2004) 91. — 19. OKEN BS, Brain, 131 (2008) 2812. — 20. GOFFAUX P, REDMOND WJ, RAINVILLE P, MARCHAND S, Pain, 130 (2007) 137. — 21. LIDSTONE SC, STOESSL AJ, Mol Imaging Biol, 9 (2007) 176. — 22. PETROVIC P, KALSO E, PETERSSON KM, INGVAR M, Science, 295 (2002) 1737. — 23. WAGER TD, SCOTT DJ, ZUBIETA JK, Proc Natl Acad Sci, 104 (2007) 11056. — 24. ZUBIETA JK, BUELLER JA, JACKSON LR, SCOTT DJ, XU Y, KOEPPE RA, NICHOLS TE, STOHLER CS, Neurosci, 25 (2005) 7754. — 25. BORSOOK D, BECERRA LR, Mol Pain, 2 (2006) 30. — 26. KONG J, GOLLUB RL, ROSMAN IS, J Neurosci, 26 (2006) 381. — 27. SCOTT DJ, STOHLER CS, EGNATUK CM, WANG H, KOEPPE RA, ZUBIETA JK, Arch Gen Psychiatry, 65 (2008) 220. — 28. BENEDETTI F, AMANZIO M, Prog Neurobio, 52 (1997) 109. — 29. MAYBERG HS, SILVA JA, BRANNAN SK, TEKELL JL, MAHURIN RK, MCGINNIS S, JERABEK PA, Am J Psychiatry, 159 (2002) 728. — 30. KLINAR I, BLAŽIN A, BAŠIĆ M, PLANTAŠ I, BIŠKUPIĆ K, Coll Antropol, 34 (2010) 481. — 31. POLLO A, AMANZIO M, ARSLANIAN A, CASADIO C, MAGGI G, BENEDETTI F, Pain, 93 (2001) 77. — 32. KIRSCH I, Specifying nonspecifics: Psychological mechanism of the placebo effect. In: Harrington A. The Placebo Effect: An Interdisciplinary Exploration. Harvard University Press, Cambridge, 1997, pp 166. — 33. GOLDSTEIN AP, Psychiatry, 25 (1962) 72. — 34. COLLOCA L, BENEDETTI F, Pain, 144 (2009) 28. — 35. FLATEN MA, SIMONSEN T, OLSEN H, Psychosom Med, 61 (1999) 250. — 36. AUKST-MARGETIĆ B, JAKOVLJEVIĆ M, IVANEC D, MARGETIC B, LJUBIČIĆ Đ, ŠAMIJA M, Coll Antropol, 33 (2009) 1265. — 37. COLLOCA L, LOPIANO L, LANOTTE M, BENEDETTI F, Lancet Neurol, 3 (2004) 679. — 38. MOERRMAN DE, JONAS WB, Ann Intern Med, 136 (2002) 471. — 39. WALACH H, JONAS WB, J Altern Complement Med, 10 (2004) 103. — 40. CRAGGS JG, PRICE DD, VERNE GN, PERLSTEIN WM, ROBINSON MM, Neuroimage, 38 (2007) 720. — 41. BINGEL U, LORENZ J, SCHOELL E, WEILLER C, BÜCHEL C, Pain, 120 (2006) 8. — 42. RADELJAK S, ŽARKOVIĆ PALIJAN T, KOVAČEVIĆ D, MARINOVIĆ D, DADIĆ-HERO E, Coll antropol, 34 (2010) 287. — 43. FURMARK T, APPEL L, HENNINGSSON S, J Neurosci, 28 (2008) 13066. — 44. HRÓBJARTSSON A, NORUP M, Evaluation & the Health Professions, 26 (2003) 153. — 45. American Pain Society (APS) position statement on the use of placebos in pain management, Journal of Pain, 6 (2005) 215. — 46. TILBURT JC, EMANUEL EJ, KAPTCHUK TJ, CURLIN FA, MILLER FG, BMJ, 337 (2008) 1938. — 47. DAVID H. NEWMAN, Scribner, 25 (2008) 134.

R. Dobrila-Dintinjana

Clinic for Radiotherapy and Oncology, Rijeka University Hospital Center, Krešimirova 42, Rijeka, Croatia
e-mail: renatadobrila@windowslive.com

PLACEBO U LIJEČENJU BOLI

S A Ž E T A K

Placebo je upotreba tvari ili primjena postupka bez specifične aktivnosti za stanje koje se pokušava liječiti. Učinak placeba u medicini je bio znanstveno dokazan 1978. g. Pronađeno je da analgezija uzrokovana placebom ovisi o otpuštanju endogenih opijata u mozgu i da se placebo učinak može poništiti upotrebom naloksona (antagonist opijata). Funkcionalna magnetska rezonanca mozga pokazala je da se placebo analgezija održava poradi aktivacije i pojačanog međusobnog funkcioniranja između određenih dijelova mozga (anterior cingulata, prefrontalni, orbitofrontalni i insularni korteks, nucleus accumlens, amygdala, periaqueduktalna siva masa i leđna moždina. Placebo također olakšava descendentnu inhibiciju nociceptivnih refleksa kroz periaquaeduktalnu sivu supstancu. Placebo učinak se može dobiti na više načina: upotrebom farmakoloških preparata ili simulacijom određenih postupaka. Taj fenomen je povezan s percepcijom i isčekivanjem pacijenta. Važan je i stupanj sugestije osobe koja propisuje placebo kao i stupanj vjerovanja osobe koja prima placebo. Očekivani učinak placeba je dostići učinak pravog lijeka. Placebo učinak ovisi o načinu prezentacije. Ako se tvar prezentira kao štetna, ona može prouzročiti štetne učinke, tzv. »nocebo« učinak. Placebo učinak nije isti u svih pacijenata,baš kao što ni učinak pravih lijekova nije isti u svih pacijenata. Aplikacija placeba u analgetske svrhe daje pozitivan učinak u oko 35% pacijenata. Gotovo isti postotak (36%) pacijenata će odgovoriti na dozu morfija od 6–8 mg. Stoga, treba zapamtiti da odgovor na placebo ne znači da osoba simulira bol i neetično je ne primijeniti pravi lijek posebice u svjetlu saznanja da se prefrontalni korteks aktivira u isčekivanju oslobođenja od boli. Ta aktivacija smanjuje aktivnost u regijama mozga odgovornima za osjećaj boli (talamus, somatosenzorni dio korteksa). Ipak, upotreba placeba je etično, zakonski i moralno vrlo dubiozna. Osnova placeba je obmana. Ona potkopava pošteni odnos i povjerenje između doktora i pacijenta koji je izuzetno važan za uspješno liječenje. Svjesna primjena placeba u pacijenata čije stanje se može adekvatno liječiti s oduzimanjem prava pacijenta na najbolje moguće liječenje otvara mnoga bioetička pitanja. S znanstvene strane, bez obzira na sadašnji nivo znanja, placebo i njegovi učinci ostaju znanstvena misterija.