SPECIAL ARTICLE

# Reviving the old sermon of medicine with the placebo effect

# Revivendo o antigo sermão da medicina com o efeito placebo

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*Abstract*

*Objective: The message of the importance of a caring doctor-patient relationship is now like an old sermon which does not impact anyone's mind or action. Observing the healing practice of the old time physicians, who valued their attitudes and relationship with their patients more than the actual interventions, this paper reviews the literature on their main therapeutic device – the placebo effect – as a novel way of delivering this old sermon of medicine to contemporary doctors. Discussion: There are countless historical and contemporary examples of the impressive placebo effect and although contested by some, it seems real and significant. The classic conditioning theory and the expectation theory explain reasonably well the mechanisms of the placebo effect, especially in conjunction with each other. The underlying biochemical pathway, according to the limited current knowledge, involves endorphins for pain and dopamine for Parkinson's disease. Finally, human factors such as the doctor's positive attitudes and a good doctor-patient relationship seem to be more essential than the placebo itself in eliciting the placebo effect. Conclusions: Given the body of evidence supporting the existence of significant placebo effect and the importance of the doctor-patient relationship in determining it, the human factors of the medical treatment should be emphasised in order to maximise the placebo effect and consequently the overall therapeutic effect of the healing acts.*

*Keywords: Placebo effect; Endorphins; Dopamine; Doctor-patient relationship; Classic conditioning; Expectation; Human factors*

*Resumo*

*Objetivo: A mensagem sobre a importância de uma boa relação médico-paciente é como se fosse um velho sermão que não tem mais impacto no pensamento ou na ação de ninguém. Observando a prática dos médicos dos velhos tempos, que valorizavam mais suas atitudes e o relacionamento com seus pacientes do que as intervenções em si, este artigo revisa a literatura sobre o seu principal dispositivo terapêutico – o efeito placebo – como uma nova forma de pregar este velho sermão da medicina aos médicos contemporâneos. Discussão: Há incontáveis exemplos históricos e contemporâneos do impressionante efeito placebo e este, ainda que seja contestado por alguns, parece real e significativo. A teoria do condicionamento clássico e a teoria das expectativas explicam razoavelmente bem os mecanismos do efeito placebo – as duas em conjunto os explicam melhor ainda. A intermediação bioquímica do efeito placebo, de acordo com o limitado conhecimento atual, envolve as endorfinas para a dor e a dopamina para a doença de Parkinson. Finalmente, os fatores humanos, tais como as atitudes positivas do médico e uma boa relação médico-paciente, parecem ser mais essenciais do que o próprio placebo para provocar o efeito placebo. Conclusões: Dado o corpo de evidências que apóiam a existência de um efeito placebo significativo e a importância da relação médico-paciente para determiná-lo, os fatoreshumanos do tratamento médico devem ser enfatizados para maximizar o efeito placebo e, conseqüentemente, o efeito terapêutico global dos atos curativos.*

*Descritores: Efeito placebo; Endorfina; Dopamina; Relação médico-paciente; Condicionamento clássico; Expectativa; Fatores humanos*

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This paper was presented at the 2004 International Conference on Eating Disorders in Orlando, Fl.
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Financing: CAPES – Brazilian Ministry of Education
Conflict of interest: None
Submitted: 19 October 2005
Accepted: 19 October 2005

## Introduction

Physicians of pre-scientific medicine, well aware of their trifling medical arsenal, used their attitude and personal charisma as the most important therapeutic weapons. A compassionate doctor-patient relationship was the core element of the healing process at that time. In the 21st century, however, maybe as a natural consequence of medical innovations, we depend more and more on sophisticated diagnostic tests, high-tech procedures and medications. The importance of human factors in the medical encounter, although every physician knows it very well, is now like an old sermon which neither touches anyone's heart nor spurs anyone to action. No doctor would feel moved or change their practice hearing this too familiar assertion.

Placebo effect seems to be the right new garment to make this old sermon look more appealing to the hard-to-please physicians of today. It is well known that almost all medical treatments dated more than 150 years ago were devoid of any scientifically proven properties and this means that the history of medicine can be considered the history of the placebo effect.[1] Actually, during the era of pre-scientific medicine, when the doctor-patient relationship was more valued, the most important component of the healing practice was the placebo effect. Physicians clearly knew that even a plain sugar pill, once given to a patient with a reassuring and compassionate attitude, could alleviate their patient's suffering. Richard Cabot, an eminent Harvard Medical School professor, wrote in 1903, "I was brought up, as I suppose every physician is, to use placebo, bread pills, water injections and other devices of acting upon a patient's symptoms through his mind... I used to give them by bushels".[2] Sometimes, not only patients but also doctors believed that an inert treatment in question was indeed effective; and this shared belief and passion could even maintain an obviously harmful procedure as a popular treatment widely accepted for centuries. Such an example is bloodletting. Now we clearly know bloodletting is not only ineffective but actually harmful except for a temporary alleviation of congestive heart failure, but the placebo effect of the procedure probably overwhelmed the actual harmful effect so that it could survive generations of doctors and patients.[3] Conversely, the essential elements of the placebo effect are human factors. Hence talking about the placebo effect can be a way of drawing health professionals' attention into this old-fashioned but important issue of the doctor-patient relationship. I therefore selectively review the literature on the placebo effect as a novel approach to convincing physicians of the value of human factors in the art of medicine.

## Methods

Medline was searched from the inception to September 2005 using the MeSH (Medical Subject Heading) term 'placebo effect' and the references were selectively checked by the author.

## Discussion

### 1. Powerful placebo

Henry K. Beecher, in his review titled "The powerful placebo", estimated an average placebo response of 35.2% across various medical conditions.[4] Since then placebo has been known to be powerful and the response rates computed in recent meta-analyses vary roughly around this classical one third, that is, from 20% to 45%. A meta-analysis of the clinical trials for irritable bowel syndrome has estimated the placebo response as 40.2%.[5] A similar approach to the treatment of duodenal ulcer suggests a healing rate of 44.2% in trials with a frequency of placebo administration four times a day and 36.2% in trials with administration twice a day.[6] Other examples are 29.7% in the anti-depressant treatment of major depression,[7] 29.0% in the acute treatment of migraine,[8] 26.8% in the treatment of reflux esophagitis[9] and 19.6% in the treatment of chronic fatigue syndrome.[10] An impressive example of the powerful placebo effect is the internal mammary artery ligation. In the 1950s, thousands of patients suffering from angina pectoris went through this operation, which would supposedly increase blood supply to heart. The results were spectacular: up to 90% of the patients experienced an alleviation of their symptoms. Media reports on this surgery heightened even more its popularity.[11] However, several cardiac surgeons remained sceptical and decided to scrutinise it carefully. Two independent teams, one led by Dimond et al.,[12] and the other by Cobb et al.,[13] using double-blinding methods, performed the internal mammary artery ligation on a group of patients and just a skin incision on the other group. In Dimond's trial, 76% of the patients who had the artery ligated improved whilst 100% of those who received just a skin incision improved. Cobb's team also demonstrated that the surgery was no better than a mere skin incision. Even more interesting was the fact that this positive effect was maintained for more than six months. The internal mammary artery ligation was just a good placebo.

### 2. Definitions

Placebo has been defined as "any therapeutic procedure which has an effect on a patient, symptom, syndrome or disease, but which is objectively without specific activity for the condition being treated".[14] Similarly, the placebo effect can be described as "any effect attributable to a pill, potion, or procedure, but not to its pharmacodynamic or specific properties".[15] The placebo effect consists not only in subjective improvement but also in objective physiologic changes. It can occur immediately after administration of a placebo like in the case of migraine and can last while the conditions which evoked it are maintained.[1] In other words, the placebo effect can last even up to a year or more if the three necessary elements are maintained: 1) beliefs and expectations of patients; 2) beliefs and expectations of doctors; and 3) a good relationship between them. This demonstrates the importance of human factors in determining the placebo effect as the final section of this review asserts further. Finally, the term *placebo response,* despite its often misleadingly interchangeable meaning with the placebo effect, is usually employed in order to quantify the placebo effect in clinical trials and accordingly defined as the proportion of responders in a placebo arm.

### 3. Powerless placebo?

Researchers have suggested that the response rate in the placebo arm of a clinical trial – *placebo response* as described

above – may include not only the pure placebo effect but also other components such as spontaneous improvement, regression to the mean, measurement bias, and unidentified parallel interventions.[16-17] A controversial meta-analysis, strategically titled "Is the placebo powerless?", attempted to distinguish the placebo effect from the other components and contested Beecher's classical thesis on the power of placebo.[18] The authors performed a meta-analysis of the clinical trials which had included a group receiving placebo and another receiving nothing. The hypothesis was that the one-third placebo response observed by Beecher and other researchers was more due to the other factors such as spontaneous remission and regression to the mean rather than due to the pure placebo effect. A comparative group of no treatment would discount those factors which are not an actual part of placebo and would demonstrate the true placebo effect. Indeed, the paper and its subsequent updates[19-21] provided evidence in favour of this reasoning: the placebo effect was almost nil except in the pain studies. Does this mean that the placebo effect does not exist? W. G. Thompson asserts in his book that "no treatment" does not actually mean the absence of any therapeutic element since the settings of a clinical trial themselves even without involving any pill or procedure are able to produce clinical improvement in patients especially when they include a doctor-patient encounter.[3] So when the authors of the meta-analysis discounted the response rate in the "no treatment" arms from the placebo arms, they may have discounted the actual placebo effect which occurred in the former as well. This idea concurs with the thesis on the importance of human factors in determining the placebo effect as described further in this review. Overall, a more balanced perspective which also takes into account numerous other placebo studies would be that the magnitude and the specificity of the placebo effect should be revised but not the existence per se. In other words, the placebo effect certainly exists and is significant but may be less powerful than previously thought and may vary according to the treated condition.

## 4. Psychological theories on the placebo effect

Several psychological and biological explanations for the placebo effect have been proposed. Two psychological theories have been widely invoked: the classic conditioning theory and the expectation theory.[22] The former suggests that the placebo effect is a conditioned response because of repeated associations between a conditioned stimulus (a neutral component such as the colour or shape of an active drug) and an unconditioned stimulus (the active element capable of eliciting therapeutic responses).[23-25] For example, migraine patients regularly taking aspirin (unconditioned stimulus) for pain alleviation (unconditioned response) can associate the colour, shape and even taste of the pill (conditioned stimulus) with pain reduction. After various associations, if they receive a sugar pill resembling aspirin and the instruction that the pill is aspirin, pain can really be relieved (conditioned response). Obviously, the aspects of an aspirin pill are not the only conditioned stimuli. Those stimuli such as syringes, stethoscopes, white coats, hospitals, doctors and nurses, if repeatedly associated with the unconditioned stimuli like effective therapies, can generate clinical improvement when presented to patients separately.

According to the expectation theory, the patient's expectation and belief of a positive result – or negative when we deal with the nocebo phenomenon – triggers the placebo response.[26-29] In studies with psychotropic medications, subjects experience effects according to what they expect from the substance given. For instance, a study showed that the effect of amphetamine depended on the verbal instruction given to the subjects.[30] The sympathomimetic effects of adrenaline could be reduced if the subjects received an instruction inconsistent with the real characteristics of adrenaline. In the same way, if the subjects received a sugar pill identified as a sedative, they would probably experience inhibitory effects like attention deficit and sleepiness because of such an expectation. Researchers also demonstrated how specific the expectation of analgesia can be.[31] All four limbs were simultaneously stimulated by means of a subcutaneous injection of capsaicin, which produces a painful burning sensation. Specific expectations of analgesia were induced by applying a placebo cream on one of these body parts and by telling the subjects that it was a powerful local anaesthetic. In such a way, expectancy of the anaesthetic effect was directed only toward the part on which the placebo cream was applied. An analgesic response indeed occurred only on the treated part, whereas no variation in pain sensitivity was found on the untreated parts. The expectation that the placebo cream would relieve the pain made it happen. Expectation is also associated with the nocebo phenomenon, in which patients who expect distressing side effects before taking a medication are more likely to develop them.[32] A systematic review confirmed the importance of expectation in the placebo effect and recommended its sensible use in health care.[33]

Researchers have long argued either for one or the other theory.[25-26] However, it is possible and even more convincing to reconcile both theories: some recent refinements of the Pavlovian theory suggest that what is learned in Pavlovian conditioning is in fact an expectation.[34]

## 5. Biochemical mediation of the placebo effect

Biological research has tried to unveil what then happens at the biochemical level after conditioning or expectation do their part in eliciting the placebo effect. There may be hormones, neurotransmitters and other biochemical agents acting in this process and the possible candidates are endorphins, dopamine, cholecystokinin, serotonin and catecholamines.[3] However, the current evidence endorses only the first two of them and there is little information on the others' role in the placebo effect. For instance, placebo analgesia can be blocked by the narcotic antagonist naloxone, which supports the idea that placebos can ease pain by releasing endorphins;[35] and de la Fuente-Fernandez, Stoessl, using positron emission tomography in patients with Parkinson's disease, provided in vivo evidence for substantial release of endogenous dopamine in the striatum of the patients in response to placebo.[36] At the moment, we at least know that endorphins and dopamine mediate the placebo effect respectively for pain and Parkinson's disease.

## 6. Human factors as essential conditions of the placebo effect

The importance of human factors to the placebo effect was briefly mentioned above. Especially, the role of the doctor is fundamental in eliciting the placebo effect. Numerous studies revealed that a sugar pill or a sham procedure do not produce any placebo effect without the positive attitude, suitable communication and compassionate contact of a doctor. For example, Thomas randomised two hundred patients into two groups of one hundred.[37] The first received a firm diagnosis and positive approach from their doctor whilst the second were told an uncertain and negative message such as "I cannot be certain what is the matter with you." In addition, half (fifty) of the patients in each group were given a placebo pill. In the first group, 64% of the patients improved and in the second group, only 39% did. Furthermore, giving a placebo pill or not made no significant difference in either group. This study suggests that the doctor himself is maybe the most vital component of the placebo effect. The placebo pill without the doctor's encouragement and reassurance would not produce any therapeutic effect in the patients. Several other studies demonstrated that reassuring and caring attitudes of the doctor increase the effect of both inert placebo and active intervention.[38-41]

## Conclusions

I have succinctly reviewed the literature on the placebo effect. There are countless historical and contemporary examples of the impressive placebo effect. Although contested by Hrobjartsson & Gotzsche's meta-analysis and the subsequent updates,[18-21] the placebo effect seems real and significant. Actually their studies, in a way, support the notion that the clinical setting and the doctor-patient relationship are more important than the placebo itself in eliciting the placebo effect as described above. Evidence available for both conditioning theory and expectation theory is not scant and they explain reasonably well the mechanisms of placebo effect, especially in conjunction with each other. The underlying biochemical pathway is progressively being clarified, our current knowledge identifying endorphins and dopamine as the mediating agents for pain and Parkinson's disease. I have also reviewed some evidence of the vital role of human factors in the placebo effect. Given the body of evidence supporting the existence of significant placebo effect and the importance of the doctor-patient relationship in determining it, I argue that the contextual factors of the medical treatment should be emphasised in our clinical practice in order to maximise the placebo effect and consequently the overall therapeutic effect of our healing acts. Maximising the placebo effect seems to be a smart and convincing way of reviving this old sermon of medicine: the importance of the doctor-patient relationship.

## Acknowledgements

I am grateful to Hilary Warner for proofreading the manuscript and to CAPES - Brazilian Ministry of Education for the scholarship.

## References

1. Benson H, Friedman R. Harnessing the power of the placebo effect and renaming it "remembered wellness". Annu Rev Med. 1996;47:193-9.
2. Cabot RC. The use of truth and falsehood in medicine. Conn Med. 1978;42(3):189-94.
3. Thompson WG. The placebo effect and health - combining science & compassionate Care. Amherst, New York: Prometheus Books; 2005.
4. Beecher HK. The powerful placebo. JAMA. 1955;159(17):1602-6.
5. Patel SM, Stason WB, Legedza A, Ock SM, Kaptchuk TJ, Conboy L, et al. The placebo effect in irritable bowel syndrome trials: a meta-analysis. Neurogastroenterol Motil. 2005;17(3):332-40.
6. de Craen AJ, Moerman DE, Heisterkamp SH, Tytgat GN, Tijssen JG, Kleijnen J. Placebo effect in the treatment of duodenal ulcer. Br J Clin Pharmacol. 1999;48(6):853-60.
7. Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: variable, substantial, and growing. JAMA. 2002;287(14):1840-7.
8. de Craen AJ, Tijssen JG, de Gans J, Kleijnen J. Placebo effect in the acute treatment of migraine: subcutaneous placebos are better than oral placebos. J Neurol. 2000;247(3):183-8.
9. Pace F, Maconi G, Molteni P, Minguzzi M, Bianchi Porro G. Meta-analysis of the effect of placebo on the outcome of medically treated reflux esophagitis. Scand J Gastroenterol. 1995;30(2):101-5.
10. Cho HJ, Hotopf M, Wessely S. The placebo response in the treatment of chronic fatigue syndrome: a systematic review and meta-analysis. Psychosom Med. 2005;67(2):301-13.
11. Ratcliff JD. New surgery for ailing hearts. Reader's Digest. 1957;71:70-3.
12. Dimond EG, Kittle CF, Crockett JE. Evaluation of internal mammary artery ligation and sham procedure in angina pectoris. Circulation. 1958;18:712-3.
13. Cobb LA, Thomas GI, Dillard DH, Merendino KA, Bruce RA. An evaluation of internal-mammary-artery ligation by a double-blind technic. N Engl J Med. 1959;260(22):1115-8.
14. Shapiro AK. A historic and heuristic definition of the placebo. Psychiatry. 1964;27:52-8.
15. Wolf S. The pharmacology of placebos. Pharmacol Rev. 1959;11:689-704.
16. McDonald CJ, McCabe GP. How much of the placebo 'effect' is really statistical regression? Stat Med. 1989;8(10):1301-2.
17. Kienle GS, Kiene H. The powerful placebo effect: fact or fiction? J Clin Epidemiol. 1997;50(12):1311-8.
18. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med. 2001;344(21):1594-602.
19. Hrobjartsson A, Gotzsche PC. Placebo treatment versus no treatment. Cochrane Database Syst Rev. 2003;(1):CD003974. Update in Cochrane Database Syst Rev. 2004;(3):CD003974.
20. Hrobjartsson A, Gotzsche PC. Placebo interventions for all clinical conditions. Cochrane Database Syst Rev 2004(3):CD003974. Update of Cochrane Database Syst Rev. 2003;(1):CD003974.
21. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. J Intern Med. 2004;256(2):91-100.
22. Papakostas YG, Daras MD. Placebos, placebo effect, and the response to the healing situation: the evolution of a concept. Epilepsia. 2001;42(12):1614-25.
23. Ader R. The role of conditioning in pharmacotherapy. In: Harrington A, editor. The placebo effect: an interdisciplinary exploration. London: Harvard University Press; 1997.
24. Voudouris NJ, Peck CL, Coleman G. Conditioned response models of placebo phenomena: further support. Pain. 1989;38(1):109-16.
25. Voudouris NJ, Peck CL, Coleman G. The role of conditioning and verbal expectancy in the placebo response. Pain. 1990;43(1):121-8.
26. Montgomery GH, Kirsch I. Classical conditioning and the placebo effect. Pain. 1997;72(1-2):107-13.
27. Price D, Fields H. The contribution of desire and expectation to placebo analgesia: implications for new research strategies. In:

Harrington A, editor. The placebo effect: an interdisciplinary exploration. London: Harvard University Press; 1997.
28. Kirsch I. Specifying nonspecifics: psychological mechanisms of placebo effects. In: Harrington A, editor. The placebo effect: an interdisciplinary exploration. London: Harvard University Press; 1997.
29. Morris D. Placebo, pain, and belief: a biocultural model. In: Harrington A, editor. The placebo effect: an interdisciplinary exploration. London: Harvard University Press; 1997.
30. Schachter S, Singer JE. Cognitive, social and physiological determinants of emotional states. Psychol Rev. 1962;69:379-99.
31. Benedetti F, Arduino C, Amanzio M. Somatotopic activation of opioid systems by target-directed expectations of analgesia. J Neurosci. 1999;19(9):3639-48.
32. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. JAMA. 2002;287(5):622-7.
33. Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H. The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review. Health Technol Assess. 1999;3(3):1-96.
34. de la Fuente-Fernandez R, Stoessl AJ. The placebo effect in Parkinson's disease. Trends Neurosci. 2002;25(6):302-6.
35. Rowbotham DJ. Endogenous opioids, placebo response, and pain. Lancet. 2001;357(9272):1901-2.
36. de la Fuente-Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Science. 2001;293(5532):1164-6.
37. Thomas KB. General practice consultations: is there any point in being positive? Br Med J (Clin Res Ed). 1987;294(6581):1200-2.
38. Vase L, Robinson ME, Verne GN, Price DD. The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients. An empirical investigation. Pain. 2003;105(1-2):17-25.
39. Egbert LD, Battit GE, Welch CE, Bartlett MK. Reduction of postoperative pain by encouragement and instruction of patients. A study of doctor-patient rapport. N Engl J Med. 1964;270:825-7.
40. Gryll SL, Katahn M. Situational factors contributing to the placebos effect. Psychopharmacology (Berl). 1978;57(3):253-61.
41. Gracely RH, Dubner R, Deeter WR, Wolskee PJ. Clinicians' expectations influence placebo analgesia. Lancet. 1985;1(8419):43.