TOWARDS CONTEMPORARY NEUROETHICS: WHY DOES IT MAKE SENSE TO RE-DEFINE PLACEBO?

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ABSTRACT

The main message we are trying to get across throughout the article is that the placebo is not an inert entity but instead it has a potential of subjective interpretation, a healing potential of its own, over and above that of any healing potential of the medication per se. Such healing potential is greatly dependent on how strong the interpretation value in being healed is that is created by the doctor. In this regard, we are also arguing that there are myriads possibilities at work that can influence how strong this interpretation value can become. The crucial role of contemporary medicine should be to expand the use of these interpretation effects even more and use them to help reduce any negative mental states that could continue to suppress the immune system after the initial healing. In other words, medicine should use the power of interpretation effect not only to re-arouse the immune system temporarily but permanently. In order to achieve a complete process of permanent healing it is necessary to take advantage of making full use of the powerful interpretation value through psychosocial context. It is possible to do that beyond the usual “sugar pill” through evidence based approach – a science of compassionate care! By introducing the new operational placebo definitions, we clearly show that the human mind (unconscious and conscious) is an inevitable substance involved in the Healing Process. The terms “placebo”, “placebo effect”, and “placebo response” are re-defined into the new working definitions. We explain how there is no more distinction (duality) such as body / mind, specific / nonspecific or health / disease, which offers new insights for future directions in contemporary Neuroethics.

KEY WORDS

placebo, bioelectromagnetics, evidence-based medicine, compassionate care, neuroethics

CLASSIFICATION

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INTRODUCTION

More than 50 years ago a revolutionary book titled “Introduction to a Submolecular Biology” announced the crucial importance of quantum physics in biological systems [1]. Less than fifteen years later research in biophysics showed that electromagnetic frequencies as energetic signaling mechanisms are one hundred times more efficient and incredibly faster in transmitting information from the environment compared to the chemical signals such as hormones or neurotransmitters [2]. Energies like microwaves, radio frequencies, extremely low frequencies, sound frequencies, and scalar energy have shown to have a significant influence on each aspect of biological regulation. Indeed discovery that quantum physics but not Newtonian laws regulate molecule movements, which in addition generate life has offered further support of previous findings [3].

Despite the fact that many of pioneering scientific reports in the past sixty years have revealed the importance of those “invisible” forces of electromagnetic spectrum and were even published in peer reviews, these finding were somehow neglected [4-11]. Many professional and locally produced devices have been constructed for research purposes in order to manipulate experimental conditions by exposing the living organisms to different ranges and frequencies of electromagnetic fields [12]. In one experimental study, the germination and growth of Lemma Minor by exposure to square pulse and 16 Hz sinusoidal magnetic fields revealed statistically significant differences [13].

Back to the very beginning of the humankind, it is not that hard to understand that culture is deeply embedded into human biology because of perceptual and attentional processes [14, 15]. Speaking about old primitive societies, they had long healing ceremonies and very complex rituals that sometimes lasted even more than a week [14]. Such meaningful healing strategies in primitive cultures were extremely impressive and respected for they were capable to induce powerful psychological (symbolic) component of the healing process, nowadays known as psychosocial context or meaning response [15]. Rituals might trigger subjective expectations of different emotional states: joy, anxiety, relaxation, altered states of consciousness through biased attention. Attentional biases can influence what information people prefer to focus upon. Indeed subjects with chronic pain and emotional problems show increased attention to information regarding their concerns [16, 17]. This bias in attention accompanied by emotional states and perceived from the cognitive perspective corresponds to hypervigilance [18]. Cognitive self-evaluation about amount of reported failures in memory and attentional domains is a good predictor of vigilance performance in complex tasks [19].

Anxiety modulates attention [20], in particular trait anxiety modulates top down, executive control network [21] while, state anxiety is more responsible for bottom up, alerting/orienting attentional networks [22]. Furthermore, in a computer-based neurocognitive test using the ANTI-V paradigm individual differences in vigilance performance were measured. A step-wise multiple regression analysis showed that vigilance performance (Signal Detection Theory – SDT indices of Vigilance), were predicted by cognitive and somatic state anxiety, but not trait anxiety [23]. Under negative psychological states usually present in subjects with health problems, it is obvious that their hyper-vigilant attentional focus depends on the level of concerns in how to get well again. In this regard, psychosocial context through a compassionate care can become an important healing determinant.

Contemporary medicine (evidence-based) has on the other hand developed scientific methods and highly sophisticated technology, which enables it to be more successful in the pharmacological and physiological component of the healing process. In his doctoral dissertation, Getz highlights an interesting topic that fits well with the concerns of Heidegger
and Foucault about the sophisticated technology. He says: “Can it be that professionals as well as lay people are currently becoming increasingly distracted and desensitized, as a result of medical technology’s particular way of enframing the human condition, in such a way that we lose sight of the essence of what it means to be human, in sickness and in health?” [24; p.113].

For our discussion, it is important that the placebo/nocebo response is an integral component of every treatment, and can not be avoided in even the most modern, sophisticated evidence-based medical treatment. Both the modern medicine and the primitive treatments of our ancestors share the same integral component of the healing process: the “nonspecific” component of the treatment. If we accept that, the history of medicine was more or less the history of the placebo response [25] than we can assume that the modern medical treatment has evolved from the placebo treatment, or to put another way, the “specific” factors have evolved from the “nonspecific” ones. Furthermore, if the primitive - nonscientific healing of our ancestors had been so useless, or if “nonspecific” factors had not played an integral role in the healing process throughout history, it is very likely that humankind would not have survived those harmful “nocebo” treatments, and thus there would have been no modern evidence-based medicine [26, 27]. Taking into account above arguments, we can hypothesize that what we perceive and to what we narrow our focus of attention on, becomes important, meaningful and makes sense for our further understanding and interpretation.

In the present article we intentionally bypass the extensive overview of the Placebo literature. Instead, we introduce the brief history of Placebo definitions to better understand their metamorphosis and point out some contemporary concepts of this puzzling phenomena. In addition we re-define Placebo terms and propose three major premises as the future standards for Contemporary Neuroethics. In conclusions we discuss that the placebo phenomena is very real and natural, and that there is nothing supernatural in its process.

**METAMORPHOSIS OF HISTORICAL PLACEBO DEFINITIONS**

In Table 1 one can see how the term Placebo has changed from the late 18th century until the beginning of the third millennium [28].

It is important to note, that the definition from the 1785 was misquoted [25] and instead of “a common place method of medicine” the actual definition was “a common place method or medicine”. So the early definitions classify as placebo not only medicines or active drugs, but also other non-drug treatments and methods such as magic, psychotherapy, hypnosis ...

Early definitions did not define placebo as an inert substance until about 1950, when the double

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Definition of Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Medical Dictionary</td>
<td>1785</td>
<td>A common place method of medicine</td>
</tr>
<tr>
<td>Hooper’s Medical Dictionary</td>
<td>1811</td>
<td>An epithet given to any medicine, adapted more to please than to benefit the patient.</td>
</tr>
<tr>
<td>Dunglison; Dictionary of Medical Science</td>
<td>1874</td>
<td>“I will please” (from placebo) – A medicine usually prescribed rather to satisfy the patient than with any expectation of its effecting a cure.</td>
</tr>
<tr>
<td>Medical Lexicon</td>
<td>1881</td>
<td>Name for a medicine given by a doctor to a patient simply to satisfy the patient’s mind; usually of a harmless nature, e.g. water colored with cochineal (dried insects used as dye).</td>
</tr>
<tr>
<td>Standard Dictionary of the English Language</td>
<td>1895</td>
<td>Any harmless substance as bread pills, given to soothe a patient’s anxiety rather than as a remedy.</td>
</tr>
</tbody>
</table>
**Table 1.** (Continuation from p.336) Some dictionary definitions of Placebo.

<table>
<thead>
<tr>
<th>Century Dictionary</th>
<th>Year</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Chalmers Twentieth-Century Dictionary</td>
<td>1911</td>
<td>A medicine given more to humor or gratify a patient than to exercise any curative effect.</td>
</tr>
<tr>
<td>Pepper, O.H.P.</td>
<td>1948</td>
<td>The giving of a placebo… seems to be a function of the physician which, like certain functions of the body, is not to be mentioned in polite society.</td>
</tr>
<tr>
<td>Stedman’s Medical Dictionary</td>
<td>1953</td>
<td>An indifferent substance in the form of a medicine, given for the moral or suggestive effect.</td>
</tr>
<tr>
<td>Oxford English Dictionary</td>
<td>1953</td>
<td>A medicine given to humor rather than to cure the patient.</td>
</tr>
<tr>
<td>American Pocket Medical Dictionary</td>
<td>1953</td>
<td>An inert substance given as a medication.</td>
</tr>
<tr>
<td>Britannica World Language</td>
<td>1960</td>
<td>Any harmless substance given to humor a patient or as a test in controlled experiments. Anything said to flatter or please.</td>
</tr>
<tr>
<td>Webster’s 3rd New International Dictionary</td>
<td>1971</td>
<td>An inert medicament or preparation given for its psychological effect, esp. to satisfy a patient or act as a control in an experimental series.</td>
</tr>
<tr>
<td>Taber’s medical Dictionary</td>
<td>1971</td>
<td>1. Inactive substance given to satisfy patient’s demand for medicine. 2. Also used in the controlled studies of drugs. The placebo is given to a group of patients, and the drug being tested is given to a similar group; then the results obtained in the two groups are compared. Also, something tending to soothe or gratify.</td>
</tr>
<tr>
<td>Brewer’s Dictionary of Phrase and Fable</td>
<td>1981</td>
<td>An innocuous medicine designed to humor a patient, and which may have a beneficial psychological and physical effect.</td>
</tr>
<tr>
<td>Collins Dictionary of Medicine</td>
<td>1992</td>
<td>1) A pharmacologically inactive substance made up in a form apparently identical to an active drug that is under trial. 2) A harmless preparation prescribed to satisfy a patient who does not require active medication.</td>
</tr>
<tr>
<td>Oxford Concise Medical Dictionary</td>
<td>1999</td>
<td>A medicine that is ineffective but may help relieve a condition because a patient has faith in its powers. New drugs are tested against placebos in clinical trials: the drug effect compared with the placebo response, which occurs even in the absence of any pharmacologically active substance in the placebo.</td>
</tr>
<tr>
<td>Dorland’s Medical Dictionary, 29th edition</td>
<td>2001</td>
<td>Any dummy medical treatment; originally a medical preparation having no specific pharmacological activity against the patient’s illness or complaint given solely for the psycho-physiological effects of the treatment. More recently, a dummy treatment administered to a control group in a controlled clinical trial in order that the specific and nonspecific effects of the experimental treatment can be distinguished – i.e. the experimental treatment must produce better results than the placebo in order to be considered effective. Active placebo, impure placebo: A substance having pharmacological properties that are not relevant to the condition being treated.</td>
</tr>
</tbody>
</table>
blind randomized clinical methodology appeared in the literature. To conclude, the metamorphosis of the term “Placebo” goes as follows: from the original definition placebo, which included not just medicines (substances) but also methods, later on the definitions of the term Placebo were limited only to medicines and further to inert substances.

Finally, due to the new scientific research methodology, the definition of Placebo was revised. Today again, any method of the treatment is proposed to be added to the definition in order to provide a broader concept, which includes physiological as well as psychological treatments (i.e. active medication, surgical procedures and psychotherapy).

Shapiro’s phenomenological definition

“A placebo is any therapy (or that component of any therapy) that is intentionally or knowingly used for its nonspecific, psychological, or psycho-physiological, therapeutic effect, or that is used for a presumed specific therapeutic effect on a patient, symptom, or illness, but is without specific activity for the condition being treated. A placebo, when used as a control in experimental studies, is a substance or procedure that is without specific activity for the condition being treated” [25; p.41]. Oddly enough, how can something causing an effect be non-specific?

CONTEMPORARY PLACEBO DEFINITIONS

If men define situations as real, they are real in their consequences, is a well-known Thomas theorem that was formulated in 1928 as a fundamental Law of Sociology [29]. Curiously how authors with their theorem, perhaps unknowingly at that time were coming close to many of the modern definitions of placebo. The definitions proposed by some of the contemporary researchers such as Barrios, Benedetti, Di Blassi, Kirsh, Moreman and others agreed that perhaps the term “placebo effect” and “nonspecific effect” have some negative connotations and should be replaced by some more proper terms. Barrios points out that the placebo response is based on the power of belief or expectation [30]. Benedetti shows that the classic concepts of “placebo effect” are too restrictive, that we need a broader term, namely the “medical context”. He argues that the context effect (meaningful induced expectations) can help to explain the placebo effect through the doctor-patient interaction [31]. Di Blassi and colleagues proposed that we should use “placebo effect” interchangeably with the term “context effect” [32].

One of the leading authorities in the field of Placebo research Irving Kirsch, also the author of the Response expectancy theory [33] noted that when a person expects something to happen that is inconsistent with the common predicted pharmaco-dynamic properties of a drug, the effect of subject’s expectations can prevail that of the medication. He defines response expectancies as anticipations for the occurrence of non-volitional responses and believes that they are the most important mediator in the placebo effect. Furthermore, according to his immediacy hypothesis [34] he suggests that an expectation for a subjective experience leads directly to that subjective experience (expectation of anxiety directly causes anxiety). In an interesting research design Kirsch and Wiexel elegantly showed how different is clinical setting from the research setting [35]. Moerman explains how meaning interacts with the illness and the healing process. He proposes the term “meaning response” as the physiological or psychological effect of meaning [14].

THE NEED FOR THE NEW PLACEBO DEFINITIONS

So far, we recognized that there is no need any more for the use of the term placebo and placebo effect. Furthermore, there is no need even for using such terms as “nonspecific”,
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“inert” or “inactive”. Therefore, we propose new working definitions of Placebo, Placebo treatment, Placebo effect and Placebo response to replace the previous ones [26, 27]:

- “Interpretation Potential” (IP) instead of “Placebo”,
- “Interpretation Value” (IV) instead of “Placebo Treatment and/or Therapeutic Treatment”,
- “Interpretation Effect” (IE) instead of “Therapeutic Effect” and/or “Placebo Effect” and
- “Interpretation Response” (IR) instead of the term “Placebo Response/Treatment Response.

According to our proposed definitions, contemporary Neuroethical standards should stand on the following three major premises [26, 27]:

- Interpretation Potential (IP) in relation with the psychosocial context and its interpretation effects (IE) is a powerful healing determinant, having an effect in every treatment,
- because of its “unpredictable” bidirectional nature and simultaneous interaction with the pharmaco-dynamic properties of a drug/treatment, this interpretation effect must be accompanied with the “Science of Compassionate Care” in every treatment,
- Interpretation Response (IR) in the form of a well controled Interpretation Effect (IE) is more powerful and long lasting than Interpretation Value (IV) per se.

DISCUSSION AND CONCLUSIONS

Instead of thinking in dualities, such as body and mind, specific and nonspecific, active and inert, which were and still are the common concepts in defining the placebo and the placebo effects, we rather changed the working definitions in such a way that polarity was eliminated. Instead, we reorganized the terms into new concepts: interpretation potential (IP), interpretation value (IV), interpretation effect (IE), and interpretation response (IR). In this way, the importance was found to be crucial on the part of the doctor-patient relationship that distributed the healing power between the external factors and the internal locus of control through interpretation effects of individual understanding and meaning. In our opinion, the re-defined Placebo definitions as proposed above suggest that it seems wise to rethink of their possible impact on future directions in neuroethics.

There is ample evidence supported by strong arguments claiming that it would be unethical to avoid Placebo effects [15]. Avoiding placebo effects means that we are avoiding real improvements of human well-being. Dorland’s Medical Dictionary from 2001 [28] demonstrates in Table 1 another conceptual inconsistency of traditional medical paradigm. While all drugs have to show they are better than placebo in order to be approved, there is one exception. Cancer drugs are never compared with placebo but instead these experimental drugs are always compared among themselves [36]. In oncology, placebo effect is regarded as unethical, but alleviating the negative psychological states with empathy and compassion could certainly help to reduce the immunosuppression thus helping patients to get well again [30]. It is now or never. Mind body interactions indicate no differences between pharmaco-dynamic and psychosocial effects, or to put another way cognitive affective events induced in a psychosocial context can trigger similar mechanisms as those activated by drugs [37]. If medical society will recognize the opportunity to define placebo as proposed above, then the art of a healing compassion can become a science - A science of compassionate care [26, 27]. By doing so the non-specific effect will become specific and the treatment will have the added effect. This effect is “gratis” and should be regarded in the future as psychosocial evidence based interpretation effect. By contrast, if medical society will insist on old definitions of Placebo in terms of duality then others will continue to manipulate and take advantage of the Placebo phenomenon. Let us here conclude with the last sentence from the book “The Powerful Placebo: from ancient Priest to modern Physician”: “If the non-specificity
of the placebo effect can be rendered specific and its strength can be unleashed, the terms placebo and placebo effect can appropriately disappear into medical history.” [25; p.237].

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PREMA S UVREMOJ NEUROETICI: ZAŠTO JE SMISLENO REDEFINIRATI PLACEBO?

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SAŽETAK

KLJUČNE RIJEČI
placebo, bioelektromagnetizam, medicina temeljena na dokazima, suosjećajna njega, neuroetika