ETHICAL IMPLICATIONS OF PLACEBO USING IN CLINICAL PRACTICE

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Abstract: Many authors consider that placebo history is in fact the history of medicine and this is probably true to a large extent. The placebo effect is still extremely used in clinical activity, between 41% and 99% of clinicians worldwide using this intervention. One definition of placebo is: “A medicine or procedure prescribed for the psychological benefit to the patient rather than for any physiological effect”. If we consider both placebo interventions and administration of placebo substances, it is impossible to separate patient-physician interaction (including the environment where the physician performs his/her activities or where the interaction takes place) from placebo effect. There are two extreme poles as regards placebo use in clinical practice: first pole – anything useful for patient’s health is good, therefore, as long as we do good to the patient, we can use any placebo variant and, the second one – the patient must know everything about his/her treatment and placebo use is absolutely counter indicated/forbidden without patient’s absolute/explicit agreement, but even in this case using placebo effect is rather non-ethical and useless. It is so difficult to separate the very complex interaction between physician-patient from placebo effect as currently defined. Therefore, we can simply renounce, up to the moment when we will have a complete and coherent definition of this effect, to use the concept of “placebo in clinic practice” because for the moment this concept doesn’t bring much clarity to the field. It is the authors believe that pushing the principle of patient’s autonomy into overdrive risks to pervert the fundamental aspect of medicine - trust and also to push this relationship into a kind of commercial relationship, it is true, one of a somehow special type.

Keyword: ethics, placebo.

The ethical environment we live in represents the surrounding climate of ideas about how to conduct a “proper” life (“proper” life meaning what most people at a certain time along history consider at least adequate at most exceptional). Basically it determines what we find acceptable or unacceptable, admirable or contemptible. In the end it gives us our standards, both formal (legislation, codes of behaviour such as Hippocratic Oath and so on) and informal (our day to day standards of behaviour as defined by common sense). The ethical environment obviously varies significantly throughout times and cultures, and any story about human nature (including ethical views) in different historical times is the result of the interaction between human nature and the contemporary climate (philosophical, cultural, social and so on) at that specific time.

During the 18-th century there was no ethical constraint to perform a surgical procedure without obtaining the informed consent, which today would be something totally unacceptable in most countries. Also, it is totally acceptable to perform a shaman session in Mongolia today and completely unacceptable and illegal to do the same thing in USA - even though there was a phase I study into the effectiveness of shamanism for chronic face and
According to dictionaries (http://www.oxforddictionaries.com/definition/english/placebo), placebo is: “A medicine or procedure prescribed for the psychological benefit to the patient rather than for any physiological effect”.

A broad and neutral definition of placebo would be “a substance having no known medicinal properties used to treat a patient” (4) or “an inert, deceptive treatment given as if it were a real treatment” (5). There are also many other definitions of different medical regulatory bodies such as American Medical Association which uses a somehow narrow definition: “placebo intervention represents an intervention that the physician believes has no specific pharmacological, biochemical or physical mechanism of action according to the current standard of knowledge, upon the condition being treated” (6). Some authors (5) consider useful to differentiate between pure (the use of an inert substance or method) and impure placebo (substances or methods that do have known pharmacological or physical activity, but used for different diseases/conditions, it is supposed to work - e.g. prescribing vitamins in depression). Moreover, we can separate placebo interventions from placebo as an inert substance.

If we consider both placebo interventions and administration of placebo substances (either pure or impure placebo), it is impossible to separate patient-physician interaction (including the environment where the physician performs his/her activities or where the interaction takes place) from placebo effect. Practically for such complex interventions, it is impossible to separate placebo interventions from non-placebo ones and it is almost impossible to find actions, interventions and treatments that do not contain elements falling within placebo effect as well. Things entirely uncontrollable from practical and ethical points of view contribute to “contamination” of each action, intervention or medication with placebo effect. In this way, administration of a medicine in a hospital has a higher effect as compared to administration of the same medicine at home (7). Is it ethical in this case to point out that even this fact will increase the dimension of medicine efficiency? From ethical point of view, pushing things into overdrive, the patient should be informed about that in order not to risk contaminating the pure medicinal action with placebo effect and the patient should have quasi-complete ownership of information necessary for giving informed consent. Things such as age and gender of the respective physician, whether he has a beard or whether he/she wears glasses, holding higher degree in medicine (for example primary physician as compared to trainee physician), coming for the visit alone as compared to coming for the visit accompanied by 5 resident physicians and 15 students etc. etc, have a certain placebo effect (even at the moment it is difficult to say what the dimensions of the effect are), are often (knowingly or unconsciously) manipulated by the physician with a view to increasing therapeutic efficiency. The method of prescribing medication, the cheap ball pen or the expensive pen used for writing the treatment are also aspects that contribute to the ritual significance of medicine and have a therapeutic effect. Also, it is likely that the same medicines prescribed under different situations and by different physicians (for example by an older physician, man, having beard, wearing glasses and holding an university professor degree, within a hospital, during a visit when the respective professor is accompanied by 5 resident physicians and 15 students, all of them watching respectfully the professor, as compared to a female physician, young, without white coat and prescribing medication at patient’s home) should act simply differently or with different intensity. Of course, under certain situations some of these aspects may act as placebo effect and under other situations as nocebo one, depending on social, cultural, educational etc. features of the respective patient. The question is how we can separate placebo effect (for the purpose of an ethical action as regards comprehensive information of the patient upon this effect) within the infinity of aspects representing patient-physician interaction? Furthermore, if the respective physician knows the neurobiology of the placebo mechanism, are the definitions above having as common element that the respective substance administered as placebo is physiologically inert still valid? Placebo may really be an inert substance, but its administration generates neurobiological changes. Is placebo an “inert” substance in this case? A study (8) of patients suffering from depression comparing changes in cerebral metabolic rate (positron emission tomography) between placebo responders and fluoxetine responders (with 6 weeks of treatment) reported considerable overlap in altered brain areas. These included cortical increases (dorsolateral prefrontal, inferior parietal, posterior insula, and posterior cingulate) and limbic–paralimbic decreases (subgenual cingulate cortex, hypothalamus, thalamus, sensory insula, parahippocampus) in metabolic activity. It is worth noting, however, that responders to fluoxetine had changes in additional areas, as well.

Another study (9) that used positron emission tomography (PET) to assess the competition between endogenous dopamine and [11C] raclopride for D2/D3 receptors (a method allowing identification of endogenous dopamine release) found that placebo administered in Parkinson disease activates endogenous dopamine in the striatum of parkinsonian patients. This does not mean that placebo medication works similarly to medication specific to a certain disease (although this hypothesis cannot be eliminated either), but highlights that, at least from neurobiological point of view, placebo is not at all inactive.

In all cases described above we can consider that an aspect usually associated with placebo- that is a degree of deception probably need to be at work in order for placebo-action to take action. Also in this case we can
wonder to which extent it is deliberately deceit. As, anticipating to a little extent, one of the ethical problems raised by placebo use in clinic is actually that one of the ethical principle of medicine – namely to be sincere with the patient – is infringed. On the other hand, sincerity and offering information to the patient are on a continuum and we believe it is practically impossible to be fully sincere (if we understand by sincerity offering complete information to the patient). It would sound at least strange to tell a patient as follows when we consult him/her: “I am 45 years old, I am a man, I am wearing white coat and I will prescribe you a blue and large medicine working as follows: full description of the working mechanism. However, I must warn you that it is possible that by a placebo effect my physical and demographical data might influence the therapeutic results and, also, besides the intrinsic working mechanism, the colour and size of the medicine have a placebo effect”.
All these arguments make us consider that we must be very circumspect against standard definitions of placebo effect. In fact, if we consider all aspects presented above, we can simply state that placebo effect cannot be separated from practical clinical activity.
On the other hand, if we use definitions and if we infinitely relativize things, we cannot progress a lot. This is why we will use the following placebo definition below: “a substance having no known medicinal properties given at is a real treatment (4).”
The placebo effects are equally important in clinical research and in clinical practice as well.
The ethics of placebo use in clinical research exceeds the scope of this paper, so we will concentrate upon ethical issues concerning placebo use in clinical practice, using the definition proposed above, but being at the same time reserved as regards any definition upon placebo effect in clinic.

**Placebo in Clinic:**
There are two extreme poles as regards placebo use in clinical practice: first pole – anything useful for patient's health is good, therefore, as long as we do good to the patient, we can use any placebo variant and, the second one – the patient must know everything about his/her treatment or/and placebo use is absolutely counter indicated/forbidden without patient's absolute/explicit agreement, but even in this case using placebo effect is rather non-ethical and useless. Of course, between these two extreme variants there is infinity of combinations. Finally, the physician's decision to use placebo or not (or any combination between these 2 extreme variants) depends on the ethical principles of the respective physician and on the legislative framework where the respective physician performs his/her activity. As regards ethical principles where the respective physician performs his/her activity, there are a few important philosophical-ethical schools (10) of thought: Axiological ("Value is any object of any interest."), Utilitarian Ethics (the broadest meaning of utilitarianism would include any kind of ethics that stresses the results of moral attitudes, volitions and activities – namely to do the best for most people), Naturalistic Ethics (the naturalist ethicist believes that ethical statements may be true and capable of verification), Analytic Ethics ("to critically examine the logics of linguistic discourse and to work out an explanation of how various meanings are best expressed in linguistic communication"), existential and phenomenological Ethics ("to be a free and real person, one must commit oneself, make a choice at the major crossroads of life"), in order to list only the most important ones and without pretending to have overviewed great ethical concepts. It is of course besides the scope of this article to overview ethical theories of these great schools of thought, but, in principle, we all perform our activities under various combinations of these schools of thought.
Of course besides each physician's philosophical principles, there are also legislative aspects under which we perform our activities. But legislation certainly does not (fortunately) cover any aspect of medical attitude. We will discuss below the main arguments of the extreme schools of thought regarding this issue:

1. placebo use is ethically acceptable and even desirable
2. placebo use under any situation is non-ethical

As we suggested before, there is a multitude of intermediary variants between these extreme schools of thought. Finally, any ethical discussion about this subject must somehow accommodate the following ethical principles (11):

a. Respect for patient autonomy (patient must be informed and he/she must choose without coercion).
b. Trust (trust it is gained only by being completely honest all the time).
c. Beneficence (provider should look out for the best interest of the patient).
d. Non-malfeasance (never harm the well being of patients).

Combinations among the variables above are practically infinite.

**1. use of placebo is ethically acceptable and even desirable.**
The main arguments used by the partisans of this idea are, as forcibly presented by Foddy (12) under the following structure:

- **Placebo works.**
  A prominent and extremely quoted (13) study concludes: “35% of psychiatric patients in 15 separate clinical trials experienced some improvement in their symptoms when prescribed only inert medications”.
  A more recent study (14) found no significant placebo effect in the treatment of any symptom except for pain. Although for the time being the dispute is not absolutely clarified as regards placebo efficacy in general, there are significant data proving placebo efficacy related to treating psychological/physical symptoms accompanying somatic and psychiatric conditions (15, 16, 17): pain, anxiety and depression symptoms.
  -placebo represents safe medication as regards severe adverse effects
  Although for certain persons nocebo effect can occur (occurrence of adverse effects on placebo administration), there are no data to show that these adverse effects are serious and/or severe.
  Sometimes placebo is the best/the only treatment
  If there were be perfect treatments for each disease, placebo use would obviously be useless, non-ethical and condemnable. But such treatments do not exist for most diseases. As we presented above, placebo is efficient especially for the treatment of pain, anxiety and depression, conditions for which there are multiple
medicines having acceptable efficacy. In most cases, placebo treatment may not and should not be used. But in other cases the situation is more complicated. Such example can be extrapolated from frequent situations where from cultural point of view, a patient/group of patients have certain intensely positive expectations (expectations being probably one of the fundamental mechanisms based on which placebo works (18)) as regards certain procedures. For example, for persons suffering from depression in the rural environment in Romania there is a strong positive expectation as regards the efficacy of administrating a treatment by means of perfusion. These expectations have been strengthened to the same extent to which the treatment of these patients (sometimes covering tens of years) consisted in adequate (anti-depressive) medication and perfusions (placebo with physiological serum, glucose etc.) and vitamins (which in this case represented an impure placebo used as amplifier of the action of the base medication) as well. In this case it is almost impossible that such patient should be convinced that perfusions have no efficient pharmacological action for depression and, therefore, it is useless to administrate this treatment. Furthermore, the discussion does not imply to the same extent the ethics of placebo administration, as in this case the patient requests, considering he/she has necessary information (regardless the source they were obtained from – things previously said by other physicians, transmitted at cultural level etc.) to receive a certain treatment. Of course, in this case another ethical dilemma occurs: “is it ethical to administrate a substance that we know it has no therapeutic indications in a certain condition, although the patient was clearly helped by this approach in the past?”

Another question occurs immediately: “whether and how much a physician should explain to his/her patient that a certain medication for a certain suffering is useless, although this medication clearly helped him/her in the past?” Administration of certain antibiotics “on request” for a virosis is obviously a non-ethical attitude (although there may be a benefit for the patient on short term) as benefits on long term are dangerous both for the patient and from public health point of view (selection of more resistant species that can affect both the patient and the humanity in general, if the process is spread enough). But is it ethical to administrate some vitamins (in non-toxic doses) for a depressive patient, alongside of the administration of the “correct” medicine from medical point of view, vitamins which were clearly good for the patient, do not have any adverse effects and are accompanied by positive expectations, which are a fundamental aspect in administrating both placebo and any medication in general?

Another example is the case of patients, which are not at all a few, which simply say “Please do as you think it is best!” fully giving the physician all the responsibility and the burden of decisions.

Another example where placebo could be the best therapeutic solution is represented by depression cases where patients, for various reasons (cultural, fear of adverse effects or fear that they would become “dependent” on the medication – and there is a large number of such patients - (19)) do not want to take an adequate treatment, they do not want or do not afford to take a psychotherapeutic treatment, but they request “something made of plants”. Is it adequate in this case to send the patient home without any treatment, although we know that, on the other hand, if we offered a placebo treatment the chances of a positive response may be be consistent? Can’t in this case be named negligence the therapeutic abandonment of a suffering patient?

Also, how can we consider placebo use in war area for patients agonizing with pain and where there is no medicine and where placebo effect can work? Quoting Goldacre (20) “Henry Beecher, an American anaesthetist, wrote about operating on a soldier with horrific injuries in a World War II field hospital, using salt water because the morphine was all gone, and to his astonishment the patient was fine” we consider that no better example can be found as regards ethics of placebo use (of course, under selected situations), or even the necessity of using placebo under certain conditions.

In order to obtain a more consistent placebo effect, a degree of degree is seems to be necessary.

There are very interesting data in literature suggesting that placebo effect can work even outside deception (21). On the other hand other data suggest that placebo effect works more efficiently in cases where a degree of deceit is present (22).

2. placebo use under any situation is non-ethical, it has low efficacy and it is desirable not to be used ever. The main arguments used by the partisans of this position are (23):

- placebo infringes the informed consent and can represent the entrance gate to applying atrocities similar to the ones committed by physicians in Nazi concentration camps or the famous Tuskegee experiment (24).

- the placebo effect does not work most probably, the design of the studies having proved placebo efficacy is most often reduced from methodological point of view (14).

- placebo does not lack adverse effects, often dangerous both at individual and at epidemiologic level (inadequate prescription of antibiotics – to a great extent either on patients' request or for placebo purpose and the significant public health problem that could be created by occurrence of multi-resistant trunks (25)).

- placebo can be associated to an increased degree of under-treatment. Furthermore, in case of certain conditions renowned for low potential for therapeutic response such as irritable bowel syndrome (where 30-50% of patients do not respond to any treatment (26)) there is a risk that, knowing that a placebo treatment is available, not to use all diagnostic means necessary for identifying similar conditions (in incipient phase) but with severe, even lethal potential (in this case for example the onset of certain forms of colon cancer that may have initially the clinical form of an irritable colon).

- lose of patient's trust. Trust is the most important aspect on which any therapeutic relationship is based. Some authors made distinctions between lying and deception (27) suggesting that deception may be morally acceptable. However, this seems rather semantic and, as important authors (23) said: “Deceptive use of placebo conflicts with the values of veracity and trustworthiness, also meaning a violation of the norm of informed consent and the principle of respect for autonomy”. Another important author (28) pointed out the importance of the same principle: “Prescribing a (non-active or not-indicated)
drug without telling the patient is an infringement of trust by violating patient's autonomy”.

- another important argument is that the use of (a pure or impure) placebo medicine/intervention can maintain a patient in a role of a sick person. Also, a scenario for people suffering from psychiatric diseases accompanied by somatic symptoms (anxiety, depression, somatisation disorder, hypochondria – especially in hypochondria cases - “clinically marginal” the risk to transform a healthy person in a person who is healthy, but believes he/she needs care is significant. Moreover, placebo administration to persons coming with somatic complaints, but without suffering from any disease – a potentially huge group - about 15-20% of primary care consultations involving a physical symptom without likely organic disease (29, 30) represents a risk of iatrogenization of normality (it may be simpler to administer placebo to a person than to explain him/her that many symptoms may occur outside existence of any disease).

But besides one or another physician’s own thoughts, their activity should be based on existing laws or on the regulations of the medical body where the respective physician belongs. It is beside the scope of this article to overview the legislative literature relevant for this discussion. The paragraphs quoted by authors are in the legislation in force (31, 32, 33, 34, 35, 36). The word “placebo” is not mentioned in the current Romanian legislation, and the legislative framework is not clear about allowing or not the use of placebo and it does not expressly forbid placebo use, but it clearly stipulates that: “The patient is entitled to information for medical treatment”. “The main purpose of the physician profession is to ensure health by preventing diseases, promoting, maintaining and recovering the health of individual and society. For this purpose, throughout professional life, the physician must prove availability, correctness, devotion, loyalty and respect towards human being. Medical decisions will be taken considering patient's interest and rights, generally accepted medical principles, non-discrimination among patients, conserving human dignity, principles of ethics and medical deontology, care towards patient's health and public health.” We can implicitly conclude that it is difficult to legislate a concept which cannot be defined by definition within the law, which should not leave room for any uncleanness and for which spirit of the law comes first as compared to letter of law, so difficult to explain to profane as the placebo concept. Afterwards placebo is a corollary of medical profession, about which we do not clearly know whether it is always good or always wrong and it is enough that physicians use it whenever necessary, to the sick person's best interest.

Also and probably for this reason in the “Code for Medical Deontology of the Romanian College of Physicians” (37) the placebo word is not used at all and the text does not allow for clear conclusions to be drawn as regards placebo use being allowed or forbidden in clinical activity.

Authors’ Personal Opinion.

It is so difficult to separate physician-patient interaction from placebo effect as currently defined. Therefore, we can simply renounce, up to the moment when we will have a complete and coherent definition of this effect, to use the concept of “placebo in clinic practice” because for the moment this concept doesn't bring much clarity to the field.

Currently Romania is an extremely mottled country from economic, social and cultural points of view, and using only one approach for this problem would obviously be naive. As a general rule, the main principles of medical ethics are essential in medical practice and should be exercised all the time, without question. The troubles arise when there exists a tension between the principle of medical care. In authors' opinion, in cases of “rational parity”, the beneficence and non-maleficeance principles must prevail upon the principle of respect for patient autonomy but only under conditions where another fundamental principle is fulfilled: trust principle.

At the moment the Romanian legislation allows fulfillment of the model we propose.

Placebo effect is on a continuum – from complete lie (given a moral action) – male patient having a leg cut who is given serum and he is told he is given morphone to a female patient suffering from chronic cephalagia resistant to therapies and at which the “Professor” casts a “wise” look accompanied by a slight approval nodding his head and by imperially filling in a prescription (action that does not represent any lie in any respect and that does not represent a non-ethical action either) with some vitamins.

There are only extreme cases where placebo effect should not be used.

Authors believe that pushing the principle of patient's autonomy into overdrive risks to pervert the fundamental aspect of medicine - trust and also to push this relationship into a kind of commercial relationship, it is true, one of a somehow special type.

However, in order to do that, it is fundamental that patients’ trust in physicians should be regained, which is quite difficult for the time being, in a postmodern world with rather loose moral concepts (38, 39).

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