Placebo and Nocebo: Legal and ethical implications for nursing practice

Abstract

Aim: The purpose of this discussion paper is to contemplate on the placebo and nocebo phenomena providing legal, ethical and clinical implications for nursing practice.

Methodology: This is a critical review for which a selection of key references were used based on a critique of placebo and nocebo that provided a balanced discussion and evaluation of the strengths, weakness and notable features of the both terms.

Results-Discussion: From a legal point of view, there is a clear reference to the informed consent of the patient involved in the investigation, the way it is carried out and the conditions to be met for the conduct of a clinical study. In Greek legislation, the rights of the hospital patient are determined ex lege and the protection of the study participants by specific ministerial decisions. With regard to the moral aspect of the use of placebo, the Helsinki Declaration refers in specific articles to medical research which should promote respect for human beings and the protection of health. More recently rather than denying the patient essential treatment by using placebo, a new drug is tested against a drug which is known to be effective to check if the new drug is more effective or not.

Conclusions: The term 'placebo' refers to a pseudo-drug or procedure i.e. an inert treatment while 'nocebo' is a phenomenon where the symptoms of a condition unjustifiably worsen when the patient is dissatisfied with a treatment**.**

There are many views on the appropriateness of the existence and use of the placebo method. From a moral point of view, one could argue that it would be unfair to use it in some cases. Yet, in the authors' view, there should be a balance between conflicting opinions and whether these relate to ethics, religion or science per se. Neither the abolition nor the excessive and irrational use of placebo would in any way serve the direct interests of mankind.

Key words: placebo, nocebo, legal, ethical

1. INTRODUCTION

In modern medical research, placebo is an important methodological tool as it is a substance or treatment which is designed to have no therapeutic value, employed to check the usefulness of another substance (e.g. drug) in controlled experimental conditions (Finniss, 2018). There are various forms of use of placebo, such as ‘sugar pills’ and even sham surgery.

Yet, the use of placebo raises both moral and legal issues. From a moral point of view, research must be subject to ethical principles in order to respect health and life and the legal issues involve protection of human rights (Sommer et al., 2010).

In this context, the term has acquired two etymological concepts: as a medicinal product administered to a patient for the purpose of psychological support and relief rather than treatment of the patient's disease; and as an inactive substance which tests comparatively the usefulness of another (e.g. medicinal product) in controlled experimental conditions. Hence, the term placebo has a dual meaning i.e.: an inactive substance administered to the patient to satisfy his requirement for a medicinal product; or a non-specific, inactive medicinal product used as a means of testing a novice therapy suspected to be useful in a particular disease or condition (Colloca & Barsky, 2020).

In this context, the placebo phenomenon is a condition in which a patient improves while taking a substance that has no known effect on the problem they are facing.

Thus, the term ‘placebo’ refers to a pseudo-drug or procedure i.e. an inert treatment. The first use of placebo in English was during the 13th century, referring to the vespers for the dead in the Roman Catholic Church. Placebo is the first word in the first line of the first antiphon, Psalms 114:9. Yet, in its current use, the term was introduced in 1955 by Henry K. Beecher in his paper ‘The Powerful Placebo’ whereby the expression "placebo effect", contrasted with drug effects, suggesting that it occurred in about 35% of people (Beecher, 1955).

Historically, the term placebo was used for the first time in the 14th century. In the Middle Ages, professional fatalists were recruited, who received a high wage from the dead's relatives. Their job was to pretend regret and start the mourning squadron with the ninth verse of the 114th psalm, which refers to Latin "placebo Domino in Regione

Vivorum", which in English translates ‘I will thank the Lord in the land of the living’. Therefore, the term 'placebo' originates from the Latin term 'Placere', which means 'thank you', while simultaneously in England the term 'sing a placebo' was used in everyday language, meaning to flatter (Faasse & Martin, 2018).

According to Andreou and Bozika (2008), placebo is defined as the ‘treatment used more for the patient's pleasure than for the treatment of a disease’.

The term ‘placebo’ was officially introduced in medicine in 1955 by Henry K. Beecher, an anesthesiologist of the US military, who discovered the strength of placebo during World War II. Beecher's medical unit when it was short of morphine, a substance that relieves the pain, and his soldiers were in agony by the pain of their wounds, surprisingly noticed that when nurses administered saline intramuscularly, which was usual practice at the time, this acted as a sedative in restless patients. Due to this observation, after the end of the war, Beecher gathered a medical team at Harvard University to study the phenomenon. The findings of his study were capitalized in a publication in 1955, entitled ‘The All-Powerful Placebo’, which was further replicated in 15 studies and which concluded that one third of all patients could react positively to placebo (Beecher, 1955).

The publication of Beecher has done much to change the way clinical experiments are conducted in biomedicine. Nowadays, when any new drug is tested it must be compared with a placebo. Thus, in contemporary medical research, the use of placebo is a crucial research element, measuring the comparative effectiveness of a drug. Thus, medical researchers routinely divide patients into at least two random groups. In the first group of patients, they administer the test drug, while in the second group, a placebo is administered (Enck & Klosterhalfen, 2017).

In this way, authorization to a new drug could only be given if it has a much better effect than placebo, i.e. than a neutral substance that looks, tastes and appears like the test medicine. It should be stressed at this point neither group knows exactly what it is receiving, as both believe they are taking the actual treatment and that they are knowingly involved in a study of a new drug (Benedetti et al., 2020).

‘Double-blind placebo investigations’ are defined as those in which researchers conceal even from the surveying physicians which group of patients receive the

placebo and the test drug. Placebo can take many forms, i.e. a pseudo-drug with all possible routes of administration, physiotherapy, psychotherapy and even surgery, where in the placebo group only skin incision and mock surgery are performed (Hurst et al., 2020).

Why the placebo works

Many interpretations have been proposed to explain why a pseudo-drug has considerable effectiveness. In a study by Wiech (2016) of the University of Oxford, a group of Catholic Christians who regularly attended church were administered electrical stimulants causing pain. Yet, previously they were given half an hour to focus on either the image of the 'Praying Virgin' (Sasoferato painting particularly popular among Catholics) or 'Lady with Ermina' (Leonardo da Vinci painting, which resembles the previous one but is not Christian). The findings showed that believers who watched the 'Praying Virgin' felt less pain.

Also to be considered is a view of the placebo advocates who stress that the physician-patient interpersonal relationship plays an important role in the treatment. This is because respect for and confidence in the physician and vice versa is an important factor, because the patient's opinion on the physician is a key factor in the interpretation of the placebo phenomenon (Evers et al., 2018).

Although placebo operates without conscious awareness, its analgesic effects are often considered as a solely psychological phenomenon and its action may modulate certain brain areas. Therefore, it is important to investigate the placebo analgesic mechanisms so as to improve the design of future clinical trials and optimize therapeutic strategies (Medoff & Colloca, 2015). Under this light, understanding the psychological and brain mechanisms underlying placebo effects is thus important for understanding all kinds of treatments (Schafer et al., 2018).

The Nocebo Phenomenon

The opposite of placebo is nocebo and in Latin it means 'I will suffer'. The term nocebo was first used in 1961 by Walter Kennedy, who pointed out that the effect of a treatment could be more in the patient's mind than in the treatments/drug per se. Nocebo effect is a phenomenon where the symptoms of a condition unjustifiably

worsen when the patient is dissatisfied with a treatment. Therefore, Nocebo means causing disease or distress from a substance or process without a ‘specific’ effect as the person already believes it to be harmful. Nocebo should be distinguished from the undesirable effects of placebo, as the effect of nocebo may be chronic or transient even leading to death. Another view expressed is that 'the ability of placebo to cause side effects is called nocebo, which originates from Latin i.e. 'I will be unhappy' (Colloca & Barsky, 2020).

In this context, a nocebo effect occurs when negative expectations regarding a treatment cause the treatment to have a more negative effect than anticipated otherwise. The nocebo effect has been called the lesser-known ‘evil twin’ of the placebo effect; just as the placebo effect creates a positive response or healing effect from an inert or sham treatment, the nocebo effect creates a negative or detrimental response (Polich et al., 2020).

2. AIM

The purpose of this discussion paper is to contemplate on the placebo and nocebo phenomena providing legal, ethical and clinical implications for nursing practice.

3. METHODS

This is a critical review for which a selection of key references were used based on a critique of placebo and nocebo that provided a balanced discussion and evaluation of the strengths, weakness and notable features of the both terms. For this reason, 25 key references were selected from both national and international literature on the basis of their merit, content and their overall contribution to the public debate on the role of placebo and nocebo in contemporary health care practice.

4. RESULTS AND DISCUSSION

4.1 Legal Issues and placebo

Placebo as part of scientific research should have been adapted to the rules of Greek and European legislation. In Articles 12, 24, 25 and 26 of the Rules of Procedure

(Law 3418/2005) the Code of Medical Ethics makes clear reference to the informed consent of the patient participating in research, to the way scientific research is conducted, to the conditions to be met for scientific research, but reference is also made to non-therapeutic biomedical research (Law, 3418/2015).

'Article 12. Consent of the informed patient.

1. The doctor may not perform any medical operation without the patient's prior consent.

2. The conditions for the patient's valid consent are as follows:

(a) to be provided after complete, clear and comprehensible information (in accordance with the preceding Article 1.)

b) the patient has the capacity to agree.

(aa) If the patient is a minor, consent shall be given by those exercising parental responsibility or having custody of the patient. However, account shall also be taken of his or her opinion, where the minor, in the opinion of the doctor, has the age, mental and emotional maturity to understand the state of his or her health, the content of the medical operation and the consequences or risks of that act. In the case referred to in Article 11(3), the consent of the persons exercising parental responsibility for the minor shall always be required.

(bb) If the patient does not have the capacity to give consent, the consent to the performance of a medical operation shall be given by the judicial officer, if one has already been designated. If there is no judicial support in situ, consent shall be given by the patient's relatives. In any case, the physician must endeavor to ensure the voluntary participation, partnership and cooperation of the patient, in particular that of the patient who understands the state of his health, the content of the medical operation, the risks, consequences and effects of the operation.

(c) Consent shall not be the result of an error, fraud or threat and shall not conflict with good morals.

(d) The consent shall cover the medical operation in full both in the specified context and at the time of its execution.

3. Exceptionally, no consent is required:

(a) in urgent cases where an appropriate consensus cannot be reached and there is an immediate, absolute and urgent need for medical care;

(b) in the case of suicide attempts; or

(c) if the parents of a minor patient or the relatives of a patient who cannot for any reason consent or other third parties with the power of consent for the patient refuse to give the necessary consent and there is a need for immediate intervention in order to avoid risk for the life or the health of the patient.

In particular, Article 12 refers to the consent of the informed patient in medical practice and analyzes the conditions of the valid consent to that consent, i.e. the full, clear and understandable information which the doctor must provide to the patient before any medical act is taken. Reference is also made to minors, where consent is given by those who practice parental responsibility or custody, and where the patient does not have the capacity to consent, a judicial officer is appointed to give his consent.

Consent shall not be required in urgent cases where appropriate consent cannot be obtained, in the event of a suicide attempt and in the case where parents of a minor patient refuse to give the necessary consent and there is a need for immediate intervention.

'Article 25. Clinical research with new drugs or new diagnostic and therapeutic methods.

1. Clinical studies with new medicinal products or the application of newer diagnostic and therapeutic methods are permitted if:

(a) comply with the general specifications and procedures as defined by the competent bodies of the European Union;

(b) there are strong scientific indications that their use or their application will increase the chances of survival or remediation of the health or relief of patients suffering from such diseases and the benefits will be significantly greater than the potential for adverse reactions;

(c) all the conditions of the previous article are met.

2. If the patient refuses to participate in such a study, the doctor must take all steps to ensure that the patient's refusal does not adversely affect the relationship between the doctor and the patient.

3. A doctor may not use new medicinal products of unknown efficacy or apply new therapeutic or diagnostic methods of unknown effect without strict application of the rules governing the design and implementation of clinical studies. It recognizes as a fundamental rule that possible diagnostic or therapeutic value, for the benefit of the patient, takes precedence over scientific knowledge, which may be obtained from new medicinal products or new therapeutic or diagnostic methods.

In Article 25, reference is made to clinical research with new medicinal products or new diagnostic and therapeutic methods and the conditions for the authorization of a clinical study are indicated. However, it should be emphasized that the doctor may not use new medicines of unknown efficacy without strict application of the rules governing the design and implementation of clinical studies.

'*Article 26. Non-therapeutic biomedical research.*

1. Medical research in humans shall be permitted, for purely scientific reasons, under the conditions laid down in Article 24 and in addition to the following conditions:

(a) the medical investigator considers the protection of the life, health and dignity of the person in whom the research is carried out, which is protected in the interest of science or society, to be his or her greatest task;

(b) the medical investigator shall take all necessary measures to ensure that the individual's participation in the research is carried out without any consideration.

2. The medical investigator shall discontinue the investigation if, in his judgment, its continuation may result in serious, dangerous or simple harm to the individual.

In Article 26, in addition to the conditions of Article 24 that must be met, to additional conditions such as the protection of the life of the person under investigation, the non-

consideration of the individual and the termination of the investigation where its continuation may cause any harm to the person (Law 3418/2005; Retsas, 2020).

Article 5 of the UNESCO Universal Declaration on Bioethics and Human Rights, on autonomy and individual responsibility, states that the autonomy of individuals in decision-making, if they assume their responsibility and respect the autonomy of others, should be respected. Special measures to protect their rights are provided for those who are incapable of identifying themselves (ten Have, 2006).

Articles 16 and 17 of the Rules of Procedure (Law 2619/1998), read as follows:

'*Article 16: Protection of persons under investigation*.
An individual investigation may be conducted only if all of the following conditions are met:

(i) There is no alternative of comparable effectiveness to human research.

(ii) The potential risks to which the person will be exposed are not disproportionate to the potential benefits of the investigation.

(iii) The research program has been approved by the competent body following an independent evaluation of its scientific value, including an assessment of the relevance of the research purpose and study, by groups of practitioners of various disciplines, as to whether this is ethically acceptable.

(iv) The persons under investigation have been informed of the rights and safeguards laid down in the law for their protection.

(v) The necessary consent provided for in Article 5 has been expressly given, in particular and documented. Such consent may be revoked at any time.

The above articles analyze the conditions for conducting a clinical study and stress that the subject, after being informed of the nature, importance, consequences and risks, shall provide written consent. The participant shall retain the right to withdraw from the study at any time by withdrawing consent, without being penalized in any way or form (Council of Europe, 1997).

4.2 Ethical considerations regarding the use of the Placebo

The Helsinki Declaration is the main reference of the World Medical Community to ethical questions in research into human beings. Article 29 on the benefits, risks and efficacy of a new method stresses that these should be controlled against those with the best current prophylactic, diagnostic and therapeutic methods. This does not preclude the use of placebo or non-treatment in studies in which there is no evidence of prophylactic, diagnostic or therapeutic method. It should be noted that the use of placebo in studies which have no proven prophylactic, diagnostic or therapeutic method is not excluded (Ballantyne & Eriksson, 2019).

Furthermore, article 8 states that: Medical research is subject to ethical principles that promote respect for human existence and protect the health and rights of people. Some research populations are vulnerable and need protection. Account should be taken of the specific needs of those with economic problems. Particular attention is required for those who are unable to give or refuse consent to the investigation (for themselves) for those who may give consent under pressure, for those who will not personally benefit from the research and for those for whom the research is linked to routine medical care (Wartolowska, 2019).

Reference is therefore made to medical research which is subject to ethical principles that promote respect for human beings and protect health. In these lines, article 9, states that those who plan to carry out research on human beings should take into account the ethical, legal and regulatory provisions of their own country and the relevant international ones. No local morality, legal or regulatory provision is legitimized if it weakens any precautions defined by this declaration concerning the human experimental substrate. It is noted that researchers who carry out research on human beings should have regard to domestic and international ethical provisions. No moral regulatory provision is legitimized if it weakens any precautions laid down in the declaration on the human experimental population (Isawa et a;., 2020).

The main concern in the double-blind placebo-controlled studies is that they put the patient receiving placebo at increased risk, and morality depends on the severity of the study condition and the possibility of causing irreversible damage from delayed treatment. The Food and Drugs Administration states that the use of placebo is inappropriate when treatment is available which is known to prevent serious harm,

such as death or irreversible morbidity in the population concerned. When there is no serious harm, the use of placebo is moral (Mestre, 2020).

In Canada, following the agreement of the Canadian Institute for Health Research, the Council of Science and Engineering Research of Canada and the Social Science and Classical Research Studies Council, decided not to accept the use of placebo in clinical trials when appropriate treatments are proven to be available. In addition, critics of the use of placebo claim that it is immoral to write out non-working drugs, that it is fraud to lie to the patient that he is allegedly receiving real treatment (Hasnain et al., 2018).

More recently rather than denying the patient essential treatment by using placebo, a new drug is tested against a drug which is known to be effective to check if the new drug is more effective or not.

5. CONCLUSIONS

As has already been pointed out, the placebo phenomenon has been known since the 14th century, yet it was first used in 1955 in medical research (Beecher, 1955). This has been a catalyst in changing the way clinical investigations are conducted. When a new drug is tested it should be compared with a placebo or placebo equivalent. This method is an important issue, because it aids the assessment of the effectiveness of a new medicine. It is known that an authorization will only be given if it has more positive effects than placebo.

From a legal point of view, there is a clear reference to the informed consent of the patient involved in the investigation, the way it is carried out and the conditions to be met for the conduct of a clinical study. The UNESCO Universal Declaration on Bioethics and Autonomy for Human Beings, as well as the Oviedo Convention on the Protection of Human Rights and Dignity of the Individual, describe in detail the protection of the persons under investigation and should be followed closely in all cases.

In Greek legislation, the rights of the hospital patient are determined ex lege and the protection of the study participants by specific ministerial decisions. With regard to

the moral aspect of the use of placebo, the Helsinki Declaration refers in specific articles to medical research which should promote respect for human beings and the protection of health.

In conclusion, there are many views on the appropriateness of the existence and use of the placebo method. From a moral point of view, one could argue that it would be unfair to use it. In the authors' view, there should be a balance between conflicting opinions and whether these relate to ethics, religion or science per se. Neither the abolition nor the excessive and irrational use of placebo would in any way serve the direct interests of mankind.

CONSENT
Not applicable.

ETHICAL APPROVAL
Not applicable.

COMPETING INTERESTS
Authors have declared that no competing interests exist.

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