

Effect nocebo, and the contextualized informed consent: some thoughts on its application in ophthalmology

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Abstract

The respect to the principle of autonomy and informed consent obligates physicians to explain patients the possible side effects when prescribing medications. This disclosure may itself induce adverse effects or negative placebo. This fact contradicts the principle of non-maleficence in vulnerable patients as in ophthalmological disease. There is some tension between information to the patient that takes into account possible side effects. The Informed consent to patient for off label drugs used for example in ophthalmology is a new contextualized legal ethical question. This article has for objective to alert to the doctor for the effect risk nocebo. The doctor has the duty to explain and the patient the right to be explained about the advantages, disadvantages, risks and benefits of any medication. The contextualized informed consent suggests a pragmatic approach for providers to minimize nocebo responses while still maintaining patient autonomy through, by means of the form as it informs.

Keywords: Informed consent. Nocebo effect. Drug prescriptions.

Resumo

Efeito nocebo e consentimento informado contextualizado: reflexões sobre aplicação em oftalmologia

O respeito ao princípio da autonomia e consentimento informado obriga o médico a explicar ao paciente os efeitos secundários das terapêuticas que prescreve. Entre eles, há o chamado efeito nocebo, cujas especificidades, detalhadas neste artigo a partir da oftalmologia, implica que o fornecimento da informação possa vir a contrariar o princípio da não maleficência a pacientes vulneráveis. O consentimento informado em oftalmologia para drogas *off-label* traz nova questão ético-jurídica, que este artigo aborda a partir dos riscos do efeito nocebo. O médico tem o dever de esclarecer e o paciente, o direito de ser esclarecido sobre as vantagens, desvantagens, riscos, benefícios de qualquer medicação. O “consentimento informado contextualizado” pretende atenuar a resposta nocebo de modo a preservar tanto a autonomia do paciente quanto a ação não maleficente do médico.

Palavras-chave: Consentimento esclarecido. Efeito nocebo. Prescrição de medicamentos.

Resumen

Efecto nocebo y el consentimiento informado contextualizado: reflexiones acerca de la aplicación en oftalmología

El respeto al principio de la autonomía y consentimiento informado obliga al médico explicar al paciente los efectos secundarios de las terapéuticas prescritas. Entre ellos, existe el llamado efecto nocebo, cuyas especificidades, detalladas en este artículo desde la oftalmología, supone que el suministro de la información pueda contradecirse al principio de la no maleficencia a pacientes vulnerables. El consentimiento informado en oftalmología para drogas *off-label* trae una nueva cuestión ético-jurídico que plantea este artículo a partir de los riesgos del efecto nocebo. El médico tiene el deber de aclarar y el paciente el derecho de ser aclarado acerca de las ventajas, las desventajas, los riesgos, beneficios de cualquier medicamento. El “consentimiento informado contextualizado” pretende mitigar la respuesta nocebo para preservar tanto la autonomía del paciente cuanto a la acción no maleficente del médico.

Palabras-clave: Consentimiento informado. Efecto nocebo. Prescripción de medicamentos.

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Declara não haver conflitos de interesse.

Recently there has been discussions about the ethical conflict represented by the duty to provide the patient with the best information regarding the adverse effects of any therapy and the possibility of a very detailed information will lead to the risk of producing discomfort, inserted in so-called nocebo effects, under the assumption that the way how certain information is given seems to modify the profile of the adverse effect expected ¹.

The ultimate goal of the medical act is to help the patient in the health restoration process. In this action is entered prescribing appropriate drugs to various nosological entities (and every patient in particular), and the explanation of its risks/benefits and possible adverse effects. In medical action it is expected the respect for the principle of the informed consent.

However, in the process of description of adverse effects, the doctor may even unwittingly, create in the patient the so-called negative placebo or nocebo effect phenomenon. This effect is reflected in the existence of discomfort responses, expressed by the patient after the information received, more than relief from suffering. Etymologically, the Latin word nocebo means "to cause harm" or "to damage", although it relates to the innocuous substance, whose action theoretically shouldn't produce any reaction but, when associated with psychological factors, ends up producing harmful effect in some individuals ².

It is thought that this nocebo effect is derived from the patient's negative expectations regarding the treatment, associated with anxiety that this state always involves ³. Such an effect can result in the significant increase of non-specific symptoms, which, as a result, changes of psychological conditions related to the information about the side effects of medicines.

The side effects do not involve serious symptoms, being the most common nausea, fatigue, lack of concentration, headache, insomnia and feeling of general malaise; do not establishing a clear correlation with the pharmacological action of the drug involved, and also independent of dosage. At the same time, they cause additional costs, triggered by the nonadherence to the medication, the demand for unnecessary medical checkups and, yet, for a non inconsiderable set of using other medicines, this time prescribed to treat the secondary results of the nocebo effect ⁴. In contrast, the specific side effects are genuine physiological changes, related to the pharmacological action and biological activity of drugs involved, and tend to be dose dependent.

In the context of the importance that is gaining in Portugal (as well as in other parts of the world) the implementation of informed consent, strengthened by the implementation of the regulation no.15, of October 3, 2013 ⁵, issued by the quality Department of the General Directorate of Health in public discussion, the question arises of how much, how and what information should be provided to patients regarding the side effects of prescribed drugs.

It is also in this sense that the ethical and legal issue regarding the prescription of off-label medicines gains relevance, given that, even without a legal coverage, these drugs prescription focuses on the doctor's good faith, who wants above all to preserve the health of his most vulnerable patients. The off-label medicine is a drug with different therapeutic indication than those registered as therapeutic approved for that medicine. The term refers to other use than the one approved in the package leaflet or to the use of a product that it is not registered in the regulatory body of the country's health authority ⁶. Its objective differs from the reach of therapeutic indications, age group, dosage or form of administration approved, including the administration of extemporaneous formulations or doses made from registered medicinal specialties.

As a result of the aging of the populations treating vulnerable patients with risk of losing central vision (if not treated) has become both the reality and an ethical imperative for the ophthalmology, such as exemplifies the Age Related Macular Degeneration (ARMD). This disease has been the leading cause of blindness (VA <20/200) in developed countries, and its neovascular form accounts for about 90% of these cases ⁷. The use of anti-VEGF (anti-angiogenics), administered by intraocular injection, proved beneficial, and prescribing off-label medication could possibly be an alternative, both in efficiency and cost-effectiveness ⁸.

However, this is an ethical crossroads. If on one hand as much information as it is possible regarding the adverse effects of any therapy should be made available to the patient, as required by the ethical standards of respect for the freedom of citizens and their right to be informed (informed consent and the right to be clarified) on the other hand the very detailed information may produce discomfort derived from the accessory nocebo effect on those most susceptible patients. In the particular case of the *off-label* drug, it becomes even more difficult for the doctor to ensure that the side

effects reported by the patient are real effects and not nocebo.

The National Authority of the Medicinal and Health Products (Infarmed), of Portugal, considers that the use of medicines outside the approved therapeutic indications is the absolute responsibility of the prescriber physician, and it is not the attribution of this organ to pronounce on its use for different indications than the one in the Summary of Product Characteristics (SPC)⁹. In case of adverse reactions or crossed effects with another usual medication, the health professional cannot ensure that the *off-label* prescription for which he chose was the most appropriate for his patient. If the doctor makes use of a drug or procedure, in an indication not registered in the package leaflet, with the intention of improving the ophthalmologic quality of life of the patient, he must be well informed about the drug, based on solid scientific reasons, and the therapeutic act must always be a result of the informed consent of the patient. As Oliveira and Pereira teach, the record of the use of *off-label* drug in the clinical process will demonstrate the good faith of the doctor¹⁰.

Thus, the physician who decides to experiment on a patient a therapeutic method that has not yet been sufficiently validated, and that is not part of medical treatment protocols, although there are indications of success stories, such as in the cited example of the *off-label* antiangiogenic treatment in ARMD, will always be at risk of being accused or even convicted for bodily harm, if he has not obtained the informed consent from the patient, according to the Portuguese Penal Code⁹.

In this sense, one has to question: how to reconcile protecting the patient against the nocebo side effects that the information may cause and, at the same time, the legal rigour which forces the doctor to inform about the secondary effects of any prescription, in which are included *off-label* medicines? The purpose of this article, therefore, is to rethink the form of provision of the informed consent, proposing a path closer to the patient as an alternative to the *checklist*, in a deeper dialogue, capable of understanding their motivations and anxieties, more dependent on *the context* and the *sensitivity* of those involved, but away from the paternalistic behavior in parallel.

It is considered, that receiving the patient's informed consent of using *off-label* medicines, it contributes to establish the required bond of trust between the patient and the doctor, but, in fact, it does not ensure that their complaints, if any, are real side effects of medication, and not the result of the nocebo

effect. So, the moment *when* and *how* the information is provided can make that trust to narrow, allowing the doctor to see more easily the real side effect.

Has the doctor to accept the role of Sherlock Holmes?

It is true that the information provided to the patient regarding the adverse effects of a given medicinal product is not totally an innocuous procedure, nor is it a neutral phenomenon for who receives it. The development of many described and experienced side effects by the patient depends on how such effects are presented.

It has been demonstrated that the use of words like "*pain*" determines, in patients that hear it, the increase of this symptom. On the contrary, if instead it is said "*a little uncomfortable cold feeling*," the pain decreases¹⁰. Recently, it was shown that the way we explain to the patient how he will be anaesthetized in an ophthalmic surgery determines the sensation of more or less pain, which seems to be related to the language used. If in a local anesthetic we say "*you're going to feel some pain similar to a bee sting*", the patient will feel more pain than if we explain otherwise¹¹, as, for example: "*we're going to anesthetize this area next to your eye, you're going to feel a numbness, which will allow us to carry out your operation without pain*".

Thereby, the way how the information is given seems to modify the adverse effect profile. It has been speculated about the existence of genuine nocebo effects in some clinical trials, in the sense of underestimating them, and their existence has been attributed to the psychological state of the participants. It is argued that many of these patients were already reluctant to receive new medications and the adverse effects would derive from anxiety and/or distrust, and its non-participation is suggested¹².

A research carried out for the detection of adverse effects in a group of patients with migraine, where in one of the test groups placebo was used, similarities of adverse effects were verified between the placebo group and the group that received anti-migraine medication¹³. The information provided to the participants of the test produced in the placebo group the same side effects, imitating the effects given by the information. In this randomized test, the placebo group patients, when feeling the adverse effects that imitated the information (nocebo effect), suspended the treatment in a variable percentage from 4% to 26%¹³⁻¹⁵.

Thus, it seems that human beings have the tendency to experience what they expect to feel¹⁶. Another study showed that patients who reported more side effects were precisely those who had more ability to develop them¹⁷. This phenomenon suggests that for some patients the very detailed information about possible side effects may lead to the appearance of these same effects, many of which would not have occurred if the information hadn't been so detailed and in such a large amount. The side effects are thus ambiguous, acting in a *chameleonic* way, although the information related to it – is in itself – a critical component of the doctor-patient relationship.

These results show that there is no, therefore, only one “*true*” to be transmitted to the patient in the process of informing, because to explain the adverse effects of a therapy cannot be summarized to the mere presentation of facts. The quality information, which can promote the well-being of the sick and don't aggravate their symptoms, is – in fact – an important component of the medical art and it requires a judicious *judgement on the part of the doctor who informs*.

Contextualized Informed consent

The so-called *contextualized informed consent* is ethical methodology used in clinical practice that considers the possibility of the existence of side effects in patients who are being treated as a result of standardized information. Such methodology admits to modulate the information to each on in particular, in an appropriate manner. This way, it intends to reduce the side effects induced by medical dialogue, often rushed, who informs the patient in order to merely comply with their legal duty. The contextualized and personalized process will reduce the anxiety induced by the knowledge of side effects listed, while maintaining the respect for the right to autonomy of the patient and their right to be informed with veracity.

Such a strategy forces the doctor to establish the right balance between the need to inform the patient and the respect for this as a person without the intention of causing any harm to him, respecting also the principle of non-maleficence. More than ever, when the principles come into conflict, one has to know how to identify the one able to cause lesser harm, since such principles are *prima facie* as expressed in the last principlialist review, which elects the principle of highest importance to solve moral dilemmas in situations of ethical embarrassment¹⁸.

The argument that the informed consent can be contextualized is based on an important bioethical analysis performed by Manson and O'Neill¹⁹, who propose a new way to think about informed consent, without wishing to return to the pre-Nüremberg “paternalism” They recognize that the information from an informed consent does not exist independently of the validation process, and that is, simultaneously, dependent on both *the context* and the *sensitivity* of those involved as to *what* and *how* the information is provided. The authors consider that the classic informed consent model is very focused on providing information as a set of stored data, without giving importance to the communication process. They propose a new consent model, centered not only in the content but also in the so-called *social transaction*, or communicational, which is established between the two agents (doctor and patient), involved in the process of informed consent.

This model recognizes the interactive character of successful communication, able to satisfy ethical standards. It also considers that the informed consent does not need to be totally explicit or overly specific. In order for a *communicative transaction* to be real, as reinforcement of such ethical standards, it is important that the information is appropriate and accurate, with contextual relevance, rather than a very thorough description of a very detailed information, whose informative meaning can just be delusional.

It arises as the result of the interaction between the *doctor* who is responsible and the *patient*, assuming that the good therapeutic alliance comes always from the willingness of the doctor to respect the particular needs of each one of their patients, following in parallel the *guidelines* of the so-called evidence-based medicine²⁰. Focusing the attention on the relationship between the doctor and patient allows intuiting that a successful relationship can probably mitigate any nocebo response²¹.

The use of the contextualized informed consent

One of the practices that discusses the subject of the contextualized informed consent is the performance, by resident doctors of ophthalmic surgical procedures, without the patient being aware of their lack of experience as surgeons. It can be argued that hiding that information from the patient, aims to protect him from anxiety and unnecessary discomfort. It will be, however, more appropriate

that the resident notifies with honesty about his level of competence, adding that he will be helped by a senior physician, which in case of difficulty will take his place²².

Another example of this type of practice arises when some doctor, while investigating the possibility of potentially serious diseases, does not immediately explicit to the patient the “reasons” for the investigation until receiving the results of additional tests, and, when questioned about the reason for the request of the tests, he answers vaguely: it is to *exclude other possibilities*, without specifically describing what is being excluded. This is the case, for example, of the ophthalmologist who diagnoses a melanocytic *nevus* in a routine examination of the fundus of the patient’s eye.

In this case, he will have to exclude the potential malignancy of that injury, even though in most of the time it is benign. He can then tell the patient that the goal is to drop a rare hypothesis, without giving other alarming details about the possibility, risks and implications of a melanoma. He thinks, thus, to protect the patient from unnecessary suffering, since the complete information about the test results shall be duly provided at the right time, when there is certainty about the diagnosis.

Other examples to be considered are the cases of somatization. The way the doctor informs the patient about their real situation, the existence of neurovegetative dystonia, for instance, is of the utmost importance to strengthen the bonds of trust. This possibility should be only considered after all tests of organic cause had been discarded. If in a first approach the patients are informed about this diagnosis in a rushed way, they immediately lose trust in the doctor²³. In fact, it is not uncommon that the eye patient, when is very anxious, to complain that they are not seeing anything, but when they start the exam their visual graduation, from a line of the eye chart higher than the usual, it is noted that their low vision is only a psychological issue. Trying to understand their anxieties and daily situation, it is possible to identify their visual problem.

A paradigmatic example about when “they do not tell the truth” to the patient is on the concept of *number needed to treat* (NNT), i.e. the total number of patients who need to receive a drug in order to verify in practice its benefits in one person. When the doctor prescribes certain therapy to treat an ocular hypertension, he knows, for example, that from 20 people treated one will develop glaucoma²⁴. However, according to the NNT statistical concept, 20 people will need to be treated of ocular hyper-

tension to prevent the glaucoma in only one patient. In these cases, the revelation that only one patient among 20 will benefit from the treatment of ocular hypertension without developing the glaucoma may reduce both the *adherence* to the medication and the tendency to *tolerate the side effects*²⁴.

Finally, it must be considered that, by receiving excessively detailed information about all the possible side effects of medications, even the most exceptional ones, some patients may experience some of the symptoms included in the cited concept of nocebo. Try to convince them of the true origin of these symptoms (i.e. the emotional misrepresentation of the information received) can interfere with the confidence of the patient in the doctor and increase the distance in the interrelation²⁵.

So we must be prudent in the form, quantity and quality of information, which should be provided in accordance with the conditions of the patient to receive it. This means, it is up to the doctor to be creative and prudent, in order not to hurt also the respect for freedom and the protection of the patient.

The arguments against the contextualized informed consent

The biggest argument against this procedure is the one that seems to fit in a paternalistic perspective, which does not value the principle of respect for the patient autonomy and respect for the truth to which he is entitled, to decide in freedom. So it seems that under the guise of the therapeutic privilege, the doctor thinks he’s in the right to determine what is best for the patient in terms of the information to be provided.

In fact, the nocebo response usually implies the development of *minor* side effects, but not to inform about these adverse effects can be disturbing to those who suffer from them. On the other hand, if we respect the autonomy of the patient as a priority, withholding information about potential side effects, especially if they result from *minor* symptoms, constitutes a disrespect to his freedom, so they should give those information.

The open and true communication is the backdrop for the patient’s satisfaction with the healthcare provided. Being regarded increasingly as a partner and to whom the well-being is promoted, the patient incorporates to this well-being the knowledge about their clinical situation and additional therapeutic effects which are applied to him.

However, it could be argued that, while providing detailed information about side effects of medicines to patients, if that information conditions their feelings and emotions, it will be creating another *nocebo* reality that may affect the clinical evaluation of the real side effects, which would be recognized and recorded if we omitted this information.

Thus, the question remains without a definite answer, demanding deeper studies about the issue, including its ethical aspects as well as the growing improvement of communication skills of doctors.

Final thoughts

The nocebo response put in motion a kind of informed consent more comprehensive as to the information to be transmitted to the patient regarding the adverse effects of medicines. These effects, especially if they are vague or nonspecific, do not constitute an objective phenomenon, being much influenced by the interaction between the physician and the patient. Non-specific adverse effects related to the nocebo effect do not involve important symptoms, being present in the so-called healthy population, which does not take these medicines⁴.

The doctor-patient relationship is the encounter of two different explanatory models, patient's and doctor's. The consent must be understood as dynamic process, which depicts specific situations, at the precise moment, instead of being a static and bureaucratic process. It's in the way which the information is transmitted, appropriate to the patient's narrative that is the key to success of good information and its comprehension. Otherwise, the medical message may not be properly understood.

One must consider, moreover, that the truth in medicine is rarely absolute, being complex, uncertain and dependent on several factors and complications. Doctors cannot withhold information from the patient, but that truth can be presented in different ways. To adjust the discussion to each specific patient not only promotes good form of communication, but also it is reflected in the good medical practice²⁶, keeping simultaneously the respect for

patient autonomy and being attentive to the impact of information on him, especially for not resulting in maleficent acts²⁷.

This idea deviates from the therapeutic privilege and classic paternalism, in which the patient knows nothing and the doctor holds the absolute knowledge. The *off-label* use of medications in diseases that seriously threaten the vision is an ethical imperative of the doctor, who aims to help improving the quality of life of his patients that are vulnerable because of the age and visual limitation. Its use, notwithstanding the good results, comes to relaunch the ethical and legal problem regarding the classic informed consent *versus* the contextualized informed consent.

The *contextualized* informed consent emerges, therefore, as the most appropriate and advantageous method in promoting the information to the patients about the side effects of medicines. The decision on how to draw this consent and to decide where is the line between specific and non-specific adverse effects is part of the judgment that commonly is called *the art of medicine*, which can (and should) be modeled and appropriate over time.

There is, therefore, no single formula to obtain the informed consent in clinical practice, and we must take into account the many variables that can affect its actual achievement, being the context a path to reduce the development of non-specific adverse effects.

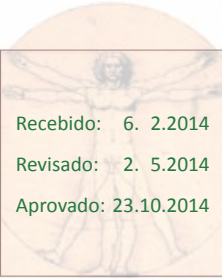
The contextualized informed consent, a tool that doctors may use to think critically over what information to provide, it is attractive and, at the same time, disturbing. Some questions will continue echoing: how will be the respect for freedom of others and the demand for reduction of the asymmetries between the two protagonists? What is the limit of what you need to inform? How to guide the relationship between autonomy and protection?

The concept of contextualized informed consent requires empirical assessments and theoretical discussions, constituting a motivator and innovator point of bioethics discussion. The purpose of this paper was, in this sense, pointing other perspectives and to stimulate the discussion on the topic.

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