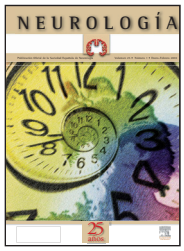
Neurología. 2011;**26(2)**:92-99

NEUROLOGÍA

www.elsevier.es/neurologia



ORIGINAL ARTICLE

Ethical problems arising from the use of placebo in clinical trials with drugs for migraine. Their analysis by the moral deliberation method

J. Frías,[a] J. Pascual,[b] J. Lahuerta,[c,*] D. Gracia,[d] R. Dal-Ré[e,f]

[a] *Servicio de Farmacología Clínica, Hospital Universitario La Paz, Madrid, Spain*
[b] *Área de Gestión Clínica de Neurociencias, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain*
[c] *GlaxoSmithKline S.A., Tres Cantos, Madrid, Spain*
[d] *Departamento de Medicina Preventiva, Salud Pública e Historia de la Ciencia, Facultad de Medicina, Universidad Complutense, Madrid, Spain*
[e] *Departamento de Medicina Preventiva, Salud Pública e Inmunología y Microbiología Médicas, Facultad de Ciencias de la Salud, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain*
[f] *R. Dal-Ré was working at the Medical Department of GlaxoSmithKline S.A., Tres Cantos, Madrid, Spain, while this paper was being drafted*

Received on 12nd July 2010; accepted on 29th September 2010.

KEYWORDS
Migraine;
Treatment;
Clinical research;
Ethics;
Cases;
Moral deliberation method

Abstract
Introduction: Migraine is characterised as episodes of headache plus a variety of accompanying symptoms. Its pharmacological control remains unsatisfactory for some patients. The use of placebo in drug clinical trials on migraine commonly leads to numerous ethical uncertainties.
Methods: The purpose of this paper is to illustrate how the deliberation method helps in analysing the issues and finding solutions to selected ethical problems. Ethical decisions that try to solve conflicts arising from placebo use in clinical trials may be adopted using the moral deliberation method. Thus, the conflict is systematically assessed by identifying the following: Relevant facts; Values in conflict; Duties, or in other words, possible courses of action. Moral duty is following the optimal course of action. To identify this, it is recommended to state extreme courses of action, then intermediate courses of action, and then to proceed to the optimal course(s) of action.
Results and conclusions: In this paper, the application of this method is shown in several conflicting situations arising in two placebo-controlled clinical trials with drugs under development for the prophylaxis and acute treatment of migraine

*Corresponding author.
E-mail: juan.m.lahuerta@gsk.com (J. Lahuerta).

PALABRAS CLAVE
Migraña;
Tratamiento;
Investigación clínica;
Ética;
Casos;
Método de deliberación moral

Problemas éticos por el uso de placebo en los ensayos clínicos con fármacos para la migraña. Análisis mediante el método de deliberación moral

Resumen
Introducción: La migraña cursa con episodios de cefalea y síntomas asociados. A pesar de los avances realizados en los últimos años, su tratamiento farmacológico sigue sin ser satisfactorio. En el desarrollo de estos nuevos fármacos para la migraña muchas veces se realizan ensayos clínicos frente a placebo que plantean numerosas incertidumbres desde el punto de vista ético.
Métodos: El propósito del artículo es ilustrar sobre cómo este método de deliberación puede ayudar a analizar y plantear soluciones a los problemas morales. Las decisiones éticas que intentan resolver los conflictos derivados del uso de placebo pueden abordarse mediante el método de deliberación de problemas éticos. Para ello, el problema o conflicto se somete a un estudio sistemático, identificándose: los hechos relevantes; los valores implicados en conflicto; los deberes, es decir, los "cursos de acción" posibles. El deber moral es seguir el curso de acción óptimo. Para identificarlo se recomienda proceder indicando los "cursos extremos" de acción, los "cursos intermedios" y el o los "cursos óptimos".
Resultados y conclusiones: En este artículo se presenta la aplicación de este método en varios supuestos de conflictos éticos en sendos ensayos controlados con placebo para el tratamiento agudo y el tratamiento profiláctico de la migraña.

Introduction

Migraine is a common episodic neurological disorder, with high rates of morbidity, deterioration in the quality of life of people suffering from migraine, and hence, high health-care, employment, and social costs.[1] Although drug treatment for migraines has improved markedly since the introduction of triptans, pharmacotherapy continues to be insufficient for many patients.[2] Likewise, migraine prevention by means of chronic drug treatments is only partially efficacious. The use of placebo in clinical trials (CT) of new drugs for migraine, although necessary for methodological reasons, arouses much uncertainty from an ethical perspective.[3-5]

The deliberation method is an approach used for the resolution of ethical conflicts that can be applied to clinical research.[6] The ethical decisions made in a CT are not terribly unlike those that are made in everyday clinical practice; the decisions have to do with specific issues, they must be practicable, and they are often made with a considerable degree of uncertainty. The aforementioned deliberation method has an eminently practical aim; i.e. to make better, more reasonable, and prudent decisions. The problem or conflict is studied in detail, in search of the best or most prudent course that can be demanded from a moral point of view.

Methods

Doctor J. Pascual presented two cases that are representative in placebo-controlled CT: one for prevention and the other for acute treatment of migraine. The authors then determined the ethical problems derived from each case and chose some of them for discussion according to the deliberation method of ethical problems. The following were identified:

1. *The relevant facts.*
2. *The values involved in each conflict.*
3. *The duties:* that is, the "courses of action" that were possible for the issue at hand. The moral duty is to follow the best course of action, the one that best promotes the application of all of the values in conflict or that are least harmful. To do so, it is recommended that the "extreme courses" of action be identified first, followed by the "intermediate courses of action" and, finally, the "optimal course(s) of action".

Briefly put, a moral problem always represents a conflict of values that, generally speaking, people attempt to resolve. When there is no way of resolving it and values are harmed but we have no way of avoiding this, we are faced with a "tragedy". If there are solution pathways, we must explore all of them so as to find the best one. The latter is known as the "best course of action". From the time of Aristotle, it has been said that the best courses of actions are usually the intermediate ones, since they aim at saving both of the values in conflict, or at least harming them as little as possible. Hence the so-called "extreme courses" (the radical alternatives in favour of one of the other value) are the most harmful in value terms, and therefore the worst courses of action to follow. For this reason, the deliberation method generally proposes beginning by identifying the extreme courses, then seeking intermediate

courses between these extremes, and finally choosing the intermediate course that seems optimal.

Cases

Case 1. Migraine prophylaxis

Ana is 32 years old and has been under treatment by the lead investigator for the last 6 years for migraine episodes without aura that respond well to triptans. She has received preventive treatment for several months with propranolol due to an increased frequency of her crises, with an excellent response. Ana is a clerk at a supermarket with 9-month contracts and has one child. She is not currently using any kind of contraception. She has come to consult again because she has been experiencing more migraines for the last two months, with at least one episode per week.

The researcher has proposed that she participate in a CT with a new anti-epileptic drug for the prevention of migraine. The study lasts for a total of 6 months. During the first month, the patient will not take any kind of preventive medication, but instead, will take a placebo and will have to fill in a daily log of migraines. If the patient suffers between 3 and 8 episodes per month, he/ she would enter into the second phase of the study. In this phase, Ana would be treated either with the new anti-epileptic drug or with placebo, at increasing doses. She would be maintained at the drug level achieved for another 3 months, after which the medication would be withdrawn and the patient would be monitored for another month without preventive treatment. The study consists of 7 monthly visits during which the subject will undergo a full analytical work-up; she will be given a pregnancy test, and her daily log of migraines will be examined. The daily log is to be filled in throughout the study period. During two of the visits, Ana will have to fill in two quality of life questionnaires, the SF36 and the MIDAS.

No economic compensation is contemplated for the participants of the CT. During the study, Ana will be allowed to treat her migraines with her usual medication, but she cannot take any other preventive drugs or contraceptives (due to the possibility of interactions), although she must avoid getting pregnant.

Ana agrees to participate in the CT and signs the informed consent document. Although the researcher insists that she read all four pages of the document, she skims over them, since she says that she trusts him. She fills in the migraine diary and after the first month she has had a total of 5 migraines. In two of them, she has had to take time off work because they failed to remit with triptans. Her boss has insinuated that if this continues, he doesn't know if they will renew her contract. The researcher reminds her that she can drop out of the CT at any time, although he encourages her to continue in the study. At the next three visits, Ana complains of sleepiness. She continues to have between 4 and 6 migraines per month, having missed seven days of work. She asks her doctor if she has to continue to be careful so as to avoid getting pregnant, because her husband doesn't like using condoms. The physician tells her that it is important that she keep from getting pregnant and encourages her to continue participating in the study because it is normal for it to take two months for preventive medications to take effect, although he reminds her that she is free to abandon the study whenever she wants to and he guarantees that he will continue to care for her as always.

Ana continues in the CT and completes the treatment period; she has had three episodes of migraine in the last month and she had to miss work because of one of them. She continues to be moderately sleepy. The researcher comments to her that she should stay off preventive medication for another month and use precautions so as to avoid getting pregnant. The patient says she can't stand it any longer and asks him to give her the preventive medications she has been taking. The researcher says he cannot do so as long as she is participating in the study; as a result, the patient decides to withdraw and abandons the CT.

Ethical problems chosen

In this case, a significant number of ethical conflicts are worth discussing. For instance, whether the process of informed consent (IC) was as appropriate as it should have been, or the justification for not giving the study participants economic compensation. Questions might even be raised as to whether the patient's clinical status made it reasonable for her to be included in the study. Nevertheless, it has been estimated that there are two ethical problems arising from the use of placebo that can illustrate decision-making very well: its use during the first phase of treatment and the assessment of the risks of employment or family issues getting worse due to the use of placebo.

1. Is it necessary to extend the use of placebo during the CT by using it during the washout period?

Relevant Facts

The CT protocol stipulates that the patient must take placebo for one month prior to the controlled phase (placebo versus active drug). It is expected that the patient will do without efficacious treatment during this period and that she may present a number of painful crises that could have been avoided.

There are several methodological reasons that justify using placebo during this initial phase. First of all, there is a high rate of response to placebo in these CT (usually greater than 30%).[7-9] The use of placebo during the washout period will also allow for any possible "after-effect" of the prior preventive medication to be eliminated. Finally, it enables the quantification of the baseline frequency of migraines without treatment. This establishes whether or not the patient is eligible for inclusion in the second phase of the CT, thereby guaranteeing that the patient population is homogenous and, moreover, that there is a reasonable probability of them suffering a migraine during the study period.

Conflicting values

The situation described above justifies the use of placebo in the CT and it would be a matter of evaluating the benefit of the new medication for Ana and for all those she may be representative of; that is, the potential benefit of the new medication. However, keeping Ana on placebo for one month is potentially harmful. In the case of our patient, her

clinical status had worsened recently and lately, she had been suffering at least one migraine per week. Since the researcher knew that Ana typically responded well to the preventive drug, he proposed to her the possibility of participating in this CT with a new drug for the same indication. The conflict is thus patent – the values in conflict are that of "do no harm" (non-maleficence) versus the potential benefit for the patients.

Moral duties

Once the conflict has been determined, if the values are clearly identified, the extreme courses of action are easily inferred, since they always consist of opting in favour of a single value, completely ignoring the other. In this case, the values are avoiding the patient's suffering and improving our arsenal of treatments for migraines. If we opt in favour of the first value, the extreme course will be that of preventing the patient from suffering any episode of migraine whatsoever and not allowing her to participate in a CT with placebo. The opposite would be to opt in favour of increasing our knowledge and the potential benefit for future patients, attempting to get Ana to participate in the study at all costs. It is obvious that the extreme courses are highly detrimental to the values at stake and for that reason, we must search for intermediate courses of action, those attempting to reconcile the two values in conflict. One intermediate course is to include the patient in the study and allow her to stop participating at any time, without being penalized in any way for doing so. Another intermediate course is to shorten the washout period as much as possible, thereby avoiding unnecessary suffering. If this is not methodologically possible, the most important thing is not to coerce the patient's decision to abandon the trial in any way. The issue is that of deciding how long the pre-treatment period with placebo should be: is one month an appropriate duration or is it too long?

Not including the initial period of treatment with placebo would mean that a great many responders to placebo would be recruited.[10] This means that a larger sample size would have to be contemplated in order to detect a significant difference in comparison with placebo in order to demonstrate the efficacy of the active drug. Therefore, the decision would entail exposing more patients to an experimental drug (with a safety profile as yet not well known), as well as incurring resources that might otherwise go towards other research projects. Extending the initial period of treatment with placebo to 3 months would make it possible to clearly distinguish between responders and non-responders to placebo. However, this long period would increase the study period and, above all, would expose patients to avoidable migraines and to the risk of decompensation of the migraine syndrome for an excessively long period of time. A one-month duration appears to be a judicious decision; it enables methodological advantages to be achieved in order to establish the validity of the experimental treatment and exposes the participants to a time that, given the frequency with which migraines tend to appear and their severity, might be deemed acceptable.

Obviously, in order to determine whether the patients are of the opinion that the one-month duration proposed is acceptable or not, the IC process should include information about the risk associated with taking placebo, the benefits expected to come out of the study, and the alternatives to the treatment proposed. Thus, the individual decision of each patient justifies the use of placebo for the one-month period proposed.

The intermediate decision adopted when the CT was designed appears to be the most prudent, as it represents a balance between the two extreme courses previously commented, enabling the obvious responders to placebo to be eliminated in a reasonable period of time. Despite the fact that in the IC process, the patient cannot be specifically informed that he/she will be receiving placebo for the first month owing to methodological reasons (i.e. unmasking the manoeuvre), in order to preserve patient autonomy, the IC must make it clear that at some point in time the patient will receive it and that he/she can withdraw from the clinical trial. It is obvious that leaving the patient without efficacious prophylactic treatment for one month implies that the participant may experience more crises than if he/she had received their preventive treatment. However, this decision is an acceptable compromise from the ethical perspective, since, on the one hand, the patient can continue to take their medication for symptoms for the episodes of migraine and, on the other hand, this month with placebo will make it possible to conduct the CT with fewer patients.

2. In the appraisal of the possible harm rising from including a placebo arm in the study, should other harms, in addition to the health risks be taken into consideration, such as occupational risks or family members? What should be assumed when referring to risk in the broadest sense of the word?

Relevant facts

The patient is asked to take placebo or an active drug for 6 months. In the event that the subject were to receive placebo, he/she will be without efficacious prophylactic treatment for a prolonged period of time. This situation may cause him/her not only health problems, but may also provoke harm to the family or occupational aspects of life derived from the increased frequency of crises.

As we have seen, the inclusion of a specific placebo treatment group is obligatory for methodological reasons if we genuinely want to know whether the prophylactic drug in question is efficacious. However, it is not entirely clear if it might have clinical consequences. On the one hand, suffering more crises of migraine, may appear at first sight to be without relevant long-term health consequences for the person suffering them, particularly if symptomatic treatment is provided and, hence, the use of placebo might be ethically justified for this period of time. On the other hand, it is not totally true that the migraine does not imply health risks. In patients who have frequent crises, not following proper preventive treatment forces them to consume an excessive amount of analgesics, which can give rise to side effects (gastric bleeding or hypertension) and contribute to the much-feared complication of migraines that become chronic due to abuse of analgesics. Therefore, the use of placebo in these patients, although methodologically justified, may add to health risks, especially if the patient has frequent crises and does not take any effective preventive treatment.

On the other hand, there are other types of common risks (harms), associated with the use of placebo instead of the

appropriate preventive treatment, in the personal and labour aspects of an individual's life. The patients who receive placebo in this study are likely to present many crises, some of which do not respond to acute symptomatic treatment and may have untoward consequences in their occupational life: loss of productivity, time off work, etc., as well as in the family: not doing housework, alterations in personal relations, loss of free time, etc. In fact, we know that migraine is one of the illnesses that has the most negative impact on a person's quality of life.[11] The risk, therefore, that the use of placebo in the CT will have negative occupational and family consequences is a real one and must be taken into account by both the researcher and the patient when considering whether or not to participate in a CT with this type of design.

Conflicting values

In this second problem, the values in conflict are those of non-maleficence and the efficiency of the study. If we fail to include social, family, occupational, etc. risks, in addition to the clinical ones, it is evident that we are not correctly calculating the risk/benefit ratio and we may be maleficent. This calculation must be made by the patient, but above all, by the researcher, and the inclusion of people at high risk should not be considered. In the case presented, the risks become progressively greater (occupational stability, relationship with the patient's partner, etc.) and the researcher should keep these from growing further. The other value at stake is the efficiency of the study. With this expanded criterion of harm that also includes social, occupational, family considerations, etc., the study will be somewhat more complex and more expensive, as a higher dropout rate must be foreseen in calculating the sample size derived from the application of measures targeting social and occupational risks.

Moral duties

The extreme courses would be, on the one hand, not to allow people with important social and occupational risks to participate. On the other hand, opting in favour of greater efficiency of the study and ruling out any consideration as to risks other than strictly clinical ones. Logically, before going any further, the issue of whether there is any study design feasible that would make it possible to achieve outcomes with a lower exposure of patients to risks. One of the possibilities would be to carry out studies using historical controls of response to placebo. Although this is an appealing option, due to the possible influence of other factors, it is impossible to be sure that the prophylactic treatment would truly be efficacious; hence, a CT of this type that does not include a placebo arm would be very difficult to justify from the ethical point of view.

Therefore, only those intermediate courses that factor in both values, and that ponder the importance not only of the clinical risks, but also the social and occupational ones can be considered, taking care so that the withdrawals do not entirely hinder the carrying out of such a study. The next consideration to be developed would whether or not the duration proposed is the minimum time necessary to make the risk acceptable. In this regard, prolonging the CT for 6 months would have the advantage of providing us with much more reliable results and that the design would be much more similar to the actual treatment recommendations.[12] The intermediate course that has been proposed in the trial appears to be reasonable, given that it is a compromise that makes it possible to evaluate the drug's action without excessive risks. We know that preventive drugs for migraine can take between 6 and 8 weeks to have an effect; therefore, the results from 3 months of treatment at full dose are considered to be reliable. Insofar as risks are concerned, this period does not appear to be excessive if we bear in mind that participants are allowed to receive symptomatic medication.

It would therefore appear that the proposed design and duration of treatment are reasonable. Be that as it may, these extremes (study duration and access to symptomatic medication), together with the possibility of withdrawing from the study at any time, must be clearly explained in the informed consent (IC) process.

For obvious reasons, the risk-benefit analysis that the researcher must perform prior to offering a given patient the possibility of participating in a placebo-controlled CT focuses on health-related issues. Nevertheless, this analysis is incomplete as illustrated by this case. In fact, not having her contract renewed at work probably represents a greater harm to this person than the pain and discomfort caused by one or more unprevented migraines. The question is how to prevent and assess this risk and, even more importantly, how to communicate it and weigh it with the rest of the negative and positive aspects of the study in such as way as to preserve the patient's right to autonomy. Only a meticulous and combined consideration of each and every one of the elements on the part of the subject and the researcher can provide the points for consideration in order to make the best ethical decision. The researcher should not advise a patient to continue in a CT when the risks for family members and/or occupational risks become highly relevant, such as in this case.

One final aspect to consider is whether it is proper to offer economic remuneration to the participants who take these non-health related detriments into consideration, without this representing an improper incentive to participate in a CT. Dal-Ré and Carné[13] have addressed the issue and find arguments that support the ethical legitimacy of remunerating study participants for the loss of productivity derived from their participation in the CT. However, they reject the "proportional" model that bases a participant's compensation on the proportion of risk his or her participation in the study represents, adducing that payment for exposure to risk (presumably a health-related risk) is not fitting. Is this opinion equally valid for economic risks? Probably not, and in this sense, compensation for participation in the study would be under question here ("salary model"). Nevertheless, this issue has not been adequately dealt with and the complexity of each individual's personal situation (salary-earner versus self-employed or unemployed) makes it difficult to homogenize recommendations.

Case 2. Acute treatment

Susana is a 32-year old laboratory technician who works in the hospital where a CT is being conducted with a new triptan. She has suffered from migraines without aura since adolescence and has been in treatment with the lead

investigator for the last 6 years. She suffers approximately 5 migraines per month that respond well to oral sumatriptan. The usual analgesics (paracetamol, aspirin, NSAIDs) are not generally very efficacious in the treatment of her crises, unless she takes them very early in the course of the crisis and it's not very intense. She tried prophylaxis with beta-blockers and with amitriptylin, without a significant reduction in the frequency of her migraine attacks and with certain adverse effects; as a result, she is currently not taking any preventive treatment at the present time.

The researcher has called her to propose that she participate in a CT since, at first sight, it would appear that she meets the eligibility criteria. On the phone, he tells her about the main features of the study, which is very similar to others in which she has participated. It consists of studying 2 acute migraines and taking note of her response to treatment – for 48 hours: pain intensity, photophobia, phonophobia, nausea, functional capacity, need for salvage medication, and possible recurrence. Patients must record their evaluations during the crisis in an electronic agenda that costs 450 euros, which is theirs to keep at the end of the study. The study consists of 4 visits for a maximum period of 8 weeks. It is a double-blind study, in which two doses of the new triptan and placebo are being studied, in a ratio of 1:1:1. If the person fails to respond to the treatment, he/ she can take paracetamol after 2 hours, up to a maximum of 1 g every 8 hours; triptans and ergot preparations are forbidden. The researcher proposes that she come to his office to sign the consent form. Participants are to be compensated with 200 euros for their time (she earns 1,750 euros per month), since at each visit a full laboratory work-up, pregnancy test, and ECG must be performed and quality of life questionnaires must be filled in.

She agrees to participate in the CT and signs the IC form. In the first crisis during the study period, the medication is not at all efficacious; nor is the paracetamol, which forces her to be off work for two days with intense nausea and vomiting. Unlike her usual crises, on this occasion she has had diarrhoea, profuse sweating, and is very weak. She goes to the follow-up visit and asks the researcher if it wouldn't be better if she dropped out of the study. The researcher reminds her that she can drop out of the study at any time and that the economic compensation is decreased proportionately to the duration of participation.

Susana continues in the study and treats her second crisis with the same results as the first, although, following an episode of repeated vomiting, she notices something that might be blood. As a result, se decides to go to the Emergency Room at her hospital. The ER physician, after finding out that she is participating in a CT, attempts unsuccessfully to get in touch with the researcher. In light of his suspicion that it may be gastrointestinal bleeding, he consults with the fourth-year resident in Digestive Medicine on duty; he decides to perform a gastric endoscopy under sedation that only reveals congestion of the mucosa without points of bleeding. Following the gastroscopy, Susana presents a very intense migraine requiring her admission for observation and the systemic administration of an opiate.

The researcher is finally located and takes Susana out of the study. Susana asks him to tell her which treatment she was given so as to avoid it in the future. The researcher calls the study supervisor who indicates to him that treatment allocation will not be unblinded until the final study analysis, unless there had been a serious adverse event, which is not the case.

Ethical problems chosen

1. Should a patient be recruited who usually responds to symptomatic treatment for a clinical trial with a placebo treatment arm?

Relevant facts

The patient has been invited to participate in a CT with a new drug for the symptomatic treatment of migraine. The patient has been under treatment for the last 6 years, but suffers a mean of five crises monthly. These crises respond to oral sumatriptan and, in contrast, generally fail to respond to NSAIDs, unless treatment is initiated early in the course of the migraine. The patient does not take prophylactic treatment because they have not been efficacious in the past.

Insofar as the study is concerned, it is a clinical trial for migraine treatment that seeks to evaluate a new member of the triptan treatment class in two different crises, with the possibility of salvage with analgesic treatment if the drugs in study are not efficacious within the first 2 hours.

One final relevant fact, although perhaps not for this problem, is the fact that the patient works in the same hospital as the researcher.

As has already been commented, the usefulness of incorporating a placebo arm in a study to appraise the efficacy of the migraine treatment has been well established from a methodological point of view. The use of placebo is the best way to determine the magnitude of treatment effect and the tolerability and safety profile of a new drug and its true efficacy. In order to evaluate the new drug, patients who usually suffer migraines, such as Susana, must be included in the CT, despite the fact that this introduces a risk for the patients. In the case we are examining, although Susana responded well to her usual treatment, she could participate in a trial, since the study pursues greater efficacy of the study drug, perhaps in terms of speed of relief, intensity of the effect, or frequency of relapse, in addition to the possibility of having another drug that is useful for society available to us. However, there is a placebo arm and if Susana were to be allocated to it, her clinical status could get worse and, in addition, the migraines Susana typically suffers are controlled well with oral sumatriptan and do not respond to analgesics.

Conflicting values

In this case the values are, on the one hand, that of doing no harm and on the other hand, promoting knowledge and benefit for future patients. In this case, the research interest in knowing the true efficacy of a new drug for migraine comes into conflict with the duty to do no harm to a patient who is reasonably well controlled with her usual medication.

The conflict arises between the benefits that Susana and society could potentially gain with a new acute treatment for migraine, and the harm suffered by the patients enrolled

in the study, who may receive non-effective medication to treat a number of migraine crises.

Moral duties

The extreme courses would be, either not allow the recruitment of these patients in whom there is already reasonable control of the illness, or not taking this value into account and to seek only to improve our knowledge about the drug.

One of the extreme courses in this hypothetical clinical trial would be to allow only those patients who do not respond well to their usual symptomatic medication to participate in this type of symptomatic treatment CT. Theoretically, these patients would not be harmed by their participation in these studies and might even benefit from them if they respond to the study drug. However, this measure introduces an important selection bias that could call the external validity of the study results into question, since this sub-population of migraine patients will not be representative at all of the population to be treated in clinical practice.

Having arrived at this point, it is worth wondering if the question to be answered should not perhaps be that of whether the new drug is better than the standard of care already available instead of placebo. From an ethical perspective, the consideration is a logical one, since having clearly efficacious drugs available to us, any new drug would have to demonstrate advantages, not over placebo, but over the active standard of care. However, it is not easy to prove significant differences with respect to an active drug in the acute treatment setting in terms of efficacy; moreover, the best way of establishing the clinical efficacy of a new drug is by comparing it to placebo. A new way of overcoming this problem has recently been proposed; that is, to carry out a three-arm study design in which the new drug is compared to the usual active agent and with placebo. Methodologically speaking, this also introduces new difficulties, given that it is debatable from a methodological point of view if even superiority over an active comparator in a CT can be interpreted by itself as proof of efficacy of the experimental drug without a placebo arm. However, from an ethical perspective, the placebo arm has yet to be justified.

The intermediate course entails evaluating the possibilities of benefit for the patient, the importance of the harm (suffering a migraine is not the same as a more serious or degenerative disease), and in the cases in which the harm is not great, as in the case of migraine, determining whether the IC process is well addressed and if we can be sure that the patient understands the risks and consciously and voluntarily assumes them, in addition to the mandatory freedom to withdraw from the CT at any time.

The conflict between the personal benefit and the benefit to society has been dealt with by several authors, analyzing the factors that must be weighed and searching for ethically acceptable compromises.[14,15] From the ethical point of view, this issue is tempered by the benign and self-limiting nature of migraine crises and the fact that these trials must allow the use of salvage medication after 2 hours in the event that the active drug or placebo have not been efficacious. Thus, the most recent text of the Declaration of Helsinki[16] allows for the use of placebo when it is indispensable for methodological reasons, as long as there is no risk of serious or irreversible harm.

2. Should a patient with some type of relation with the lead study investigator be recruited for a CT with a risk-benefit ratio that might be inadequate for the use of placebo?

Relevant facts

The patient works as a lab technician in the same hospital as the CT investigator and is a regular patient of this neurologist. The fact that the patient knows the lead investigator, not only as his patient, but also as a colleague in the same workplace, might limit her freedom of choice in some way; even more so when this patient's occupational status is inferior to that of the lead investigator, as one finds in a hierarchical organization, such as a hospital.

Conflicting values

The first value is, undoubtedly, avoiding harm in a person who suffers frequent bouts of migraine. In contrast, the other is a value that has undoubtedly been very significant for the patient: that of maintaining a good relationship with the physician who has been treating her for the last six years, who is also her superior at work.

The inclusion of a given patient in a CT should be governed by norms of absolute respect for the autonomy of the patient, who should not feel coerced or concerned that a possible refusal to participate in the trial might be detrimental to the quality or quantity of care subsequently received. Even more so, if there is any degree of employment dependence, be it direct or indirect, there may be situations of induction to make a given decision, which may not even be evident to the patient or the researcher.

It would not be bizarre to think that the lead investigator is taking advantage of the situation in some way (former or future "work favours", usual in these cases), and that the patient somehow feels obliged to participate in the CT. We might also interpret the fact that the participant can keep the electronic agenda used in the study as an enticement, or even, the fact that a certain amount of money is paid as compensation for the visits to the hospital.

In contrast to these considerations, the researcher may have requested the participation of this patient in the CT simply because he knows that she meets the eligibility criteria and that, because he knows her well, he foresees good collaboration that will make it possible to obtain highly reliable results. For her part, the patient, given her prior relationship, can trust the researcher's professional integrity, and for that very reason, not consider that he might be exercising any kind of influence over her by asking her to participate in the study.

The conflict of values posed here is between patient autonomy and the suitability for participation of a person who has a work-related relationship with the lead investigator. Discussion surrounds the issue as to whether this conflict can be offset if the researcher makes it clear to patients at all times that they have absolute freedom of choice and that their decisions will not have any kind of repercussions on their future physician-patient relationship. However, there is a consensus in that measures aimed at

respecting full freedom of choice must be maximized in these cases; for instance, informing about the study at length and in appropriate conditions and insisting that patients read the entire IC form at their leisure.

Moral duties

The extreme courses here would be to forbid the participation of patients who have any kind of personal or professional relationship with the lead investigator in one case and to actively promote it in the other. In the first case, given that the patient has achieved good control with triptans, by not allowing her to be enrolled in the CT, the principle of doing no harm is being completely respected, but it keeps the study from being performed or, at least, makes it more difficult to do so. On the other hand, actively promoting her participation in the clinical trial makes it more viable, albeit at the cost of making the patient suffer frequent migraines and ever-growing side effects.

Absolute permissiveness in these cases of conflict is not easy to justify from an ethical viewpoint, since there are relationships of dependence that are expressly banned by the code of ethics.[16,17] Thus, it would appear that forbidding people with a relationship to the sponsoring company that is funding the study and family members of the lead investigator from participating in a CT is a wise one. The opposite would represent a clear conflict of interests.

Various intermediate courses can be identified, but it seems that the best one is to separate the relationship patients have with their physicians from the relationship they have with their superiors at work and to consider that patients should be allowed to enrol in a CT, but not those where they have a direct working relationship with the lead investigator. Likewise, it is wise for special caution to be exercised with respect to economic remuneration for the time and bother incurred in these cases. Although at first sight, equity should prevail (equal compensation for equal dedication), it might be appropriate to consult with the Clinical Research Ethics Committee (CREC) regarding these specific cases. These consultations must, obviously, preserve the confidentiality of the researcher and of the CREC.

Comments and conclusion

The purpose of this article is to illustrate, by means of two cases of migraine sufferers taking part in CTs involving migraine medication, how the deliberation method can help to analyze ethical problems and pose solutions. Establishing the relevant facts surrounding every potential ethical problem and identifying the values in conflict in each case can help bring to light the many aspects and nuances concerning any morally conflictive situation. Going on to detail the courses of action, beginning with the most extreme ones can also force deliberation and thereby conclude in an intermediate course of action that is often the most prudent and, hence, the most suitable.

The two cases narrated here may lead readers to consider many other conflicts of interest not evaluated in the text and that might also have served to illustrate the method.

In our opinion, it would be very useful for this deliberative ethical analysis be generalized and for the responses to the different problems posed to be made public, at least the most common ones, so that a repertoire of guidelines could be developed that could orient the evaluation and resolution of the most common ethical problems arising in clinical research.

Conflict of interest

The authors declare no conflict of interest.

References

1. Lipton RB, Stewart WF, Scher A.I. Epidemiology and economic impact of migraine. Curr Med Res Opin. 2001;17(Suppl 1):S4-12.
2. Pascual J, Mateos V, Roig C, Sánchez-del-Rio M, Jiménez D. Marketed Oral Triptans in the Acute Treatment of Migraine: A systematic review on efficacy and tolerability. Headache. 2007;47:1152-68.
3. Emanuel E.J. The ethics of placebo-controlled trials – A middle ground. NEJM. 2001;345:915-9.
4. Lahuerta J, Gutiérrez Rivas E, Frías J, Gracia D, Dal-Ré R. Controversias éticas sobre la utilización de placebo como tratamiento control en los ensayos clínicos en neurología. Neurología. 2007;22:106-13.
5. In: Pascual J., editors. El ensayo clínico en neurología. Madrid: Ediciones Ergon, S.A; 1998.
6. Gracia D. La deliberación moral: el método de la ética clínica. Med Clin (Barc). 2001;117:18-23.
7. Diener HC, Schorn CF, Bingel U, Dodick D.W. The importance of placebo in headache research. Cephalalgia. 2008;28:1003-11.
8. International Headache Society Clinical Trials Subcommittee. Guidelines for controlled clinical trials of drugs in migraine: second edition. Cephalalgia. 2000;20:765-86.
9. Linde M, May A, Limmroth V, Dahlof C. Headache Masters Programme. Ethical aspects of placebo in migraine research. Cephalalgia. 2003;23:491-5.
10. Leon A.C. Can placebo controls reduce the number of nonresponders in clinical trials? A power-analytic perspective. Clin Ther. 2001;23:596-603.
11. Menken M, Munsat TL, Toole J.F. The global burden of the disease study: implications for neurology. Arch Neurol. 2000;57:418-20.
12. Grupo de Estudio de Cefaleas de la Sociedad Española de Neurología. Guías para el diagnóstico y tratamiento de cefaleas. Mateos V, ed. Prous Science, Barcelona, 2006.
13. Dal-Ré R, Carné X. ¿Los pacientes deben recibir una remuneración económica por su participación en ensayos clínicos terapéuticos? Med Clin (Barc). 2006;127:59-65.
14. Senn S. Ethical considerations concerning treatment allocation in drug development trials. Statistical Methods in Clinical Research. 2002;11:403-11.
15. Evans H.M. Should patients be allowed to veto their participation in clinical research? J Med Ethics. 2004;30:198-203.
16. World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. 59th WMA General Assembly, Seoul, October 2008. Available at: http://www.wma.net/en/30publications/10policies/b3/index.html. Accessed on December 29th, 2009.
17. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont report: ethical principles and guidelines for the protection of human subjects of research. Washington, D.C.: Government Printing Office, 1979.