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ETHICAL OVERVIEW OF PLACEBO CONTROL IN PSYCHIATRIC RESEARCH - CONCEPTS AND CHALLENGES

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SUMMARY

Permissibility of placebo controls in psychiatric research is raising everlasting controversies. The main ethical issue remains: whether, when, under what conditions, and to what extent is it justifiable to disregard subject's present (best) interest for the presumably "greater" ones. In relation to this main ethical concern, two distinct arguments arose: proponents of placebo controls trials (placebo ortxodoxy) and proponents of active controls trials (active-control orthodoxy). More recently, in new ethical guidelines, Declaration of Helsinki and International Ethical Guidelines for Biomedical Research Involving Human Subjects, a "middle way" approach was formulated, acceptable to both sides of the argument, saying placebo controls can be justified under certain conditions: when and only when, they firstly present undisputed methodological reasoning, and secondly, fulfill certain ethical considerations – mainly regarding the permissibility of accompanied risks. These ethical evaluations are inevitably contextual and evoke the need for the principle of proportionality. In scope of recent findings of substantial and progressively increasing placebo response in psychiatric research, contextual factors are identified and both theoretical and practical challenges are discussed.

Key words: *clinical research - clinical trials - research ethics – placebo - psychiatry*

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INTRODUCTION

The usage of placebo as comparative neutral control in clinical trials is controversial from its very beginnings, presumably somewhat 80 years ago (Emanuel & Miller 2001, Emanuel et al. 2004a). But more recently debate intensified after an influential paper by Rothman and Michels, "The Continued Unethical Use of Placebo Controls", was published in 1994 (Rothman & Michles 1994). The authors provided numerous examples where placebo controls were used against the ethical guidance of the World Medical Association's Declaration of Helsinki (further in text Declaration), reasoning that continued unethical use of placebo controls was promoted by regulatory agencies' insisting on such "golden standard" evidence for evaluation of trialed treatments' efficacy and safety (Rothman & Michles 1994; Michles & Rothman 2003). The main ethical consideration that emerged is the question whether, when, under what conditions, and to what extent was justifiable to sacrifice/omit/disregard subject's present (best) interest for the presumably "greater" ones (individual's in foreseeable future, fellow patients', of science, society and so on) (Emanuel et al. 2004a).

So far, this "heated debate" - although of utmost importance - didn't yield any conclusion nor consensus, just the opposite, it polarized interests to two distinct and opposite perspectives: "placebo orthodoxy", as proponents of placebo controls; and "active-control orthodoxy", as proponents of active controls (Freedman et al. 1997a, Freedman et al. 1997b, Emanuel & Miller 2001). A major contention is permissibility of placebo controls in clinical trials that investigate conditions where the effective treatment is established, and where withholding treatment could generate/promote a degree of risk for trial participants. Use of placebo controls in clinical trials is clearly justifiable and undisputable for conditions with no proven therapeutic method. Conversely, usage of placebo controls is clearly indefensible in clinical trials researching therapy of life-threatening conditions where there is well established effective treatment available, especially when established treatment's efficacy is considered in terms of disease specific activity and is clearly beneficial for reducing mortality and morbidity ("meaningful life prolongation") (Emanuel et al. 2004a). Ethically and scientifically unambiguous determinant of placebo controls acceptability in these two situations is universal and has reached the level of firm consensus.

However, the binary perspective is not only viewed in academic, and research communities, it is also reflected in the array of different outlines proposed by various institutions involved in the process of new drugs development and evaluation (Ehni & Wiesling 2008, Gispen-de Wied et al. 2012). Most recently, the unsustainability of these occupied positions became obvious and "a middle ground" approach emerged (Emanuel & Miller 2001, Emanuel et al. 2004). The most obvious evidence of "conciliating forces" is evident in the shift within recent revisions of the Declaration of Helsinki. In its previous revisions, the Declaration strictly disregarded the possibility of placebo controlled trials when proven therapeutic method exists, and from publication of the Note of

Clarification in 2002, placebo controls are permitted under certain conditions (Lewis et al. 2002, Carpenter et al. 2003). Last revision of Declaration, adopted in Fortaleza in October 2013, stands on these foundations (World Medical Association 2013).

Nonetheless, the acceptability of placebo controls in condition where effective or standard treatment exists, calls for ethical and scientific justification of the "exceptional" usage. The Declaration is a critical and most internationally most influential statement of ethical principles for physicians conducting medical research, but obvious variability regarding permissibility of these "exceptional" usages exists in various international or local, ethical or legal codes and regulations (Emanuel et al. 2004, Ehni & Wiesling 2008, Gispen-de Wied et al. 2012). This evident variability of existing regulative is understandable if perspectives of the different stakeholders in medical research is considered: government (cost-effectiveness perspective; protection of public); regulatory medical agencies (insisting on efficacy indicators needed to protect public from under-researched and thus potentially dangerous treatments); researcher (finding scientifically valid and clinically applicable knowledge); patients (wanting recovery and/or relief of suffering). From the beginning of this year, Croatian psychiatrists have to comply with a new Law on the Protection of Persons with Mental Disorders (further in text the new Law) (Republic of Croatia Ministry of Justice, 2014). Amongst some procedural challenges, the Law introduces a certain restrictions on placebo use in clinical trials. In this paper the authors will investigate whether this level of scrutiny is in accordance with the accepted ethical dictum.

PLACEBO CONCEPTS

Recent breakthroughs in the field of "placebo research", and exponentially growing insight in the concept of placebo phenomenon and its effect (or response), provide possible additional dimensions of disputes (Jakovljević 2014b). Although conceptual confusion is evident regarding this complex multifactorial and multidimensional phenomenon, at the current state, placebo effect is viewed as psycho(bio)social response shaped by overall therapeutic context (Price et al. 2008, Finnis et al. 2010, Enck et al. 2013, Požgain et al. 2014). Other conceptualizations of this genuine therapeutic action exist, for example as changes emerging from symbolic interaction, for instance, the meaning response ("placebo effect as the meaning of an intervention"); the healing encounter; interpersonal healing and so on (Walach 2011). Underlying psychological mechanisms of placebo effect involve expectancy (considered as primary psychological mechanism, and is referring to patients expectations of future treatment responses); and classical (behavioral) conditioning (non-conscious learning, where placebo effect is viewed as Pavlov's conditioned reflex) (Price et al. 2008, Meissner et al. 2011, Benedetti et al. 2011, Jakšić et al. 2013, Enck et al. 2013). Different underlying neurobiological (alterations of activity in different brain regions; involvement of endogenous opiate, cannabinonid and dopamine systems) as well as peripheral physiological mechanisms (including immune, neuroendocrine, cardiovascular, respiratory, gastrointestinal systems) have been introduced as ones being triggered by abovementioned physiological mechanisms (Price et al. 2008, Meissner et al. 2011, Benedetti et al. 2011, Enck et al. 2013).

Placebo as concept used in clinical trials is defined as inert, neutral substance (with no treatment properties). Its usage in clinical trials is based on „additive model", the assumption that true ("net") drug efficacy can be calculated by subtracting the efficacy in placebo arm (placebo efficacy) from the efficacy in drug arm of trial. Since the additive concept assumes that treatment unspecific responses are equal in both arms of trial, it was recently challenged by „interactions model" that questioned the equality of unspecific responses (and thus placebo response) (Enck et al. 2011). From researchers' perspective, placebo effect is consisted of participants factors; treatment factors (defined by expectancy-based effects and effects of therapeutic setting); measurement factors; and natural history factors (Enck at al. 2013). Some of these factors are adjustable and could be used to enhance trial's sensitivity, validity, reliability, and therefore generalisability (Rief et al. 2011, Enck & Klosterhalfen 2013).

In clinical trials, placebo is used to control for unspecific effects so that the "true effectiveness" of treatment could be extracted. Having these properties, randomized controlled placebo trial, alongside with open-label randomized controlled trial is considered as "golden standard" in establishing safety and efficacy of new medical treatments, and is considered as a cornerstone of evidence-based medicine (due to concepts of double-blinding and randomization). Placebo controlled trials are often required, especially in field of psychopharmacology, by registration agencies (as United States Food and Drug Administration and European Union European Medicines Agency) as evidence and proof of treatment's efficacy and safety (Laughren 2001, Gispenn-de Wied at al. 2012, European Medicines Agency 2012, European Medicines Agency 2013).

From researcher's point of view, placebo effects should be minimized in order to improve scientific strength of clinical trials, whereas from clinical perspective, the imperative would be to maximize as well as personalize placebo effects in order to enhance benefits arising from medical treatment (Finnis et al. 2010, Enck et al. 2013). Numerous different measures to minimize and control placebo response, and thus enhance drug-placebo difference in clinical trials have been proposed (Rief et al. 2011, Enck & Klosterhalfen 2013). Although placebo effect and placebo response are viewed as somewhat different concepts, the trend is to use them as synonyms, and we use them accordingly for the purposes of this article (Benedetti 2013).

REGULATIONS

The Declaration states (Article 33): „The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable;

or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and

the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.“(World Medical Association, 2013) It is also implied in the Declaration (Article 6): „(…) Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.“(World Medical Association, 2013) The Council for International Organizations of Medical Sciences (CIOMS) and World Health Organisation (WHO) allows “exceptional” usage of placebo controls „when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious if irreversible harm to subjects“ (CIOMS & WHO, 2002).

The Declaration as well as CIOMS and WHO postulates do not take stance to the either side, but one may come to the conclusion that the active control proponents' arguments outweigh the placebo orthodoxy approach. Both regulations takes so called “precautionary approach”, meaning that placebo controls can be acceptable only if they express certain methodological justification and fulfill ethical considerations – mainly regarding the issue of acceptability of perceived risk of conducting such trial (Carpenter et al. 2003, Ehni & Wiesling 2008). Three main contextual criteria emerge that should be taken into account when evaluating placebo acceptability: criteria of risk of harm or burden, criteria of compelling scientific reasons, and criteria of availability of proven treatment. All of these criteria are somewhat vague and indecisive and are open to different interpretations. Further in text, we are going to discuss first two criteria in details. The last criteria, pertaining to the availability of proven treatment is the most controversial and complex, involving ethical principle of justice and reasonable share of burdens and benefits. These issues are closely related to the risk of exploitation and “double standard” issues, created through financial as well as regulatory immaturities of developing countries (Emanuel et al. 2004, Wendler et al. 2004, Ehni 2006). Further discussion regarding these issues would be beyond the scope of this article.

CRITERIA OF “COMPELLING AND SCIENTIFICALLY SOUND SCIENTIFIC REASONS”

Most generally speaking, there are two different and distinct strategies for proving efficacy of new treatment: one could demonstrate that new treatment is superior to control treatment (either active or placebo comparator), or one could demonstrate non-inferiority (equality), within predefined ranges, to established effective treatment (Temple & Ellenberg 2000, Vieta & Cruz 2012).

Proponents of placebo controls claim that trial design including placebo comparator is ethically justified even if the proven effective intervention exists, because of the methodological limitations that can be found in the studies with the active control (Temple & Ellenberg 2000, Miller 2000, Miller & Brody 2002, Vieta & Cruz 2012, Millum & Grady 2013). In recent years, it has been increasingly difficult to detect and prove drug efficacy even against placebo, so the ethically more preferred comparison against active drug (even a “weak” one) could - at least under currently available scientific paradigm - seem as an unachievable and over idealistic aim (Kaptuchuk 2001). Variable, high and rising placebo response as well as diminished drug-placebo differences, more than lowered drug response, could be identified as one of the major contributors for so-called “psychopharmacology in crisis” (Möller & Broich 2010, Alphs et al. 2012, Rutherford et al. 2013, Agid et al. 2013, Jakovljević 2014a, Rutherford et al. 2014). A substantial proportion of failed psychopharmacological trials - an ethical problem per se - and development and registration process of psychopharmaceuticals seem to be costly, so these new trends as well as intrinsically longer investigational path raise the treatment price (Möller & Maier 2010, Möller & Broich 2010).

Recent findings of placebo response in clinical trials in psychiatry bring up some important issues into consideration. Placebo response in clinical trials of psychiatric treatments seems to be both substantial and progressively increasing, fuelling the argument whether both depression and schizophrenia could be highly responsive to placebo (Walsh et al. 2002, Kinon et al. 2011, Alphs et al. 2012, Rutherford et al. 2013, Agid et al. 2013, Rutherford et al. 2014). In adult antidepressant trials placebo response has risen at rate of seven percent per decade between 1981 and 2000, while the mean placebo response rate was 31% (range 13-52%), compared to mean antidepressant response rate of 50% (range of 32-70%) (Walsh et al. 2002). Another analysis showed that the average difference between antidepressant and placebo groups of six points on the

Hamilton Rating Scale for Depression (HAM-D) scale in 1982 fell to an average of three points in 2008 (Khan et al. 2010). The increase in placebo response could be demonstrated from randomized (placebo) controlled trials concerning some other affective disorders as well (Yildiz et al. 2011). Recent meta-analysis showed similar but particular trends in schizophrenia trials: since 1960 mean treatment change increased in the placebo group (average increase of 2.2 points on the Positive and Negative Syndrome Scale (PANSS) per decade), yet decreased in the treatment group (average decrease of 3.8 points on the PANSS per decade) (Rutherford et al. 2014). In one analysis, estimated mean placebo response rate in schizophrenia clinical trials was 25% (range of 0-41%) (Kinon et al. 2011).

So, when evaluating criteria of "best proven intervention", especially concerning psychiatric conditions, a legitimate controversy arises, especially when efficacy of the available treatment is modest and inconsistent, while tolerability issues exist. As proposed by some authors, certain fields of medicine (and consequently medications used in that field) have inherent problems trying to establish different treatments efficacy ("treatments with assay sensitivity problems") (Temple & Ellenberg 2000, Ellenberg & Temple 2000). In other words, established effective medications (considered as standard treatment) are missing reliability regarding superiority to placebo (missing "historical control assumption").

Consequently, without a placebo control that ensures „internal validity" of the trial, the conclusion that there is no difference (in equivalence or non-inferiority trials) between the standard and the studied treatment are frequently uninterpretable: both treatments could be either equally effective or equally ineffective. The conclusion is based on the assumption of inadequacy of existing (standard) treatment as reliable and valid reference point in the function of active comparator (Temple & Ellenberg 2000). Precisely this issue has been minutely elaborated within the concept of assay sensitivity – "the (studies) ability to distinguish an effective treatment from less effective or ineffective treatment" (Temple & Ellenberg 2000). Basically, it means that interpretability of such trials depends and relies on data external to study, although it could be argued, and quite firmly, that interpretability and strength of any trial conclusions inevitably depends on the source of external information – especially since placebo shows great variability as well and thus precludes veracity of "additive model" (Anderson 2006).

However, new interventions, not proven to be more effective than standard treatment, can still be of clinical value if they introduce smaller incidence of side-effects or provide a better response to a certain group of subjects (especially relevant for schizophrenia, with a lack of effective treatments for cognitive and negative symptoms; or depression, with a considerable incidence of treatment unresponsiveness and/or refractoriness) – so-called "the logic of clinical purpose" (Miller 2000, Amdur & Biddle 2001, Carpenter et al. 2002).

More generally, it could be stated that legitimate controversy exists whenever standard treatment does not "meaningfully improve quality and length of life", or is having unfavorable safety and tolerability profile (so that patients are frequently non-compliant). Furthermore, placebo controls opponents find the placebo controls inadequate, since the clinically relevant question should not be whether the new drug is better than nothing, but whether it is better than existing treatment – in other words, the clinically relevant question would not be whether to treat, than how to treat (Miller 2000). Thus, a fundamental objection to placebo study is putting scientific scrutiny before the welfare of study participants. As evidence in favor of an effective treatment increases, ethical justification for the use of placebo decreases (Amdur & Biddle 2001, Emanuel et al. 2004).

Another important consideration is a principle of clinical equipoise, defined as a state of „genuine uncertainty in the expert community about the preferred treatment", formulated before a placebo controlled trial should be deemed as ethical (Freedman 1987). Another perquisite concerning this principle is a well elaborated clinical trial hypothesis that has a potential to disturb an initial state of equipoise and to influence clinical practice accordingly (van der Graaf & van Delden 2011). This principle raises another issue: dual role of treating physician as an investigator that creates certain tension. Since physician's fiduciary obligation is one to the patient no matter under what context their current relationship is embraced, it is critical to emphasize differences between clinical research and clinical medicine, as mirrored in existence of two distinct ethical disciplines - clinical and research within the discipline of medical ethics (Wertheimer 2010). Beneficence, as basic and universal medical ethics principle, exists in both contexts but differs in scope. In clinical medicine physician needs to oblige to so-called "standard of individualized beneficence", where in research physician has a duty to respect the „standard of competent care", alongside with the aim of generating generalizable scientific knowledge (Anderson 2009, van der Graaf & van Delden 2011, Touwen & Engberts 2012). Having that in mind, the dichotomy between robust scientific principles and ethical subject protection is false. Also, the scientific validity is prerequisite of every research and itself represents a fundamental ethical protection.

In other words, no matter how beneficial risks versus benefits ratio it brings to the subjects, poorly designed trial cannot be ethical. So, if a placebo trial design is desired or required for compelling scientific reason, ethically it may be a valid reason, although not a sufficient reason for a study - if risks of placebo administration outweigh the benefits of conducting possible alternative design study with comparably robust scientific methodology. Additional safeguard

introduced in the new Croatian Law is strengthening this particular evaluation: newly established National Board for the Protection of Persons with Mental Disorders has to approve "biomedical research" based on the "careful review of scientific importance, its significance and ethical considerations of proposed research" (Republic of Croatia Ministry of Justice, 2014).

CRITERIA OF „RISK OF HARM" AND „BURDEN"

Criterion of risk of harm or burden is another principle underlying ethical legitimating of placebo controls. This normative condition takes into consideration two universal bioethical principles: beneficence ("do good") and non-maleficence ("do not harm") (Beauchamp & Childress 2009). The extent of possible risk and harm cannot be circumvented in ethical judgment, so the resolute rejection of placebo is a prohibitive attitude (Miller 2000, Emanuel et al. 2004, Weijer & Miller 2004). Risks and benefits of conducting placebo control trial must always be assessed in relation to risks and benefits of conducting other possible trial designs. Likewise, as risk of omitting standard treatment increases, justification of the need for exposing subjects to the risk must be more compelling (Amdur & Biddle 2001, Weijer & Miller 2004). Ethical evaluation calls for contextualized judgment, and evokes the need for the principle of proportionality. In evaluation of this criterion it is extremely important to take into considerations local and regional contexts and it needs to be made by "case-to-case" analysis (Amdur & Biddle 2001).

The guidelines proposed by CIOMS and WHO provide most careful formulation regarding this issue: „When withholding an established, effective treatment would expose subjects to, at most, temporary discomfort or delay in relief of symptoms" (CIOMS & WHO 2002). The Declaration uses somewhat different approach by prohibiting "additional risks of serious or irreversible harm as a result of not receiving the best proven intervention" (WMA 2013). Both statements include concepts that allow different interpretations. Exactly what constitutes "serious or irreversible harm" has never been precisely defined (Weijer & Miller 2004). Most generally approach would be: whenever there is no significant difference regarding subjects' risks in placebo trial and in active control trial, the use of the placebo study design is ethically justified (Roberts et al. 2001). Evident criteria for ethical justification would be an absence of risk of serious harm or a minimal burden accompanied by placebo usage.

It is important to emphasize that a much greater number of subjects could be exposed to harm in active control trial than in placebo control study. For example, when comparing two drugs in equivalence or non-inferiority drug trial, in order to obtain the statistical power of the study, a larger sample is required, since the important difference in the parameter of interest between the two drugs is smaller than between the drug on trial and placebo (so called "low signal detection potential"). As already mentioned, failed trail, whether with active or placebo comparator is ethical issue per se, and when that occurs the amount of harm should be properly considered. Furthermore, the advocates of placebo trial design usually consider only the physical aspects of suffering, and our profession should stand against the acceptance of such criterion. Emotional suffering, loss of employment, the disruption of interpersonal relationships and the array of many other possible psychological and social consequences are overlooked (Weijer 1999, Roberts et al. 2001, Emanuel et al. 2004). This is an obvious paradox: even though many of the psychological and social consequences of mental illness are ignored in the study outcome, they are usually invoked in order to justify the treatment study, especially in the concept of "social value" (Millum & Grady 2013).

Safeguards should be implemented in clinical trial protocol that should preclude risks to its subjects, as emphasized in the Declaration (Article 17): „Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher" (WMA 2013). Subjects at increased risk of substantial and sustained harm (from non-response) should be excluded; the placebo period should be as minimal as possible to secure scientific validity; subjects should be carefully monitored; rescue medications should be available; established explicit and specific withdrawal criteria should be implemented (Emanuel & Miller 2001, Emanuel et al. 2004).

The welfare of prospective trial participants seems furtherly protected by the new Croatian Law, stating in Article 19: "study involving person with mental disorders is permitted under condition when it is justifiable, according to subjects' clinician (psychiatrist), to expect that study results are going to be useful for the health of the subject, and without accompanying consequences" (Republic of Croatia Ministry of Justice, 2014). Having in mind earlier mentioned logic of clinical purpose, we believe that every scientifically sound and ethically justifiable drug trial in psychiatry can provide a potential benefit for the health of the subject, therefore, such legal constriction could be a redundancy.

DISCUSSION

No drug should get the approval unless it confirms being undoubtedly superior to placebo, of course, when superiority over proven (standard) treatment is clearly out of question. Vice versa, hypothetically it could be the case that treatment proven to be more effective than placebo is actually less effective than standard treatment. So, it is important to emphasize that these two different approaches have distinct set of objectives, as well as distinct separate roles in the following evaluation of new therapeutic interventions (Walach et al. 2006). Therefore, insisting on opposing views cannot be sustained or be a part of the scientific culture of

dialogue. It is necessary to preserve a „middle way", acceptable to both sides of the argument. Placebo trial design must be considered as important in the evaluation of new therapeutic approaches, as well as in the strengthening the results of larger studies, in which new treatments effectiveness is compared with the standard. When a high level of placebo response is anticipated, and that is the case in field of psychiatry, the placebo group may be instrumented for strengthening internal validity of trial under certain and strict ethical conditions.

Finally, when effective treatment exists, the undisputed methodological reasoning for placebo-controlled studies has to be given. Placebo-controlled study can have a sound scientific footing if: a high rate of placebo response rate is expected; the condition in question usually has a waxing and waning course; studied condition usually has spontaneous and/or frequent remission; existing treatment are only partially and/or dubiously effective or have severe side effects (question of "net-therapeutic" advantage); availability of validated treatment is not widely available due to cost constraints; the incidence of studied condition or disorder is so low that the equivalence trial design, considering the sample size, could not be done (Carpenter et al. 2003). When and only when, methodology criteria are met, the further evaluation should include the ethical permissibility of risks accompanied with conducting placebo-controlled trial, as follows.

Research subjects in the placebo group should not be substantially more likely than those in the active treatment group to have increased mortality, to have irreversible morbidity or disability, to suffer reversible but serious harm, and to experience significant discomfort. The terms „serious" nor „significant" must not be omitted or relativised. Public health, ethical and legal bodies should list, categorize and ethically evaluate these terms and pertaining events and conditions.

After all the criteria above are met and study gets the approval, the obligation of constant monitoring and good clinical as well as research practice remains, among which we strike the importance of informed consent (Miller & Colloca 2011, Bagaric et al. 2014). It should be mentioned that even here certain issues exist, one mirrored in the question what extent of risk and burden is it tenable to ask a well informed and voluntary person to bear in the research ("the credibility of altruism argument") (Brody 2003)? This is especially relevant as therapeutic misconception - a mistaken belief held by research participants that research would directly benefit them - is prevalent, and as research is involving vulnerable population of mentally impaired persons (Miller & Brody 2003, Bagaric et al. 2014). Regarding this issue the Declaration states (article 9): "the responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent" (WMA 2013). Nonetheless, when adopted before conduction of placebo-controlled trial informed consent process should clearly disclose rationale for using placebo, explain randomization process, and state the risk associated with not receiving medication, consequences of omitting standard treatment, as well as information regarding all possible treatment alternatives (Lidz et al. 2004, Henderson et al. 2007).

CONCLUSION

Finally, scientific considerations should not take precedence over the ethical ones. We would like to emphasize again: no matter what, physician's fiduciary therapeutic obligation is the one to the patient, and thus, "if one has to err, one should err to the patient's side" – preserve patient's welfare over scientific rigor.

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