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Placebo Use in Depression Research: Some Ethical Considerations

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1. Introduction

Placebo use in depression research is under discussion. The World Medical Association (WMA, 1964; 2008) states in their Declaration of Helsinki that ethical principles for medical research involving human subjects are important. Accordingly, benefits, risks, burdens and effectiveness of new interventions must be tested against those of the best current proven intervention, with some exceptions.

Some present-day ethical reviewing committees do not allow the use of placebos in depression research. On the other hand, some government organizations (among them the Food and Drug Administration in the USA and the European Medicines Agency in Europe) will not authorize new interventions or medications in healthcare systems unless their effectiveness has been proved in randomized placebo-controlled trials.

In this chapter, we will discuss the principle that the use of a placebo condition is not allowed in depression research if an effective treatment is already available. This issue is important in research investigating the effects of new interventions or medications. In this chapter, considerations for and against placebo use, based on the literature, will be discussed. It will be argued that the use of a placebo condition is ethically defensible.

2. History

Public knowledge of the abuse of humans for scientific research led to legislation to end this abuse. The best-known example of abuse is that by the Nazi physicians during the Second World War, who forced prisoners to participate in their investigations. In 1946 a trial started at Nuremberg against 23 physicians and their assistants (the so-called "Doctors' Trial") for their actions as criminals of war. In 1947, this trial led to the Nuremberg Code, in which, for the first time, conditions and criteria were formulated describing what makes research on humans acceptable (López-Muñoz et al., 2007; Markman and Markman, 2007). The Nuremberg Code pays special attention to informed consent and freedom of choice for participants', the relation between the study's risks and benefits and the participant's right to end their collaboration at any time (Rice, 2008). In 1964 the World Medical Association presented the so-called Declaration of Helsinki, which since has been updated several times, which the most recent update in Seoul in 2008 (<http://www.wma.net/en/30publications/10policies/b3/>). Apart from this most countries have their own regulations.

At first it was widely believed that the abuse of humans for research purposes only occurred in countries with oppressive totalitarian regimes and not in modern democratic societies. In reality, however, unethical investigations in which research harmed the participants have also been performed in Western countries. An example is a study from the USA, in which the researchers withheld an effective treatment for a long time (1932-1972) from humans suffering from syphilis (Brandt, 1978). The discovery of these facts resulted in the Belmont Report (National Institutes of Health, 1979) which provides guidelines for research with humans in the USA.

Recently, more unethical behaviour of physicians from the same period (\pm 1940) was published. In Guatemala, US Public Health Service researchers deliberately infected patients with syphilis, without their consent, which led to the death of at least 83 of them. A presidential US commission investigated this abuse. According to an announcement of the chair of the Presidential Commission for the Study of Bioethical Issues (2011), an extensive report with recommendations will appear at the end of 2011 to assure the public that today's scientific and medical research is conducted in an ethical manner.

3. Legislation

The Declaration of Helsinki is used worldwide as a starting point to establish the acceptability of research on humans. In addition to this declaration most countries have their own legislation. In the Netherlands, the Law on Medical Scientific Investigation in Humans (Wet Medisch-Wetenschappelijk Onderzoek; WMO, 1998) decides, among other things, that every investigation with humans must be approved by an ethical reviewing board (Institutional Reviewing Board (IRB)).

According to the Declaration of Helsinki, it is important that the physician acts in the patients' best interest and that participating in a research study will not adversely affect the health of the patients serving as research subjects.

In the placebo discussion section 32 of the Declaration of Helsinki is highly important:

'The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- *The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or*
- *Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who received placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.'*

4. Depression

Lots of people feel down or sad sometimes. These feelings are usually short-lived and only last a few days. Patients suffering from a depression are in a state of low mood for a long time (at least 14 days) with a loss of interest and pleasure in daily activities. Depression is a common, but serious illness which influences daily life and well-being negatively and which can be accompanied by a number of symptoms. Depressed people may feel sad, anxious, empty, hopeless, pessimistic, helpless, worthless, guilty, irritable, or restless. They may lose

interest in activities that once were pleasurable, experience loss of appetite or overeating, or problems concentrating, remembering details or making decisions. They may also contemplate or attempt suicide. Insomnia, excessive sleeping, fatigue, loss of energy or aches, pains and digestive problems resistant to treatment may be present (National Institute of Mental Health, 2011).

Depression interferes with daily life and well-being. Most people who experience depression need treatment to get well again. Medications, psychotherapies, and other methods are effective treatments for patients with depression.

A classification system, used by psychiatrists and psychologists worldwide, is the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, American Psychiatric Association, 1994). The DSM-IV formulates criteria and distinguishes different forms of mood disorders by severity and duration. Patients with a:

- major depressive disorder or major depression suffer for at least two weeks from a combination of symptoms interfering with their ability to work, sleep, study, eat, and enjoy once-pleasurable activities. Major depression is disabling and prevents a person from functioning normally. Some people may experience only a single depressive episode in their lifetime, but more often they will have multiple episodes.
- dysthymic disorder, suffer from long-term symptoms. These symptoms are not severe enough to disable the patient but can prevent normal functioning or feeling well. People with dysthymia may also experience one or more episodes of major depression during their lifetimes.
- minor depression have symptoms that do not meet the full criteria for major depression for two weeks or longer.

Different forms of mood disorders are specified on the basis of the symptoms, for example:

- Patients with a psychotic depression are severely depressed and also suffer from a form of psychosis, such as experiencing delusions or hallucinations
- A seasonal affective disorder (SAD) is characterized by the onset of depression during the winter months, when there is less natural sunlight. This type of depression generally disappears in spring and summer. An effective treatment for SAD is light therapy.
- A bipolar disorder (also known as manic-depressive disorder) is characterized by cyclic mood changes – from extreme highs (mania) to extreme lows (depression). There are two types of this disorder. A Bipolar I Disorder is mainly defined by manic or mixed episodes lasting for at least seven days, or manic symptoms that are so severe that the affected person needs immediate hospital care. The depressive episodes usually last for two or more weeks. The symptoms of mania or depression must be a major change from the person's normal behavior. A less severe disorder is a Bipolar II Disorder which is defined by a pattern of depressive episodes shifting back and forth with hypomanic episodes, but with no full-blown manic or mixed episodes (American Psychiatric Association, 1994; National Institute of Mental Health, 2008).

5. Effectiveness of evidence-based treatments for depression

Antidepressants are considered effective in patients suffering from depression and are recommended in guidelines, such as those of the APA guidelines in the US (American

Psychiatric Association, 2006), the NICE guidelines in the UK (National Institute for Health and Clinical Excellence, 2004) and the Multidisciplinary Guidelines for the Treatment of Depression in the Netherlands (Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ, 2010), as evidence-based treatments. Nevertheless, their effectiveness is sometimes questioned (Enserink, 1999; Kirsch et al., 2008; Turner et al., 2008). Some authors state that the effects of antidepressants are not much higher than those of sophisticated placebos (Antonuccio et al., 1999; Kirsch & Sapirstein, 1998).

Moreover, the placebo effects of treatments are not just found in controlled studies, but are also present in clinical practice, even when no placebo is given (Finniss, et al. 2010).

Treatment modalities other than medication are also relevant to this placebo discussion. For example, light treatment is highly effective as a treatment for seasonal affective disorder (SAD) (Pail et al., 2011) and according to the multidisciplinary guidelines mentioned above it is the treatment of first choice. A meta analysis by an APA work group shows that the effects of light treatment in SAD are comparable to the effects of treatment of non-seasonal depressions with antidepressants (Golden et al., 2005). In a recent study, Lieverse et al. (2011) found that bright light treatment was more effective than a placebo (dim light) in the treatment of non-seasonal depressions in the elderly. The authors stated that in this population, light treatment had the same effect as anti-depressants in the treatment of non-seasonal depressions.

Notwithstanding these studies, the Swedish government is still unconvinced of the effectiveness of light treatment, and is still waiting for a large placebo-controlled study to be conducted. Without such a study it does not want to recognize and approve the therapeutic value of light treatment (SBU, 2007).

An important problem is that the working mechanism of light treatment is still unknown (Meesters & Van den Hoofdakker, 1998). There is no clear methodologically justified placebo condition available for light treatment. For this reason, in light treatment research different placebo-like conditions have been used, such as imaginary light (Richter et al., 1994), invisible light (Meesters et al., 1997), extra-ocular light (Koorengel et al., 2001), low-intensity light (Lieverse et al., 2011) or sometimes a placebo totally unrelated to light, such as a deactivated ion generator (Desan et al., 2007). Responses to these 'placebo' conditions varied from 36% to 46.6%.

It is also unknown what other factors, such as attention and accompaniment or healthcare system-related aspects like referral and reimbursement play a role in the therapeutic effects of light treatment (Reesal & Lam, 1999).

6. Pros and cons of placebo use in depression research

As is the case in other more or less controversial issues, there are supporters and opponents of placebo use in the field of depression research. Opponents of placebo-controlled studies object to the fact that a physician in the placebo condition does not offer the best-known effective treatment to the patient or withholds this treatment for a certain amount of time (Miller, 2000; 2002; Pużyński, 2004; Waring, 2008).

According to the Declaration of Helsinki participants of placebo-controlled studies should not run any more risks than they would in accepted regular treatments. These risks are increased mortality, permanent serious harm and reversible but serious harm or greater discomfort than

usual. The greatest risk for humans with a severe depression is without doubt the risk of suicide. Khan et al. (2000) used data from the Food and Drug Administration (FDA) concerning 45 placebo-controlled studies on 7 new medicines against depression. 34 out of 19,639 participants committed suicide and 130 made a suicide attempt. There was no difference in the rates of completed suicides or suicide attempts between patients who were given active medication versus those who received the placebo. The same conclusion was drawn in a meta analysis of data from the European Medicines Agency (EMA) (Storosum et al. 2001). This indicates that the fear of an increased suicide risk for participants receiving a placebo condition is not evidence-based. A possible reason for this is that most studies exclude patients with an increased suicide risk (those with previous attempts and suicidal ideation).

Nevertheless, there may be other risks than suicide, for example the consequences of a long-lasting depression, such as the risk of losing a job, or a serious deterioration of the relationship with a partner or children. These possible consequences have not been well investigated (Kim, 2003; Kim and Holloway, 2003).

In efficacy studies of new medicines or other interventions such as light treatment in an acute phase of depression these risks would seem limited. The duration of these studies is short: mostly 6-8 weeks. If the effects are disappointing, a different, hopefully more effective treatment can be tried. Therefore, participation in a placebo-controlled study can result in a delay of up to 1 or 2 months before patients receive an active treatment.

Perhaps placebo-controlled studies in more vulnerable groups need more careful attention, as in the case with patients with very severe depression (e.g. psychotic depression), patients with increased suicide risks, or patients with depressions during pregnancy. So far, in the last group, very little evidence of an effective treatment has been found. Depressions are known to be harmful for the mother and her unborn child, so it is important to find a treatment that is harmless to both. This treatment has to be both safe and effective. Nowadays many physicians advice against antidepressant medication because of the uncertain effects on the unborn child. In those cases the mood disorder continues to exist, and this is also harmful. Therefore, it is stated that well-conducted placebo-controlled studies are ethically justified in these cases (Coverdale et al., 2008).

An alternative for a placebo-controlled study is a study in which the new intervention is compared with an active comparator. The power of this type of study is far less than that of a placebo-controlled study. Therefore more participants have to be recruited for the study to be able to draw conclusions. When the new intervention turns out to be ineffective, more patients will have received an ineffective treatment as compared to those in a placebo-controlled study (Berk, 2007).

Supporters of placebo-controlled studies first of all argue that it is the only way to show the efficacy of a new intervention. Even if a study shows that a new intervention does not differ in its effects from a well-known existing treatment, there is no evidence for the efficacy of the new intervention if no placebo condition is included. In the field of psychiatric research there are many similar studies. We mention two examples here.

In a study with people suffering from a bipolar I disorder it was found that in maintenance treatment the effectiveness of divalproex was not different from lithium. Without a placebo-arm the conclusion might have been that divalproex is as effective as lithium, the effectiveness of which had been shown in previous studies. However, in this study, both active drugs were not more effective than placebo (Bowden et al. 2000).

In another study with patients suffering from a major depressive disorder it was shown that the use of hypericum (St John's Wort) did not differ from the well-known antidepressant sertraline. However, in this study too, the effects of the two treatments were not different from placebo (Hypericum Depression Trial Study Group, 2002).

In both of these studies it was impossible to show the efficacy of the new interventions (divalproex, hypericum) because they were not more effective than placebo, despite the fact that they did not differ from the two well-known existing interventions with proven activity (Quitkin, 1999; Kupfer & Frank, 2002). This conclusion would not have been possible if there had not been a placebo condition. The reasons for such 'failed trials' are open to speculation. Differences in study populations may be a cause of this:

- Participants may have been suffering from another type of bipolar disorder or depression.
- Patients may have been less severely ill.
- Patients may have been included who had been treated unsuccessfully before with the same or similar drugs.
- There may have been high drop-out rates.
- Other methodological limitations may have been present.

In studies investigating the effects of new interventions in the treatment of depression it is therefore necessary to include a placebo condition in the research program.

Secondly, it should be clear that the response to placebo in depression research varies widely, between 10% to 50% and in the majority of studies amounts to at least 30%. Moreover, the response to placebo has increased over time with about 7% per decade (Walsh et al., 2002; Kahn et al., 2005). In a recent meta analysis of 96 studies it was found that 68% of the effects of antidepressants could be explained as a placebo effect (Rief et al., 2009). If we keep these data in mind, it is clear that in new studies it is impossible to rely on a 'historic placebo condition', i.e. the response to placebo in previous studies.

Third, restriction or prohibition of placebo-controlled studies makes it impossible to discover more effective treatments or treatments with fewer disturbing side-effects. In a placebo-controlled study the conclusion that the side-effects of a new intervention can be distinguished from the side-effects of an existing treatment must be inconclusive. However, without a placebo condition the question about the effectiveness of the new intervention must be inconclusive (Baldwin et al. 2003).

Fourth, another reason to defend the use of placebo is that new medicines or interventions can have unknown safety issues. It is argued that for the treatment of major depression with a new medicine, placebo-controlled studies are the best way to take these aspects into account. Abandoning placebo controlled studies would lead to less certainty about the safety and effectiveness of the new medicines (Dunlopp and Banja, 2009).

Finally, in placebo-controlled studies fewer participants are needed to show an effect when compared with studies without a placebo condition. Therefore, studies with a placebo are less expensive and easier to realize. This is the point of view of forums in the field of depression research. These forums, such as the European Expert Forum on Ethical Evaluation of Placebo-Controlled Studies in Depression (Baldwin et al., 2003; Adam et al., 2005), the National Institute of Mental Health (NIMH, Hyman and Shore, 2000), the National Depressive and Manic-Depressive Association (Charney et al., 2002) and the FDA

(Laughren, 2001) made a plea for the inclusion of a placebo condition in depression research and emphasized its necessity. The Council of Ministers of the European Union and the EMA (Helmchen, 2005) will not exclude the possibility of placebo-controlled studies.

7. The role and functioning of medical ethical reviewing boards

A medical ethical reviewing committee or institutional review board (IRB) is an independent committee which has been appointed to approve, monitor, and review biomedical and behavioral research involving humans. Its purpose is to protect the rights and welfare of the research subjects. The aim of an IRB is to review critical functions (scientific, ethical, and regulatory) for research on humans.

Few researchers would question the usefulness or necessity of medical ethical reviewing committees. In the Netherlands it is unlawful (WMO, 1998) to start an investigation with a new intervention in humans without the approval of an ethical reviewing committee. Sponsors, funding agencies, insurance companies and scientific journals (see among others Touitou, et al., 2006) demand this approval before giving their support to studies involving humans or publishing results.

This makes an IRB a very powerful institution. Its opinion about a study is decisive for whether this study will be conducted. The way in which the IRBs are fulfilling their mission is not always satisfactory for the investigators in the research field (Van Santvoort, et al., 2008). Sometimes bureaucratic procedures or excessive attention to formalities cause serious delays (Alberti, 2000; Nicholl, 2000; Tully et al., 2000; Giles, 2005; Keith & Koocher, (2005); Martinson et al., 2005; Dingwall, 2006; Yawn et al., 2009). Another problem may arise when different IRBs judge research projects in different ways. Sometimes IRBs in the same country judge differently (Van Teijlingen et al., 2008).

However, there are more basic reasons leading to dissatisfaction, such as the rejection of placebo conditions on principle by IRBs. There are several international guidelines in relation to placebo-controlled research, varying from a total ban to acceptance with some restrictions (Ehni en Wiesing, 2008). The IRBs' requirements for non-invasive intervention research differ widely in different European countries (Hearnshaw, 2004) despite the fact that all European countries have signed the Declaration of Helsinki.

Another complicating issue is the opinion of major government institutions. Although many countries endorse the Declaration of Helsinki, these institutions have formulated regulations which are not in line with this declaration. For example, the FDA in the United States has decided that clinical trials performed outside of the USA no longer have to conform to the Declaration of Helsinki when they are used to support applications for products in the USA and follow other standards (DHHS, Food and Drug Administration 2008). This decision has been heavily criticized (among others: Lurie and Greco, 2005; Normile, 2008; Goodyear et al., 2009). Also, the European legislation as implemented by the EMA has been criticized as favouring the interests of pharmaceutical companies above patients' interests (Garattini et al., 2009). These discrepancies in rules and opinions can be rather confusing, especially in multicenter studies in different countries with different IRBs.

The discrepancy between everyday practice together with the requirements of FDA or EMA and the Declaration of Helsinki is also criticized as being unethical (Rothman & Michels, 1994; Michels & Rothman, 2003).

In the Netherlands the acceptance of a placebo condition is also under discussion in those cases where an existing treatment is available in the field of psychiatric research. Most IRBs act pragmatically, however. If an existing treatment is available, a placebo condition is often accepted if the burdens and risks for the patient are limited and a clear rule for the collaboration on the study is included in the protocol in the case of deterioration of the patient's condition, together with the proposal to the patient, that, if necessary, they will receive the best-practice treatment after finishing their collaboration to the study (Nolen and Engberts, 2000).

8. Discussion

For a long time the opinion among experts has been that well-known treatments for depression are effective. This opinion is becoming less pronounced. For instance, a meta-analysis showed that antidepressants were only effective in placebo-controlled studies with patients who had severe depressions. No differences with placebos were found in patients with mild depressions. Moreover, antidepressants (and other treatments used for depression) are not effective in all patients (Kirsch et al, 2008; Whitaker, 2010). Up to 40-50% of patients do not show a satisfactory response. Therefore, the development of new, effective treatments is highly important, which makes the use of placebo-controlled study designs still necessary.

In this chapter it was argued that there is no sufficient evidence for a treatment of depression where the treatment outcome is the sole result of this treatment. According to the exceptions mentioned in section 32 of the Declaration of Helsinki, there is currently no best proven intervention available. This justifies the use of a placebo condition in depression research if the effectiveness of a new intervention or medicine is the subject of research. Besides, methodological reasons make it unacceptable to initiate research into new interventions for the treatment of depressions without a placebo condition. This is caused by the great heterogeneity of depression and the unpredictability of a placebo response. Therefore, it can be argued that the inclusion of a placebo condition in efficacy studies with new compounds or interventions to treat depression should be a standard rather than an exception (Meesters, et al., 2009, 2010). As long as new compounds or interventions are not more efficacious than standard treatments, the only way to show their efficacy is to compare them with a placebo. Performing efficacy studies without a placebo and taking the risk that no valid conclusions can be drawn at the end of the research because a placebo arm is missing, can also be considered unethical.

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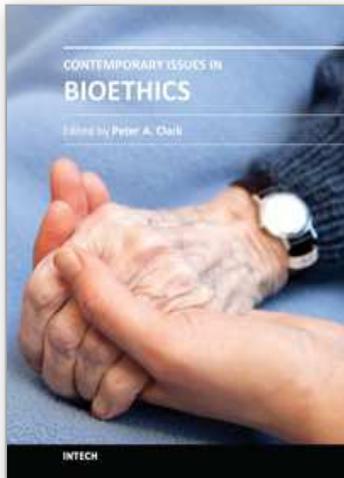
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The main strength of this book is the international exchange of ideas that will not only highlight many of these crucial bioethical issues but will strengthen the discipline of bioethics both nationally and globally. A critical exchange of ideas allows everyone to learn and benefit from the insights gained through others experiences. Analyzing and understanding real medical-ethical issues and cases and how they are resolved is the basis of education in bioethics for those who will have to make these decisions in the future. The more we examine, analyze, and debate these bioethical issues and cases, the more knowledge will be gained and hopefully, we will all gain more practical wisdom.

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