

Ethical Issues of Placebo-Controlled Studies in Depression and a Randomized Withdrawal Trial in Japan

Case Study in the Ethics of Mental Health Research

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Abstract: The use of placebo controls in psychiatric research is controversial. In this article, we focus on a troubling Japanese case of a randomized withdrawal trial of the antidepressant sertraline and analyze the ethical issues underlying it. First, we consider whether a placebo-controlled withdrawal trial should, in general, be considered more ethical than a standard placebo-controlled trial. We argue that the use of a placebo arm in this trial is ethically permissible but that there is no good reason to use a withdrawal trial design. Second, we discuss whether our moral evaluation of the use of placebo in this case should change when the special Japanese regulatory environment is taken into account. We argue that it should not and conclude that the use of withdrawal design in this case is ethically unacceptable.

Key Words: Research ethics, placebo, withdrawal trial, antidepressant, Japan. (*J Nerv Ment Dis* 2012;200: 255–259)

THE RESEARCH PROJECT

On July 22, 2006, the Asahi newspaper released an odd article concerning an antidepressant, sertraline, which had recently been introduced in Japan. Although sertraline was among the most popular of the serotonin reuptake inhibitors (SSRIs) developed in the early 1990s in the United Kingdom and the United States, its approval had been awaited for many years in Japan. According to the article, the Japanese Association of NEURO-Psychiatric Clinics (JAPC, a professional association composed of over 1400 Japanese psychiatrists) had written a letter to the pharmaceutical company demanding a release of data from clinical trials of the drug because of the conflicting descriptions in the drug package insert.

The JAPC had questions about one particular pair of statements in the drug company's information booklet for domestic sales promotion. The booklet's opening paragraph described the results of clinical trials conducted in Japan, saying "... it was indicated that sertraline worked effectively." However, in an annotation on the same page they said, "none of these results was sufficient to prove the effectiveness of sertraline." This confusing information meant that psychiatrists could not give a responsible explanation to their patients regarding the effectiveness of the drug.

The psychiatrists' concern partly stemmed from the placebo-controlled, randomized withdrawal trial design used in the trial whose data led to the approval of sertraline in Japan. Withdrawal designs are usually used to investigate the continuation of treatment or long-term

maintenance treatment of a drug. For instance, to study the relapse/recurrence of depression, the investigator first gives a certain medication to all research patients for a certain period of time, chooses only the treatment responders from the initial cohort, and then randomizes these responders to a placebo arm or a treatment arm. After randomization, the patients in both arms are followed up for a designated period of time. If the trial shows that the patients in the treatment arm are significantly better off than those in the placebo arm, it confirms the efficacy of the treatment to prevent the relapse/recurrence of depression. What was unusual in this case was that this design was used in a trial for the initial approval of a drug. In other words, the result of this withdrawal trial seemed to be regarded as evidence for the acute-phase treatment of depression, not for maintenance treatment.

Why did the researchers choose this controversial design instead of a standard placebo-controlled trial? In fact, there were ethical concerns regarding the use of placebo, and the researchers thought that a placebo-controlled withdrawal trial was ethically more acceptable than the usual placebo-controlled design (Kamijima et al., 2006).

We begin analyzing this case by reviewing the clinical symptoms and latest treatments of depression. We then turn to the ethical issues regarding this randomized placebo-controlled withdrawal trial. First, we show that the subjects who participate in a withdrawal trial will be deprived of a standard treatment for a longer period of time than those who join a normal placebo-controlled trial. Therefore, we conclude that a placebo-controlled withdrawal trial is actually more ethically problematic than a normal placebo-controlled trial. In the last section, we discuss an objection that might be raised against our conclusion. Some might argue that, even if our argument is sound in most other contexts, there is a special sociocultural backdrop in Japan that makes this withdrawal trial ethically acceptable. We provide reasons to think that the alleged special Japanese sociocultural context does not justify this withdrawal trial.

BACKGROUND: MAJOR DEPRESSION

Major depressive disorder is one of the most common mental diseases and one of the severe illnesses that cause disabilities and social dysfunction. Its core symptoms are a continuous low mood and/or loss of interest or pleasure in previously enjoyable activities. Depressed people may be preoccupied with thoughts and feelings of worthlessness or inappropriate guilt or regret and are often observed to be either agitated or lethargic. They may think of death or suicide repeatedly with no hope for the future. Statistics from various countries show that between 29% and 88% of all people who committed suicide had depression or another mood disorder (Takahashi, 2006).

Major depressive disorder is also characterized by physical symptoms, such as insomnia (and less commonly hypersomnia), decreased appetite and weight loss (or, occasionally, increased appetite and weight gain), reduced sex drive, general fatigue, headaches, and digestive problems. Other symptoms include poor concentration and difficulty in making decisions. In severe cases, there may be symptoms of psychosis, such as delusion.

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ISSN: 0022-3018/12/20003-0255

DOI: 10.1097/NMD.0b013e318247d24f

The Epidemiology of Depression in Japan

The latest survey in Japan (conducted between 2002 and 2003) reported a 12-month prevalence rate for major depression of 2.9% and a lifetime prevalence rate of 6.7% (Kawakami et al., 2005). The 12-month and the lifetime prevalence rates among Japanese women were double those among men.

Diagnosis of Depression

In general, a diagnosis of “major depression” is based on the patient’s subjective symptoms and information about his or her recent behavior offered by his or her family, friends, or colleagues. Psychiatrists will observe the patient’s looks, behavior, and way of speaking. Mental status examinations are sometimes used to support the diagnosis, but there is no laboratory test to specify major depression. Accordingly, the diagnosis process is more or less subjective; therefore, the diagnosis has traditionally varied widely between psychiatrists. Although there are several technical attempts to standardize criteria (such as ICD-10 and *DSM-IV*), the category of major depressive disorder itself is not scientifically homogeneous because the disease’s pathophysiology is not completely understood. Because those technical criteria are also merely a way to describe tentatively the patient’s current symptoms, the diagnosis at one time may differ from the diagnosis at another.

Pharmacotherapy

Although the causes and nature of depression remain incompletely understood, it is now apparent that various biological, psychological, and social factors are involved. As a result, pharmacotherapy, electroconvulsive therapy, psychotherapy, and environmental approaches are used as treatments.

In pharmacotherapy, antidepressants are the main treatment tools. Antidepressants are considered effective in 60% to 70% of depressed patients (Japan Committee for Prevention and Treatment of Depression, 2008; Kanba and Shioe, 1999). Classically, tricyclic and tetracyclic antidepressants have been used for treating depression. Although effective, these antidepressants also have serious adverse effects such as anticholine reactions and cardiac toxicity. Accordingly, since the late 1980s a new class of antidepressants—SSRIs—have been developed. Most SSRIs have fewer adverse effects, higher safety, and almost equivalent efficacy to classical antidepressants (Anderson, 2000; Shioe et al., 2005). In Japan, fluvoxamine and paroxetine have been used for a decade, and SSRIs are now considered primary drugs for the treatment of depression, together with the recently developed new class of serotonin-norepinephrine reuptake inhibitors.

The most distinctive feature of antidepressants is that they take a long time to have an effect. According to a widely used algorithm for mild to moderate major depressive disorders developed by the Japanese Psychopharmacology Algorithm Project, it is necessary to wait 2 to 4 weeks before evaluating the primary efficacy of an antidepressant and to increase the doses of the antidepressant after another 2 to 4 weeks even if there is no sign of efficacy (Seishinka Yakubutsuryohou Kenkyukai, 2003). Consequently, once a treatment is started with one antidepressant, it generally takes between 1 and 2 months to judge whether the drug is effective.

ETHICAL ISSUES

In this article, we analyze the ethical issues underlying this Japanese sertraline trial in the following stages. First, we consider whether a placebo-controlled withdrawal trial would normally be more ethical than a standard placebo-controlled trial. We argue that the use of a placebo-arm in this trial is ethically permissible, but we do not think that there are good ethical reasons for the use of the withdrawal trial design. Second, we discuss whether this judgment about

the ethics of the trial should change when we take the Japanese regulatory environment into account. We argue that it should not and conclude that use of withdrawal design in this case is ethically wrong.

Study Design: Placebo-Controlled Trials in Psychiatric Research

The use of placebo in randomized controlled trials has raised controversy for a long time. Some bioethicists insist that the use of placebo is always unethical when an effective treatment exists because it deprives a patient of the opportunity to receive treatment and therefore puts her at unnecessary risk of harm (Freedman et al., 1996; Rothman and Michels, 1994). Others argue that the use of placebo is sometimes ethically acceptable, or even required, provided that the subjects receiving placebo are not at great risk of serious harm and give informed consent (Levine, 1999; Temple and Ellenberg, 2000). They take the position that we can use placebo controls unless the condition the intervention treats causes death or irreversible morbidity. Current international guidelines on research ethics state that placebo use is permitted, even when an effective intervention exists, under certain conditions. For example, Guideline 11 of International Ethical Guidelines for Biomedical Research Involving Human Subjects developed by the Council for International Organizations of Medical Sciences (CIOMS) states,

Placebo may be used...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 or irreversible harm to the subjects.

In this sentence, they specify two concrete conditions for allowing the use of placebo: a) a placebo comparator is necessary for securing scientific validity and b) use of placebo adds no extra serious or irreversible risk. (The CIOMS Guidelines also mention that the use of placebo is acceptable “when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms.” However, we are not going to address this point in our discussion here.) Article 32 of the Declaration of Helsinki (World Medical Association, 2008) sets out two similar conditions. Therefore, we now need to consider whether these two conditions are fulfilled in the present case.

Depression has a high placebo response rate, and the standard treatments for depression have limited efficacy. For example, Laughren (2001) demonstrated that approximately half of randomized placebo-controlled clinical trials of antidepressants that were already approved by the US Food and Drug Administration actually failed to show that the active drugs were more effective than a placebo (Laughren, 2001). This means that active-controlled trials that show the equivalence of experimental and standard drugs do not give reliable evidence that the experimental drugs are better than placebo. Therefore, Miller (2000) argues that placebo-controlled trials are necessary to gather reliable data on certain psychiatric drugs for treating depression. A consensus now seems to exist in the psychiatric research community that clinical trials of antidepressants need placebo arms for scientific validity.

What about the risk condition? The risk of greatest concern in the clinical treatment of depression is suicide. Numerous previous studies have indicated, however, that the suicide risk among those in the placebo arm in clinical trials of antidepressants is not significantly higher than among those in the active arm (Khan et al., 2003). If this is true, then we should focus our concern on the risk of deterioration of symptoms. In general, in depression or mood disturbance, patients randomized to placebo are likely to experience deterioration to some extent. However, it has been argued that such deterioration does not constitute a serious irreversible harm (Miller, 2000). In fact, there is

no evidence that short-term placebo administration in psychiatric research results in lasting harm to the patient (Quintin, 1999).

Taking these points into consideration, it would be inappropriate to claim in this withdrawal trial that the use of a placebo arm itself is unethical. Certainly, the trial poses some additional risks to subjects in the placebo arm. However, the risk is not so great that the trial is thereby unethical. It would be unethical if it were possible to run a trial with a lower level of risk to subjects. In the next section, we discuss how the risks could be reduced.

Risks and Benefits

To reduce risk, the CIOMS Guidelines (2002) propose, for instance, the use of an add-on trial design or the provision of an independent Data and Safety Monitoring Board (DSMB). An add-on design is usually adopted in clinical trials of anticancer drugs, in which the treatment to be tested and placebo are each added to a standard treatment. This means that neither group gets deprived of a treatment that is known to be effective. The DSMB is a safeguard to protect research subjects from unknown adverse reactions and to prevent them from unnecessarily prolonged exposure to an inferior treatment.

Like an add-on design, the withdrawal trial design was adopted in the present case with the intention of minimizing the risk to the subjects by modifying the trial design. The ICH E10 Guidelines (2000) designate a randomized withdrawal design as one example of a study design that can resolve ethical, practical, or inferential issues in placebo-controlled trials, along with add-on designs, three-arm designs, and early escape designs. The guideline describes the advantage of a withdrawal trial design as follows:

The general advantage of randomized withdrawal designs, when used with an early-escape endpoint, such as return of symptoms, is that the period of placebo exposure with poor response that a patient would have to undergo is short. (p. 17)

Did the use of a withdrawal trial design really contribute in the sertraline case to a reduction of the risk compared with a standard placebo-controlled trial? As Charney et al. (2002) mention, it is true that making the period of time on placebo as short as possible is one important way to reduce the risk to subjects. However, when we compare a withdrawal trial with a standard placebo-controlled trial, it is doubtful whether a withdrawal trial design can really decrease the risk to the subjects.

Consider, first, the situation in the abstract. Assume two trial designs, A and B, which are proposed for the evaluation of an experimental antidepressive treatment X whose effectiveness is unknown. Design A is a standard placebo-controlled trial, in which the research subjects are randomized from the beginning of the trial for 16 weeks to the placebo arm or the active arm. In Design B, a withdrawal trial, all subjects receive the test treatment X for the first 8 weeks, and those who are judged to be responders to the treatment are then randomized for the next 16 weeks to the placebo arm or the active arm. Assume all other safeguards are in place.

Does Design B reduce risk to the subjects more than Design A? At first glance, Design B appears to be reducing the risk to the subjects because they are all “treated” before randomization, and any subject who does not respond to the intervention is excluded from the trial. However, we have assumed that the efficacy of treatment X itself is not proven and therefore unknown. As long as we do not know the efficacy of X, we cannot tell before doing the trial that “treating” the subjects for 8 weeks with X is going to benefit the subjects.

Moreover, even if the condition of some subjects who receive X for 8 weeks improves, we cannot conclude that receiving X has caused the remission or cure: the true causal factor could be something other

than X, for example, spontaneous improvement. As a consequence, therefore, the risk-benefit ratio to the subjects seems to be the same in both trials. Indeed, considering the duration of trials, Design A seems to be a better choice than Design B because B requires the subjects to stay in the trial 50% longer than A. In other words, the subjects in B are deprived of a treatment known to be effective 50% longer than those in A.

Moreover, considering the scientific benefits of the trials, we can also conclude that Design A is a better trial design than Design B because in A, if treatment X is proven to be effective, X is highly likely to be eventually marketed as a new intervention for the acute phase of depression. Conversely, Design B cannot yield such a meaningful result because it can prove only that the recurrence of depression is suppressed by X; it cannot show that X is effective for the acute phase of depression. Kurihara and Saio (2007), who criticized the sertraline withdrawal trial, emphasized that a withdrawal trial like this cannot give evidence of efficacy for the acute phase of depression. We agree with their judgment on this point.

Taken altogether, it looks like Design A (standard placebo controlled trial) is better than Design B (withdrawal trial) in terms of the risk-benefit ratio because A deprives subjects of effective treatment for a shorter period than B. Design A is also better than the Design B in terms of the social value of its results. Accordingly, use of a withdrawal trial design is an ethically worse decision for investigating the efficacy and safety of a new antidepressant. We think that more attention should have been paid in this trial to efforts other than the modification of the trial design, such as requiring more stringent screening and exclusion criteria to protect patients at higher risk of deterioration, giving a rescue treatment when the subjects' condition worsened, and providing active treatment for a period of time after the trial was completed.

Study Population: The Sociocultural Backdrop

We have demonstrated that use of a withdrawal design is ethically inappropriate for the sertraline trial. Nonetheless, some people may think that our argument ignores the special Japanese context and argue that this gives a distinctive reason for using a withdrawal design.

“Drug Lag” in Japan

To understand why some people consider this sertraline trial acceptable (Higuchi, 2005, Miyoshi et al., 2006), we need to look at the social and cultural complexity surrounding the Japanese drug approval process. First of all, in Japan, not only sertraline but also various other internationally standard drugs are not approved. This “drug lag” has recently become an issue of great public concern in Japan. A recent study covering 370 new drugs that were approved either in the United States, European Union, or Japan between 1999 and 2006 shows that almost 80% were approved in the United States and European Union, but only 50% were approved in Japan (Tsuji and Tsutani, 2008). This study also shows that the mean approval lag for Japan was 3.1 years after approval in the United States and European Union.

A major source of delay in drugs reaching the Japanese market is that for regulatory reasons, in Japan, in many cases, drug approval data must be obtained from trials using Japanese subjects. This means that pharmaceutical companies who want to sell their drugs in Japan must repeat their trials using Japanese subjects, even when a drug is already used outside Japan as a standard treatment worldwide. Sertraline was no exception to this rule. Because of these circumstances, most Japanese physicians and patients perceive involvement in a clinical trial not as enrolment in a research study but more as a form of clinical practice in which patients can get early access to new treatments. As a natural consequence, they are apt to prefer active controls in any clinical trial.

Criticism of Placebo in Japan

Japanese people also have a strong aversion to placebo, which has obstructed its use in clinical trials. This negative image of placebo is well reflected in the term *Giyaku* (偽薬 in the Japanese Kanji characters), which is a translation of “placebo.” *Giyaku* means a counterfeit or fake drug, even though the meaning of placebo in English does not have such a negative connotation. Such a stigma on placebo in Japan is highly related to the historical process of importing the notion of placebo from the West (Tsutani, 1997). Therefore, it was difficult to get acceptance of placebo use in clinical trials in Japan.

Policy Change by the Japanese Regulatory Agency

In contrast with the cultural presumption against placebo use, the Pharmaceuticals and Medical Devices Agency (the Japanese regulatory agency) began to require placebo-controlled trials in the 2000s, partly because the latest ICH E10 Guideline recommended placebo controls. As a result, the drug company that wanted to introduce sertraline to the Japanese market found itself in a bind. The company had to find a compromise between active- and placebo-controlled trials and finally used the withdrawal trial design. The withdrawal design appeared at a glance to most of the researchers to offer an active, real “treatment” to all the research subjects, especially at the beginning of a trial. Consequently, it was regarded by both clinicians and patients in Japan as much more acceptable than the standard placebo-controlled design.

Reconsidering Ethical Issues in the Withdrawal Trial

However, as we argued above, this is an illusion: withdrawal trials cannot reduce the risk of subjects compared with a standard placebo-controlled trial. Let us return to the comparison of Design A, a placebo-controlled trial, with Design B, a placebo-withdrawal trial, to see this point. Previously, we assumed that the intervention being tested was a drug X whose effect for the early, acute phase of disease was unknown. Suppose, instead, that the test drug X is sertraline. Does this change our conclusion? If the test drug X is already known to be effective for not only the acute phase but also the maintenance phase of disease, research subjects receiving X will apparently benefit more when involved in Design B than Design A because in B, all subjects receive an active “treatment” for the first 8 weeks before randomization.

On the other hand, based on this presumption, not only Design A but also Design B faces an ethical problem. If the efficacy of X is already proven, the use of placebo in the trial is unethical regardless of whether a withdrawal design is being used or not. Moreover, planning and conducting such a trial itself is never justified regardless of trial designs because the efficacy of X is already established and the trial is thus not expected to add any novel, useful scientific knowledge and will therefore not benefit society.

Accordingly, we come to the same conclusion. A withdrawal trial is inferior to a standard placebo-controlled trial in terms of risk-benefit ratio if there is insufficient knowledge of the efficacy of sertraline with Japanese patients. Alternatively, both trials would be unethical if there is sufficient knowledge of the efficacy of sertraline with Japanese patients. As a consequence, it is difficult to justify the use of the withdrawal design in this Japanese sertraline trial; therefore, even considering the unique Japanese context does not change our initial judgment.

CONCLUSIONS

Placebo-controlled trials can deprive subjects of an opportunity to receive a standard treatment. Researchers are therefore responsible for making efforts to reduce the risks to subjects when they use placebo. In this Japanese sertraline trial, the researchers thought that

they could make the use of a placebo control more acceptable by using a withdrawal design. However, as we have argued, the use of the withdrawal trial design did not improve the risk-benefit ratio. In fact, the withdrawal design needs 50% longer than a standard placebo-controlled trial. This means that subjects who join a withdrawal trial will be deprived of a standard treatment for a longer period of time. Moreover, withdrawal trials produce less useful knowledge than standard placebo-controlled trials. The use of the withdrawal design in this case was therefore not ethical.

Some might oppose our conclusion, claiming that there were good reasons to use the withdrawal design in the sociocultural context of drug development in Japan. Given the “drug lag” in Japan, a withdrawal trial was expected to give subjects better access to an effective drug (that had been tested outside Japan). However, there must be insufficient knowledge about the efficacy of sertraline to justify the conduct of clinical trials. If we already know that sertraline is effective for Japanese patients, conducting a withdrawal trial is unethical, as is a standard placebo-controlled trial, because neither of them leads to any useful scientific knowledge. Therefore, the Japanese context does not change our conclusion.

FUTHER READINGS

The Use of Placebo in Randomized Controlled Trials

There are many articles regarding the ethics of placebo-controlled trials. Below, we list two articles that take opposing positions and one article that considers the ethics of placebo-controlled trials in psychiatric research.

Freedman B, Glass KC, Weijer C (1996) Placebo orthodoxy in clinical research. II: Ethical, legal, and regulatory myths. *J Law Med Ethics*. 24:252–259.

Temple R, Ellenberg SS (2000) Placebo-controlled trials and active-control trials in the evaluation of new treatments: Part 1 ethical and scientific issues. *Ann Intern Med*. 133:455–463.

Miller FG (2000) Placebo-controlled trials in psychiatric research: An ethical perspective. *Biol Psychiatry*. 47:707–716.

Drug Regulation in Japan

There are no good articles in English that provide an overview of the Japanese regulatory environment. However, the following articles give useful information about the sociocultural backdrop to psychiatric drug development in Japan.

Berger D, Fukunishi I (1996) Psychiatric drug development in Japan. *Science*. 273:318–319.

Kiemayer LJ (2002) Psychopharmacology in a globalizing world: The use of antidepressants in Japan. *Transcult Psychiatry*. 39:295–322.

ACKNOWLEDGMENTS

The authors thank Joseph Millum and Reidar Lie for helpful comments on earlier drafts of this paper.

DISCLOSURE

This study was supported by the Grant-in-Aid for Young Scientists (Start-up) (no. 21830031) of the Japan Society for the Promotion of Science and the research grant in 2010 from the Japan Medical Education Foundation.

The authors declare no conflict of interest.

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