Asian Journal of Pharmaceutical Technology & Innovation
ISSN: 2347-8810

Review Article

Received on: 01-11-2014
Accepted on: 21-11-2014
Published on: 15-12-2014

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Implication of Placebo Upshot in Biomedical Investigations: False Hope and Best Clinical Data

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ABSTRACT

Placebo is used as a substance, medicine and procedure that the physician believes has not known certain pharmacological action against the condition that being treated. If this produces an effect in patients resulting from its unquestioning or manifesting purpose and not from its specific physical and chemical properties. Placebos often take in the form of sugar pills, saline injections, miniscule doses of drug or sham procedures designed to be void any therapeutic value. In medical research placebo given as control treatment depend on the use of measured suggestion the based on false information. Some of physician believes that placebo can be produces an effect negative or positive based on patients psychological thinking. The ethical aspect of the use, act of placing patient in placebo group has been equated with the negligent withholding of treatment. This could be interpreting as a violation of beneficence. The use of placebo controls touch main of four ethical principles that are principle of autonomy, beneficence, paternalism is the special type of beneficence and nonmaleficence. Both the World Medical Association's Declaration of Helsinki and Council of International Organization for Medical Sciences' International Ethical Guideline for Biomedical Research Involving Human Subjects have recently been revised in a way that seems to support wider use of placebo controls. Ultimately, deceptive use of placebos is not ethically acceptable because it may potential harm to patients to greater degree than it helps them. Biomedical Research and development of new drugs and implies an important investment of human and economic resources for conducting clinical trials designed to evaluate efficacy and safety of new medications. Knowledge of mechanisms of placebo effect and how the latter can influence the different efficacy variables in these research studies appears essential in order to optimize the available resource in application to development of new drugs.

Key-words: Beneficence, Nonmaleficence, Sham procedure, miniscule doses of drug, Clinical trial, Negative effect and Positive effect.

Cite this article as:
Pramod Singh Khatri, Brajpal Singh, Implication of Placebo Upshot in Biomedical Investigations: False Hope and Best Clinical Data, Asian Journal of Pharmaceutical Technology & Innovation, 02 (09); 2014. www.asianpharmtech.com

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Introduction

Although there is evidence of the use of placebo effect in medical experiment dating back to the 18th century, no consensus based definitions of the word placebo (Figure 1) and its effect have been established to date. The real interest in the placebo effect began with the generalized use in medical research of randomized and controlled clinical trial designed during Second World War, resulting from the observation that the patient included in group receiving placebo effectively improved of their disease condition, in some case to a spectacular degree. This led to the publication of famous article "The powerful placebo", which generated growing interest in medical research of this peculiar psychobiological effect[1]. This effect persists to the present day. In effect, the number of publication addressing this subject has increased 5-fold in the last 23 years. The use of placebo in biomedical research has received much more attention than has their use in clinical practice. Clinical use of placebos in a way that respect patients' autonomy by allowing them to participate actively in the medical decision making-process. A placebo has defined as the substance, medicine and procedure that is objectively without certain the action against the condition that being treated. Placebo can be therapeutically beneficial for some patients when they give rise to the so called placebo effect. Positive placebo effect may include symptoms reduction and improvement physiological parameters (e.g., blood pressure) and are trusted to be due to mind-body or interpersonal (e.g., stance and intent of caregiver) factors.

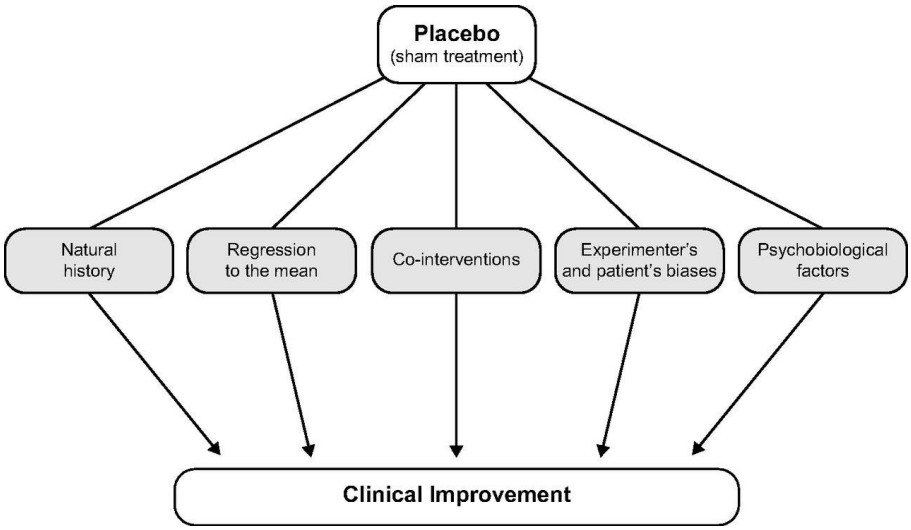

Figure 1:- Impact of Placebo in clinical study

Negative placebo effect, ranging from minor discomforts and life threatening complications. Most commentators agree that these trial acceptable when aimed at testing a new treatment for disease for which treatment is currently available[2]. They are, however, deeply divided about appropriateness of placebo-controlled trials involving patients when an effective treatment already exists for their conditions. The concealed use of placebo carries risk liability, fraud, malpractice breach the contract and a violation of informed requirement. Attorneys of different part of country have concurred that use of placebos in trial is a violation of informed consent. The Spanish Language Dictionary of the Spanish Royal Academy (22nd edition) defines placebo as "a substance which, while lacking therapeutic action in itself, is able to induce a healing effect in the patients, if latter is convinced that the substance truly has such an effect"[3].

Placebo Effect Mechanism

The studies carried out in the last decade support that the placebo effect is a genuine psychological event resulting from interaction of individual patient factors, physician-related factors and other related to therapeutic environment, including the nature of intervention, the form of administration, and inherent characteristics in physician-patient relationship[4]. The mechanism involved placebo type interventions are still subject to debate, but may be summarized in correspondence into three groups:

Anticipation and Conditioning

This variety of mechanisms consequences that there are multiple placebo effects not just single effect. The psychological mechanism includes perception, expectation conditioning, learning, motivation, somatization, reward, the lessening of anxiety and significance. If the substance thought helpful, it can treat, but, if it is produced harmful effect, it cause negative effect which called as nocebo. Because placebo effect based upon the expectation and conditioning, the effect is vanishes if the patient is told that their expectation are unrealistic. A conditioned pain reduction can be totally removed when its existence explained[5]. It has also been reported of subjects given placebos in a trial of anti-depression, that once the trial was over and patient who had been given placebos were told as much, they quickly deteriorated.

Placebo described as a muscle relaxant will cause muscle relaxation and, if described as opposite, muscle tension. A placebo presented as a stimulant will have this effect on heart rhythm, and blood pressure, but when given as a depressant, the opposite effect. It perceived ergogenic aids can increase endurance, speed, and weight-lifting ability, leading to the question if placebo should be sport competition.

Body and Brain Mechanism

The brain has be wield over the body systems influence by placebos. In conditioning, nonaligned stimulus saccharin is duo in a drink with an agent that produces an unintended response. For example the agent might be cyclophosphamide that causes immunosuppression. After understanding this duo, the taste of saccharin by itself through neural top-down control create immunosuppression, as a new attributable response[6]. Such conditioning has found affect a diverse variety not just basic physiological processes in immune system but ones such serum iron levels, oxidative DNA damage levels and insulin secretion. Recent reviews have argued the placebo effect due to top down control by brain for immunity and pain. Pacheco-Lopez and colleagues has raised the possibility of neocortical-sympathetic-immune axis provide neuroanatomical substrates that might explain the link between the placebo/conditioning and placebo/expectations response.

Evolution of Health Wellness

Evolutionary medicine recognized many symptoms such as fever, pain and sickness behavior as evolved response to protect or enhance the recovery from infection and injury. Fever, for example, is transform self-treatment that discard bacteria or virus by raising body temperature. These progressed responses, nevertheless, also have a cost that relying on situations can outweigh their benefits[7]. According to health management system theory suggested by Nicholas Humphrey, the brain has been selected to assure that the progressed responses are deployed only when the cost benefit is biologically advantageous. To do it, the brain factors in a variety of information source, indulging the likeliness derived from trust that body will get well without deployed its costly evolved responses. This source of information is the knowledge the body is receiving care and treatment. The placebo effect in this perspective arises when incorrect information about medications misleads the health management system about the likeliness of getting well so that it selected not to apply a progressed self-treatment[8].

Ethical Arguments toward Placebo Research

Ethical arguments against placebo-controlled studies

The act of placing patient in placebo group has been equated with the negligent withholding of treatment. This could be interpreting as a violation of beneficence. In some study however, the standard therapy may not be otherwise available to the study group[9-11]. The Helsinki Declaration of world health organization has been used as percussion against placebo-controlled studies. The Declaration of Helsinki interpret as a statement that individual should never be placed in a condition where they receive inferior treatment. This argument touches the principle of paternalism: the idea that researcher know best and will make ethical judgment for all subject. However, this is in disagreement of with the principle of autonomy, which retain that educate individuals should have option for participating in the clinical study if they are willing to take risk of receiving placebo. They may want to assist to the study that can ultimately help or prevent harm to themselves and others, or they may want to risk placement in a placebo group for chance to receive a superior treatment[12-14]. In this way principle of autonomy states that this wish belong to the informed subject. Paternalism also ignores the fact that some patient do not want standard treatment. They can be more respond to the placebo because many factors such as increase sensitivity to side effect, a desire to become pregnant or coexisting medical condition. The issue defining the meaning of Helsinki Declaration raise the ethical concern that arbitrary definition effective and proven can lead to the licensure useless and harmful drugs. Aside from a violation of principle of nonmaleficence, the legalization of such drug have also negative consequence that are less readily apparent.

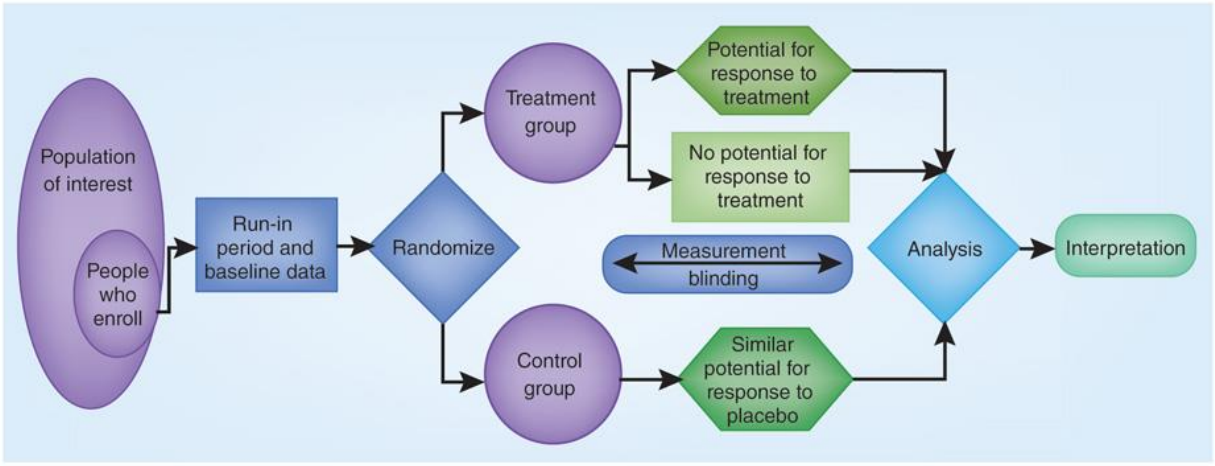

Figure 2:-Mechanism of placebo-controlled studies

Resource and time will wasted while evaluation the drug's long term effects and compliance to the drug even though it may not be better than the placebo. This point does not elucidate a weakness of placebo-controlled studies, but rather one of drug-regulating bodies and vagueness of their statutes[15]. Consent- which is integral to the exercise autonomy- has also been fiercely debate issue. For these reasons, treating clinicians should exclude from their research any patients with whom they have personal or significant professional history.

Ethical Argument in support of placebo-controlled studies

Some theoretician authenticate that the object of research to find out the therapy that is more effective than current standard. Instead of focusing on and debating how to define such a gold standard, our objective should be spread out the list of efficacious drug and wider access to treatment. Integrate with the principle of autonomy, expand the list of efficacious drug would allow the patient to weigh the relative benefit and harm of each treatment and an informed decision on which is the best for them. When the World Medical Association (WMA) propose the limiting use of placebo in research only studies

involving interventions lacking a comparator group demonstrate efficacy pressure from the different investigating group caused it to quickly issue an amendment to Declaration of Helsinki accepting use of placebo, provided such use does not pose an important risk for the subject participating in the study[16]. In this way it admitted that the comparator group with placebo allows much better evaluation of true efficacy and safety of any medical intervention. According to the principle of beneficence, few drug available that may appear consistent with principle. Another aspect of patients' standard treatment as 'harmful' if there is a high probability of unpleasant side effects. Some of side effect may be irreversible, tardive dyskinesia resulting from use of phenothiazine to treat schizophrenia. For some reason patients should know their option and have the power to make decision about treatment, such as denying the patients a wider range of treatment options the autonomy of patients violated (if they capable). Biomedical research for the development of drug involves an incalculable investment of human, material, especially economic resources[17]. As a result in most cases the statistical power of clinical trial for detecting difference between medical intervention and placebo is limited by the cost, since it is essential depend on study sample size.

Legal Standard for Research

We have analyzed four jurisdiction in which in our view the law only permit use of placebo as control arm of a clinical trial when there is no effective therapy available. We are confident that other jurisdiction in the world have similar legal standard. These legal standard could be invoked to challenge regulatory policies of some regulatory agencies that impose a placebo control even when standard therapy is available[18]. They could also lead to legal liability when subject are harmed in placebo-controlled trials and causal relationship can be established between harm and the inclusion in a placebo arm. In our view, two relative concept deserve our attention for a legal discussion of placebo rules in these ethics documents: (1) the notion of primary of the human subjects, which has been recognized in many ethics guidelines, but is also increasingly finding its reflection in law; and (2) the physician duty of care and the notion of fiduciary relationship. It suffices for the purpose of our critique of the CIOMS placebo rules to point out how it permit a violation of legal standards in the following four different jurisdictions: Canada, Belgium, Switzerland, and South Africa. We do not claim that these countries, three of which industrialized nation, can be used as paradigm jurisdiction for all legal issue in research. However the legal principle that we discuss here are fairly standard among civil law, common law and mixed jurisdictions. Legal system in southern nations have been heavily influenced by and often based on common or civil law[19]. Belgium and Switzerland are traditional civil law countries, Canada has both common law and civil law. South Africa is a good representative of Southern country where much pharmaceutical research is taking place.

Scientific Argument toward Placebo-Controlled Studies

The main criticism in placebo controlled-studies is that they do not use proper blinding procedures. A recent textbook on clinical drug trials advocates using them because "if a new drug has only been compare to an active control (without a placebo controlled trial), this is not convincing proof of efficacy (even if equivalence may be demonstrated)." Without justification. Many of them spent time to guessing which condition they are in, further, because they must be told beforehand a potential side effect, subjects can often guess what treatment they are given. "To have truly blind procedure, the active placebo must have an identical physiological effect to those of medication being studied"[20]. This orientation seems unfair because it demands strict physiological matching between new therapies and placebos, but not between new therapies and standard treatment. It is satisfactory to assume that new treatment will often no induce physiological sensation that are identical to that ones, that the standard treatment does; therefore, the 'differential effect' argument is not specific to placebos, but to drug trials in general. The question of utilization has raise by those who feel that placebo-controlled studies are only

useful in proving that treatment is not better than placebo. Interpreting the acceptance of null hypothesis in these way, however, is contrary to statistical practice and is not parsimonious. Aside from actual equivalence of two treatment many reason may exist for null finding such as poor design, improper execution of methodology, or too few subjects. Therefore negative result are more likely to be interpretable than positive ones. Past placebo research has criticize because of inconsistent administration method. Color, shape, and dose schedule of placebos have all varied in past experiments[21]. We agree that such administrative variables should be kept constant in order to compare past studies. A placebo should be delivered in the same way as comparative treatment.

Scientific Argument in Support of Placebo-Controlled Studies

Placebo arm can distinguish side effect of medication from effect of disorder. Although the study of ethics inform us of what we should do with the placebo trials, science give us impulse for why we will want to use them. In general it is difficult to determine drug efficacy on its own because of the unpredictable courses of many disorders. State that placebo are better used when placebo response rate are high, variable or close to response rate of 'effective' therapy; when the standard therapy carry high risk negative side effect; or when a standard therapy is only effective against certain symptom of disorder. Placebo trials permit us to curb for the factor that could enigmatic and confound the demonstration of drug effect such as time, attention from others, and a change of setting, pampering, hope, and legitimization of sick role. Placebo trial could be used to calibrate the skill of research group by focusing on sensitivity of the instruments used and accuracy and reliability of raters. This important because no statistical analysis can be correct the poor design of a study. Placebo arm permit scientist to judge the conclusions of other studies. For example, one study may find the drug to be no more effective than placebo and conclude that such a drug is not effective[22]. However if placebo response rate was high, then the subject chosen may not have required any medication and would not have been expected to respond differently to a drug condition. If possible, the three arm trials are best design. This design involves comparing anew treatment, a standard treatment and placebo group. Active controls attempt to replicate to side effect of standard treatment purpose of blinding. By examining the standard treatment, new treatment and placebo, the three arm study allow one to simultaneously study test efficacy of new treatment as well as its benefits relative to standard treatment. While it is true that some of subject will be deprived access of standard therapy, placebo arm need to be judge whether a change in symptoms is associated to treatment. Even if new treatment and standard treatment are found to be equally effective, it important to determine their efficacy above and beyond placebo. To prevent a conflict of interest and confusion on the part of subject, researchers should not be those involved in a subject's clinical treatment. Clinical work and researcher work different object, as evident by their differentiation under the law.

LIMITATION

Even though there is much ethical and scientific merits to the use of placebos, this practice is not without its limits. For instance debate exists as to whether placebo should be given to those with severe disorder because they may be more likely to experience negative outcomes[23]. we think that placebo trial can never be ethically administered if high probability of harm exists, as is the case of severe disorder in which individual deprived of medication may harm themselves or others. Another limitation that short term placebo-controlled trials may not elucidate long term effects. This is problem with all comparison tests, including testing new therapies against standard ones.

CONCLUSION

Even though many criticism have been raised against use of placebo control, many of these concern faulty, general to most research, rooted in paternalism or do not provide better methods to testing of

drug efficacy. Placebo controls can provide important information about treatment and help broaden the range of choices that individual have in making autonomous decision about treatment. Therefore, because of their scientific merits and consistency with the principle of autonomy and beneficence, placebo-controlled study are indeed ethically and necessary in biomedical research and clinical trials.

Conflicts of Interest Statement:

The Authors declare no conflicts of interest.

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