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EDITORIAL

Design flaws in randomized, placebo controlled, double blind clinical trials

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Abstract

The hypothesis in drug clinical trials is that the drug is better than a placebo in patients suffering from a disease. The unstated assumption is that the drug cures the disease or is a powerful treatment for the disease. This is an incorrect assumption. Drugs do not cure or treat diseases. The body heals itself; drugs promote this ability of the body to heal itself. Placebos are assumed to be inactive; however, placebos can also promote the ability of the body to heal itself. Placebos are actually treatments that can stimulate endogenous healing mechanisms. The possible place of placebos in health management is controversial. Clinical trial design should be altered. The hypothesis of clinical trials should be that the drug speeds up or improves the healing of the patient, putting patient healing as the first objective. Placebos should not be used as controls but could be tested as drugs in their own right. The control in clinical trials should be no treatment. Alternatively, new drugs could be compared to existing drugs in clinical trials.

Key words: Randomized clinical trials; Placebo effect; Drug efficacy; Healing

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BACKGROUND

The basis of clinical pharmacology is the randomized, placebo controlled, double blind clinical trial (RCT). Design recommendations for RCTs can be found at www.consort-statement.org. The hypothesis in RCTs is that the drug will produce a greater response than a placebo in patients suffering from the same symptoms caused by the same disease. RCTs are designed to prove the power of new drugs. This design comes directly from laboratory pharmacology experiments, such as when receptor activation by a drug is tested in comparison to a placebo. These laboratory experiments can be carefully controlled, especially in purified receptor preparations. There are many difficulties in extrapolating from experimental design in purified receptor preparations to RCTs in diseased patients. Purified receptor studies do not contain endogenous agonists and antagonists that confound RCTs. A basic assumption in RCTs is that healing is the same as efficacy in comparison to a placebo. This assumption is frequently not true[1].

HEALING THE PATIENT IS THE FIRST PRIORITY

RCTs seek first to prove the efficacy of a drug but do not seek to heal the patient. In fact, some RCTs seek receptor interactions or symptom reduction as the end point, not

healing. It is assumed that activating receptors is enough to heal the patient. This is not always true. Several drugs have been approved for use in the USA by the FDA after extensive RCTs, only to be shown to be ineffective at healing patients in post marketing studies. Examples of this are: gemtuzumab ozogamicin, erityl tetranitrate, propoxyphene (not recommended in elderly patients in California), trimethobenzamide hydrochloride and midodrine.

BODY HEALS ITSELF

Each receptor in the body has one or more endogenous agonists and endogenous antagonists[2]. These agonists and antagonists exist in a balance that is called health. When this balance is corrupted, disease may occur. This is similar to the Chinese concept of balancing yin and yang in health. For instance, insulin is an endogenous agonist that binds to and activates the insulin receptor and increases the uptake of glucose into cells. Insulin receptor activation is inhibited by a variety of endogenous antagonists including: ceramide, TNFα, visfatin, IL-6, resistin and RELMs[3-5]. When the balance of agonists and antagonists is altered, insulin resistant diabetes can occur. In hypertension, resistin, an endogenous antagonist, inhibits bradykinin, an endogenous agonist, induced vasodilation[6]. Vascular tone is decreased by a variety of endogenous agonists, including PGI_2, nitric oxide and acetylcholine. Blood pressure is increased by several endogenous compounds such as endothelin, angiotensin, renin, aldosterone and other factors. Anxiety is another example, where receptor dysfunction is learned by the patient. In other words, a cognitive act of the patient causes an imbalance in the agonist antagonist balance in the brain and results in receptor dysfunction. The receptors involved include: norepinephrine, arginine vasopressin, neuropeptide Y, galanin, dopamine, serotonin and GABA[7,8]. Anxiety may decrease the healing of some diseases.

Hormones and other endogenous compounds have releasing agents and release inhibition agents that exist in a balance required for health, such as somatostatin and somatocrinin. In disease, the balance is prevented by increased production of endogenous compounds that promote disease. For instance, endocannabinoids increase in obesity, inhibit the secretion of anti-inflammatory adiponectin and increase the secretion of inflammatory adipokines[9] that are involved in atherosclerosis, arthritis, diabetes, hypertension and other chronic conditions[10].

PLACEBOS ARE TREATMENTS THAT STIMULATE ENDOGENOUS MECHANISMS

Recent authors defined "a placebo as any treatment that is used for its ameliorative effect on a symptom or disease but that is ineffective for the condition being treated"[11]. However, many substances can be effective for the condition being treated since they stimulate the body's ability to heal itself through endogenous mechanisms. In contrast, a drug is itself capable of interacting with receptors that stimulate endogenous mechanisms and promote the body's ability to heal itself. It might be more appropriate to define a placebo as an agent that acts only by stimulating endogenous agonist antagonist mechanisms. Even this definition is troublesome. For instance, morphine is an endogenous agonist that is made in the human body. Therefore, administering morphine stimulates endogenous agonist antagonist mechanisms.

Most studies use a solvent, capsule or tablet that does not contain the drug as a placebo. A recent review discussed data showing that placebos increase the healing of many diseases, or at least decrease the symptoms of many diseases[12]. Placebo effects cannot be dismissed and may be clinically significant. Recent guidelines advise using the placebo effect to augment analgesia[13]. However, a recent meta analysis of 202 RCTs found that placebos did not have clinically significant effects[14]. Placebos are very good at increasing dopamine release, decreasing pain, decreasing headaches, increasing endogenous opioid release, decreasing β-adrenergic activity, anxiety relief, immunosuppression and other specific pharmacological effects[12,15-18]. It is very possible that treating anxiety may help with healing of many diseases[12]. Similarly, treating pain may improve healing of some diseases. Placebos, like drugs, can facilitate the ability of the body to heal itself through endogenous agonist and antagonist mechanisms. The exact mechanism (s) of action of placebos is not known. In other words, it is not known how placebos reestablish endogenous agonist and antagonist balance.

A confounding factor in placebo mechanisms is that, since they stimulate endogenous opioid release, some patients like them. This has prompted some scientists to conjecture that anything that stimulates endogenous opioid release is a placebo. This argument is used as proof that acupuncture, which stimulates endogenous opioid release, is a placebo treatment. However, acupuncture also stimulates type Ⅱ and Ⅲ small diameter, myelinated afferent nerve fibers in muscles that send impulses to the spinal cord and activate analgesia centers in the spinal cord, midbrain and hypothalamus-pituitary[19]. The spinal cord neurons are endorphinergic and release enkephalin or dynorphin to block pain transmission. Periaqueductal gray matter cells in the midbrain secrete enkephalin, which results in serotonin and norepinephrine release in the spinal cord to inhibit pain transmission. The pituitary gland releases β-endorphin into the blood to cause analgesia at remote sites. Acupuncture is useful therapy in many patients[20], is FDA approved and is covered by many medical insurance companies. It should also be remembered that many drugs stimulate the release of endogenous opioids, such as capsaicin[21], alcohol[22], cocaine[23], propofol[24], ibuprofen[25], clonidine[26] and serotonin releasing drugs[27]. If endogenous opioid release

is specifically characteristic of placebos, then some drugs are placebos.

Several studies have sought ways to predict which patients will have placebo responses in order to eliminate these patients from selection. Some studies have suggested that the placebo response is predicted by beliefs and expectations of patients[28-30]. Other studies have found placebo response correlates with Caucasian patients, study duration, disease severity, dosing regimen, type of RCT, doctor patient communication and other factors[31-33].

CARPENTER APPROACH

One of the purposes of RCTs is to find more powerful or more specific drugs. Medicine is dominated by the carpenter approach; if the hammer does not work, get a bigger hammer. This is especially evident in pain patients where initial use of nonsteroidal anti inflammatory agents can lead quickly to opioids and the fentanyl patch. Some doctors tell patients that they should not be in pain. However, pain is a necessary part of life. Pain protects patients from damaging themselves from burns, bruises and other problems. Typically, pain patients become tolerant to opioids and increase the dose. Toxicity may occur, including respiratory depression and seizures. As of 2011, there are approximately 10 000 US patients dying yearly from prescription opioid overdose. The body has natural pain relieving agonists that are produced as needed in the brain, act locally and have short half lives. These agonists, endorphins, enkephalins and dynorphins, are very safe and are in a balance between synthesis, release, catabolism and natural antagonists. They are greatly superior to an administered opioid that must penetrate into the body and reside in the body for a convenient length of time. Administered opioids shut down the synthesis of natural opioid agonists[34]. When administered opioids, including the fentanyl patch, are gradually removed from the patient, the body may not respond quickly to reestablish the natural pain relieving mechanisms due to long term opioid receptor desensitization[35]. This may leave the patient in much more pain than was experienced before the opioid interventions.

Another example of the carpenter approach is the overuse of antibiotics. The body has an endogenous immune system to fight bacterial infections. Over prescription of antibiotics in otitis media has led to bacterial resistance such that the body can no longer heal itself from infections[36]. In addition, antibiotic toxicity is becoming more of a problem as the doses used and the number of antibiotics used at the same time increase. It is better to use a couple of drops of olive oil in the auditory canal for otitis media[37].

SHARPLY FOCUSED APPROACH

Funding agencies have expressed a need for a more sharply focused approach to RCTs and the use of specific biomarkers to prove the efficacy of new drugs[38]. This approach makes biomarkers more important than patient healing. This may be the result of reports that RCTs examining the same drugs find conflicting results[39], doctors use placebos in their patients[40], RCT design and placebo responses have changed over the years[41-43] and funding sources affect the outcomes of RCTs[44]. Many drugs have been tested in extensive RCTs and have been FDA approved in the USA inappropriately. Examples of this are rofecoxib and valdecoxib, which were approved even although they caused severe toxicity (myocardial infarction and stroke). These drugs were developed as the result of intensive, sharply focused investigations to find COX-2 inhibitors for use in pain patients. Other examples of FDA approved drugs that were removed because of toxicity problems include: azaribine (stroke), ticrynafen (liver toxicity), benoxaprofen (liver toxicity), zomepirac (fatal allergic reaction), nomifensine (hemolytic anemia), suprofen (flank pain syndrome), encainide (fatal arrhythmia), temafloxacin (kidney failure), flosequinan (increased deaths), fenfluramine (heart valve disease), bromfenac (liver toxicity), mibefradil (fatal arrhythmia), grepafloxacin (fatal arrhythmia), cisapride (fatal arrhythmia), troglitazone (liver toxicity), cerivastatin (muscle damage leading to kidney failure), rapacuronium (severe breathing difficulty), etretinate (birth defects), levomethadyl (fatal arrhythmia), gemtuzumab ozogamicin (myelosuppression and no efficacy), terfenadine (fatal arrhythmias), astemizole (fatal arrhythmias), propoxyphene (fatal arrhythmias) and conjugated estrogens (heart attack, stroke, breast cancer, Alzheimer's disease).

The approval of these drugs is symptomatic of the over anxious need for ever more powerful drugs and ever more specific drugs. Clearly, as toxic lifestyles produce more chronic diseases, there is an increasing insistence from patients that drugs should be produced to cure them of these diseases. However, the danger of toxicity from more powerful and more specific drugs must not be overlooked. What is routinely overlooked is that prevention of these chronic diseases should be the first priority[10,45-47].

PROTECTING THE PUBLIC FROM FRAUD

One of the stated purposes of RCTs is to demonstrate the power of drugs such that the public can be protected from products that lack efficacy but are available on the market. The National Center for Complementary and Alternative Medicine is especially vigilant in this regard and seeks to protect the public from plant derived medicines that lack efficacy but may be toxic[48]. Prior to 1960, most drugs were derived from plants and natural sources. *Homo sapiens* has survived for 200 000 years by using plants as medicines. There has been an enormous natural selection where people who responded to plant medicines survived. Today most drugs come directly or indirectly from plants or natural sources, including cancer drugs, most

antibiotics, vitamins, minerals and other prescription drugs.

TRILLION DOLLAR FRAUD

Patients are led to believe that powerful drugs are available to treat diabetes, cardiovascular disease, congestive heart failure, arthritis and other chronic diseases. Many drugs have been tested in RCTs and have been approved for use in these diseases. There is no drug that cures diabetes, cardiovascular disease, congestive heart failure or arthritis. Drugs are available to manage these diseases and allow patients to live with their pathology. These chronic disease processes can be partially slowed down by drugs; however, even with the best drugs, these chronic diseases progress. One of the problems with treatment of these diseases is that the drugs used are too specific and usually treat only one symptom. The goal of medicine should be to heal the patient. Unfortunately, with many chronic diseases, the goal has become keeping the patient alive. These diseases are caused by adopting toxic lifestyles that produce weight gain, muscle loss, fat accumulation, toxic adipokine secretion, toxic lipid accumulation and other detrimental changes[3,9,10,47,49,50]. Patients are advised to change their lifestyles, including lose weight, exercise more and eat healthy diets, in order to help them manage these chronic diseases. There is evidence that lifestyle changes can greatly improve the management of these chronic diseases[45,46,51,52]. Yet, many patients do not make lifestyle changes and prefer to rely on drugs. The emphasis in healthcare should be prevention of these chronic diseases by teaching patients to avoid toxic lifestyles[45-47].

Of course, there are some diseases for which prevention is not possible. These diseases include genetic diseases and type I diabetes; although, recent work has shown that the onset of type I diabetes can delayed by nicotinamide[53].

DESIGNING RCTs IN THE FUTURE

RCTs should be designed with healing the patient as the primary goal. The hypothesis should be that a drug will promote healing better than no treatment. This removes placebos as a confounding variable. It is important to remember that some patients get a placebo response just from visiting the doctor's office, even without seeing the doctor[12]. These patients may have to be removed from statistical analysis of the data. Comparing a drug to no treatment means that double blinding cannot be possible. Such trials can still be randomized and can still be statistically valid. The results from patients tested with new drugs can also be compared to historical patients receiving no treatment in the same hospital.

Of course, the danger in comparing a drug to no treatment is that a drug that works only through placebo mechanisms may become approved. As demonstrated above, several drugs that lack efficacy have already been approved. As more drugs become available, new drugs should be compared to existing drugs, rather than placebos or no treatment. Such trials can be performed in randomized, double blinded designs.

In patients afflicted with chronic, incurable diseases, lifestyle changes, not drug therapy, should be the primary goal. Toxic lifestyles prevent the body from healing itself or at least reestablishing normal agonist antagonist balance. These chronic diseases include hypertension, cardiovascular disease, congestive heart failure, arthritis, insulin resistant diabetes and others. In patients with long standing chronic illnesses, healing may be impossible due to extensive pathology, in which case, disease management becomes the secondary goal. Pain patients can be difficult to heal, especially in diseases where the cause of the pain is not completely known, like neuropathic pain or fibromyalgia. These patients can be tested in clinical trials where no treatment is compared to a treatment[54]. Of course, in patients that have life threatening symptoms from chronic diseases, symptom management must be a secondary goal. Placebos or no treatment are not ethical in diseases with life threatening symptoms that have effective drug therapy[55]. An alternative hypothesis in RCTs could be that a new drug promotes healing better than a conventional drug or has equal ability to promote healing compared to a conventional drug. Comparing drugs removes confounding effects of placebos.

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