Mini Review

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Revisiting the Placebo Effect

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ABSTRACT

Abbreviations: RCTs: Randomized Clinical Trials; PUFAs: Pentoxifylline And Polyunsaturated Fatty Acids; IBS: Irritable Bowel Syndrome

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Ever since the 14th and 16th centuries, Chaucer and others used the name "placebos" to describe the presumed fake procedures that separated imagination from the reality of treatment and behavior in clinical medical practice [1,2]. Placebos were conceptually inert substances used by the end of the 18th century as controls in science and medicine to study the efficacy of treatments intended to make patients comfortable. However, the effects of placebos had and has endured a tainted reputation that extends to the present time [3-12]. Denouncement of placebos and their purported effects has historically been connected to pseudoscience, religious extremism since the 16th century, and claims of notoriety [1,2,4]. The popularity of placebo-controlled randomized clinical trials (RCTs) has reinforced this reputation, although these trials rarely included a third group receiving no treatment to serve as controls for the natural history of patients and their capacity for healing (i.e. spontaneous remission).

Today, the prior prejudicial concerns of inert or sham administrations to patients in RCTs have been replaced with growing evidence of the true capacity of placebo effects to achieve healing responses. The terms "honest placebo" [8], "open-hidden paradigm" [1] and "evidence -based practice" rather than evidence-based medicine [11] have be introduced, along with the opposite "nocebo effect" which is believed to occur through anticipatory anxiety mechanisms [1,2]. Further, placebo effects have been shown to be inherent in clinical practice even when no placebo is given [1]. This practice has been extended from human medicine to veterinary medicine in laboratory animal and animal patient settings for many years [2,3,5,6].

Proposed mechanisms involved in the placebo effects include:

Psychological Mechanisms

Psychological mechanisms that underly the placebo effects need to be compared to the expected sociological responses of group bonding and boundaries. Importantly, significant medical and veterinary practitioner effects are also seen [1,2]. When physicians and veterinary treaters believe that no treatment could be given, the observed placebo effects were much lessened.

Neurological Mechanisms

The neurological effects equate to analgesia and the perception of analgesia [10-12].

Ethical Considerations

Is placebo based RCTs deceptive practice? Do they violate the patient or pet owner's Informed Consent? There is no uniform consensus to answer these real -world concerns [1,2]. Ethical disclosure is essential for securing evidence-based practice [11].

Expectations

Expectations in RCTs reflect behavioral conditioning from the anticipated positive effects in both human and animal studies [1,5,6]. The "open-hidden paradigm" where the ritual of study, unique

environment, realistic use of devices, and length of administration is known to create more pronounced positive effects [1,2]. In this paradigm, patients are given treatment without their knowledge. However, the 'open-hidden paradigm' is markedly less effective than the "open-revealed" administration RCTs. This is explained by the placebo's component based upon expectancy.

Applications in Clinical Practice and Research

Current clinical and applied research shows that there is not one placebo effect, but many [9-12]. Some examples are discussed below:

Chronic Pain: [10] Patients with chronic back pain demonstrated in RCTs that their placebo analgesic pill response was dependent upon brain structure and function. Psychological traits of awareness and openness indicated that the degree of patient response and long-term benefits in clinical settings was partially predictable. Additionally, the magnitude of the placebo response was often equal to the active treatment(s) studied, and even greater that that seen with conventional therapy. Some have described this phenomenon as a "confounding nuisance" in RCTs, as the patient models conducted in laboratory settings are not equivalent to true clinical settings. But this belief remains controversial [10,12].

Osteoarthritis: [7] Osteoarthritis of the knee was studied in RCTs comparing efficacy and safety of intra-articular injections of the homoepathic remedies, Traumeel (Tr14) and Zeel (Ze14) [Heel GmbH] to intra-articular placebos. Statistically significant, clinically relevant pain relief was seen on days 15-99 in comparison to placebo.

Acupuncture: [1,2,10,12] Studies with acupuncture have examined the placebo effect in patients with placebo acupuncture versus an oral pill in patients with chronic arm pain brought on by repetitive use. Thirty percent of the patients reported adverse effects which mimicked information they had been provided in the Informed Consent given. Larger trials from Germany [10,12], compared acupuncture based upon traditional Chinese medicine to sham acupuncture (superficial needling at non-acupuncture sites), no treatment groups, and those receiving typical clinical care. The conditions studied were migraine, tension headaches, chronic low back pain, and osteoarthritis of the knee. No differences were seen between the real and sham acupuncture groups, although both groups had substantially greater improvement in symptoms than either the no treatment or usual care control groups. These beneficial effects lasted for one year.

Alzheimer's Disease: [9] Both positive and negative outcomes have been reported in recent years with RCTs for Alzheimer's disease. Initially, a commercial drug, aducanumab [Biogen/Eisai], RCT study showed it shrank amyloid protein deposits that accumulate in the brain of these patients and slowed the resultant cognitive decline by 15-27% as compared to placebo. But, analysis of the initial RCTs showed that the benefits, though dose-dependent, were insufficient to expose patents to potential adverse side effects and the trials were terminated. However, re-analysis of these trials proved that the conclusion was incorrect; the drug had efficacy after all [9].

Periodontitis, Rabbit Model: [6] Two control groups were compared in a periodontitis rabbit model, baseline periodontitis and non-treatment, with the treatment groups of 1-teradecanol complex, an esterified fatty acid mixture, and olive oil placebo. While trea5ed animals showed statistically significant reduction in activity of their dental osteoclasts, compared to baseline, the no treatment and placebo groups, the placebo groups receiving olive oil also had beneficial effects on reducing dental inflammation. As olive oil is a monounsaturated fatty acid (MUFA), subsequent trials used mineral oil, whereby no placebo effects were found.

Atopic Dermatitis, Dog: [5] In dogs, management of chronic atopic (inhalant) dermatitis has been studied with a combination of pentoxifylline and polyunsaturated fatty acids (PUFAs). This placebo-controlled study showed significant decreases in pruritis scores after 30 days with this protocol.

Thymic Hormone: [3] A placebo-controlled trial showed that thymic hormone treatment benefitted patients with recurrent Herpes simplex labialis infections.

Depression: [10] Like Alzheimer's patients, patients with depression are known to benefit from the psychosocial and neurobiological mechanisms operative during RCTs, including positive placebo responses.

Irritable Bowel Syndrome (IBS): [1,2] Several long-term studies over recent years have documented the beneficial responses of IBS patients to conventional therapies that control intestinal dysbiosis, a gut-brain-linked phenomenon, which included positive patient expectations in the placebo groups.

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