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PLACEBO - A WONDER DRUG

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INTRODUCTION

The use of the word "placebo" in a medical context to describe innocuous treatments to make a patient comfortable dates to at least the end of the 18th century. Mainstream interest in placebo effects only began with the widespread adoption of the placebo controlled randomized controlled trial (RCT) after World War II, as it was quickly noticed that people improved; sometimes dramatically, in placebo control arms.[1] The placebo effect has been a source of fascination, irritation, and confusion within biomedicine over the past 60 years. Although scientific investigation has accelerated in the past decade, with particular attention to neurobiological mechanisms, there has been a dearth of attention to developing a comprehensive theory of the placebo effect.[2] A *placebo* is a treatment that is expected to have no inherent pharmacological or physical benefit - for instance, a starch capsule given for anxiety or pain, or sham surgery in which the critical surgical procedure is not performed. Placebos are often used for comparison in clinical studies, as a baseline against which to evaluate the efficacy of investigational clinical treatments. However, placebo treatments often elicit observable improvements in signs or symptoms on their own - these are placebo effects.[3] For this reason, placebos have been used as healing agents for a variety of ailments; they have had a place in the healer's repertoire for thousands of years, and they are still used as a viable treatment option by physicians in industrialized countries with surprising frequency.[3]

Mechanisms

A key shift in the emerging mechanistic understanding of placebo effects is the recognition that there is not one placebo effect but many (Figure 1). These mechanisms can be broadly discussed from psychological and neurobiological viewpoints.

DISEASE/SYSTEM	MECHANISMS	REFERENCES
Pain	Activation of endogenous opioids and dopamine (placebo). Activation of CCK and de-activation of dopamine (nocebo)	Levine et al 1978, Benedetti 1996, Amanzio and Benedetti 1999, Benedetti et al 1997, 2006; Scott et al 2008
Parkinson's disease	Activation of dopamine in the striatum and changes in activity of neurons in basal ganglia and thalamus	de la Fuente-Fernandez et al 2001 Benedetti et al 2004, 2009
Depression	Changes of electrical and metabolic activity in different brain regions, e.g. ventral striatum	Leuchter et al 2002, Mayberg et al 2002
Anxiety	Changes in activity of the anterior cingulate and orbitofrontal cortices. Genetic variants of serotonin transporter and tryptophane hydroxylase 2	Petrovic et al 2005 Furmark et al 2008
Addiction	Changes of metabolic activity in different brain regions	Volkow et al 2003
Autonomic responses to DBS	Change of neuronal excitability in limbic regions	Lanotte et al 2005
Cardiovascular	Reduction of β -adrenergic activity of heart	Pollo et al 2003
Respiratory	Conditioning of opioid receptors in the respiratory centres	Benedetti et al 1999
Immune system	Conditioning of some immune mediators (e.g., IL-2, IFN-γ, lymphocytes)	Ader et al 1975 Goebel et al 2002
Endocrine system	Conditioning of some hormones (e.g., growth hormone, cortisol)	Benedetti et al 2003
Physical performance	Activation of endogenous opioids and increased muscle work	Benedetti et al 2007 Pollo et al 2008
Alzheimer's disease	Prefrontal executive control and functional connectivity of prefrontal areas	Benedetti et al 2006

Figure 1: The principal placebo mechanisms that have been unraveled across different medical conditions and systems/apparatuses.[1]

Psychological mechanisms

From the psychological viewpoint, a multitude of mechanisms contribute to placebo effects. These include expectations, conditioning, learning, memory, motivation, somatic focus, reward, anxiety reduction and meaning.[4, 5] Whilst there is a growing amount of research into these mechanisms, two principal mechanisms are well supported.

One principal mechanism involves expectancy: expectations of future responses following administration of a placebo.[6] Many experiments have used simple verbal cues as modulators of expectancies.[7-9] For example, a research subject receiving experimentally induced pain is given a topical placebo cream in the context of two different cues: the first that the cream is inert and will have no effect and the second, that the cream is a powerful pain killer.[7] This paradigm demonstrates that such verbal cues can manipulate expectations and mediate placebo effects, including placebo analgesic effects in experimental[9] and clinical pain[10]; and placebo induced changes in motor performance in Parkinson's Disease[11,12] and changes in emotions[13] and brain responses in addiction.[14]

Another principal mechanism of placebo effects involves classical conditioning.[15] Repeated associations between a neutral stimulus and an active drug (unconditioned stimulus) can result in the ability of the neutral stimulus by itself to elicit a response characteristic of the unconditioned stimulus.

The interaction between expectancy and conditioning mechanisms remains an area for further research, which may be particularly relevant to exploring the clinical implications of these mechanisms.

Neurobiological Mechanisms

Most research into the neurobiology of placebo responsiveness has addressed placebo analgesia; accordingly, the neurobiology of placebo effects is commonly considered in terms of opioid and non-opioid mechanisms.[16,17] Several studies have demonstrated that placebo effects can be completely[18,19,20] or partially reversed[21] by the opioid antagonist naloxone, supporting the involvement of endogenous opioids in some placebo analgesic effects.[22] Furthermore, placebo analgesic effects are likely to be inhibited by the peptide cholecystokinin (CCK),[20] for they are potentiated when a CCK antagonist is administered.[23] Taken together, these studies demonstrate that some placebo mechanisms operate by altering the activity of both CCK and endogenous opioids.[24]

Not all placebo effects are mediated by opioids. Growing evidence illustrates that many placebo effects are mediated by other mechanisms, such as the release of different neurotransmitters and neuromodulators.

Placebo treatments in experimental research versus clinical studies

The potential significance of the placebo response has led to the standard use of placebo groups in clinical trials examining the efficacy of medicine or other specific treatments on clinical conditions. Patients are assigned to receive either active treatment or placebo, and comparisons between groups are performed to test whether the active treatment elicits greater improvement than placebo. Two critical assumptions underlie the rationale behind the placebo - controlled clinical trial. First, it is assumed that psychological and nonspecific effects, such as natural course of disease, effects of being in a healing environment, and patient expectation and motivation to heal, have equal effects on outcomes in active treatment and placebo groups. Second, it is assumed that nonspecific effects and treatment effects combine additively, so that subtracting outcomes for the placebo group from the treatment group will reveal the specific effects of the drug or procedure. Although these assumptions may not always hold, the placebo - controlled randomized clinical trial is perhaps the best tool for medical practitioners and pharmaceutical companies to determine treatment efficacy.[3]

Ethical principles of placebo effects in clinical care

Any ethical evaluation of efforts to promote placebo effects in clinical practice first requires knowledge as to the clinical relevance and significance of placebo effects. More studies of placebo effects in specific clinical settings are required before the use of treatments with the primary aim to promote placebo responses can be recommended as evidence-based practice.[1]

A second important ethical consideration relates to whether and how placebo effects can be promoted without deception. Since it has been demonstrated that placebo effects are inherent in routine clinical care, and that the psychosocial context surrounding the patient (including the patient-Doctor interaction and the therapeutic ritual) can be augmented to improve these placebo effects, it is ethically sound, not to mention clinically relevant, to provide a supportive clinical encounter that relieves anxiety and promotes positive expectations along with honest disclosure of the expected benefits of a medically indicated therapy.[1]

To recommend or administer a placebo intervention to a patient presented deceptively as a therapy with specific efficacy for the patient's condition violates informed consent and threatens the trust that is central to clinical practice.[25] Recent data indicate that the administration of sugar pills and saline injections is in fact very low,[26,27] but that clinicians commonly prescribe various active treatments with the primary intent of promoting a placebo response or complying with the wishes of the patient. The available evidence suggests that the practice of disclosure to patients regarding such placebo treatments is deceptive or at least not sufficiently transparent.

CONCLUSIONS

It is evident that placebo effects are real and that they have therapeutic potential. Laboratory and clinical evidence supports the existence of numerous placebo mechanisms and effects in both healthy volunteers and patients with a variety of medical conditions. Although substantial progress has been made in understanding placebo effects, considerable scientific work remains to be done in both laboratory experiments and translational clinical trial research, with the ultimate aim of harnessing placebo effects to improve patient care.

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