PLACEBO

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When used as a noun, placebo means a treatment that lacks any specific therapeutic effect. In the case of a drug, a placebo would be an agent that lacks any pharmacological effect. In the case of a procedure, a placebo would be one that lacks any specific anatomical or physiological effect. Nevertheless, in other respects a placebo has all of the features of an intervention that should work.

When used as an adjective, placebo occurs in two forms: the placebo effect, and the placebo response. Placebo effect is the presumed or perceived effect that a placebo has on an individual. Placebo response is what the individual reports after having been administered a placebo, and is ostensibly due to the placebo effect.

Essentially a placebo is not supposed to work. Any effect or response that it evokes is, therefore, paradoxical. The resultant paradox is difficult to handle in clinical practice. Consequently, placebo is commonly misunderstood concept that is subject to abuse, misinterpretation, and myths.

PLACEBO RESPONDER

When patients exhibit a placebo response, practitioners and authors sometimes, if not often, refer to them as 'placebo-responders'. This term implies that the patient has an inherent trait that means that they will consistently respond to placebos. This is wrong.

There is no personality trait or psychological trait that causes individuals to respond consistently to placebos [1]. Experimental studies have shown that any individual at any time is liable to express a placebo-response, depending on the circumstances; but also that such responses are not consistent [1,2,3]. Indeed, one authority has ventured to conclude that proneness to placebo is universal [4].

The placebo response is a variable phenomenon, and does not reflect anything about the individual who reports it. The term – placebo responder, therefore, can have only a pejorative connotation, to dismiss or relegate patients for having exhibited a paradoxical phenomenon. When used, it expresses more about the prejudices of the practitioner than anything about the patient. Consequently, the term should be expunged from clinical vocabulary, and never used.

PLACEBO RESPONSES ARE FAKE

Some practitioners handle the paradox of placebo responses by dismissing them on the grounds that the patient has a psychological problem, is malingering, or is frankly lying. This is both a misinterpretation and misrepresentation of the placebo response.

The distinction is that a placebo response occurs after the intervention, ostensibly because of it. In contrast, malingering and lying require premeditation. To accuse a patient of malingering or lying, because they have a placebo response, is therefore tantamount to accusing them of premeditation. The placebo response provides no evidence of this. Such an interpretation, therefore, reflects the prejudices of the practitioner.

Nor is the placebo response a feature of psychological distress. Placebo responses occur under experimental conditions in individuals with no evidence of psychological disturbance [5,6]. Amongst patients with chronic pain, profiles of psychological distress do not differ between patients who have true-positive responses to placebo-controlled, diagnostic blocks and those who have placebo responses [7]; or between patients who have successful outcomes after treatment and those who do not [8].

NOT IN CLINICAL PRACTICE

A common belief, though rarely enunciated, is that placebo responses occur only in research studies; and reciprocally, that they do not occur in 'real' practice. Implicitly, placebo responses are somehow precipitated only if and when patients enroll in controlled trials.

This is a self-serving belief, designed to excuse practitioners in the 'real' world of any responsibility to be alert to placebo responses, or to have their practices accountable to placebo effects. The belief conveniently ignores the realization that controlled trials are

simply the means by which placebo responses can be demonstrated and quantified. That having been done, practitioners are warned to expect the same phenomenon, with the same prevalence, in conventional practice. Practitioners choose to ignore this warning. They prefer, instead, to believe that all positive therapeutic effects of their practice must be due to the specific effects of their ministrations, and that their successes could not be due to something as ephemeral as a placebo effect. Under these conditions, ignoring the prevalence of placebo effects serves to protect the ego of a practitioner, while offending scientific accountability to the truth.

CONSTANT RATE

A widespread urban myth is that about one third of patients in any cohort will express a placebo-response, implying some sort of endemic influence. This myth has been traced to an early study of placebo responses [1,3]. In reviewing the literature, Beecher [9] encountered a wide variety of placebo response rates, ranging from 15% to 58%. A figure of 35.2% arose as a numerical average of these rates, unweighted for sample sizes. Subsequent studies have encountered placebo response rates from as low as 0% to as high as 100% [1]. There is nothing constant about 35%. Placebo response rates differ considerably according to the circumstances of the study.

MECHANISM

In the context of Pain Medicine, a placebo would be an agent or a procedure that should have no effect on pain by pharmacological, anatomical, or conventional physiological means. A placebo response would be relief of pain despite this lack of a conventional means by which the pain could be relieved. The occurrence of a placebo response implies a placebo effect.

The mechanism or mechanisms of that placebo effect remain largely elusive. Theories have been proposed; but, of late, experimental studies have pursued its physiological basis.

The fact that pain is relieved implies that whatever the mechanism is of placebo effects, it must involve the nociceptive system. The prevailing theories about placebo invoke some sort of suppression at one level or another of the nociceptive system.

Conditioning

Conditioning is a prominent theory amongst psychologists who seek to explain the placebo effect [2,3]. The theory is based largely on data from experimental studies, in which subjects previously exposed to an intervention have continued to express positive responses when that intervention was surreptitiously or progressively replaced with a sham intervention.

However, it is hard to reconcile this theory with the nature of Pain Medicine. If anything, patients are likely to encounter repeated failures of treatment and, therefore, would be conditioned not to respond. Indeed, the conditioning theory has been adapted to fit this phenomenon by becoming an explanation for nocebo responses or 'placebo sag' [2]. In contrast, if the contention is that patients expect relief when they consult a doctor, instead of conditioning theory, expectation is a more appetite explanation.

Expectation

One of the prominent explanations for the placebo effect is that patients who undergo a treatment for pain expect the treatment to work [2,3]. This expectation can be reinforced if the practitioner engenders or fosters the expectation. It is reinforced if the treatment is undertaken in an impressive manner in an impressive setting, such as a high-tech facility. Indeed, factors found to enhance the placebo effect are: the credibility of the therapist, the credibility of the therapeutic setting, the credibility of the treatment, the credibility of the administrative setting, and the nature of the interaction between the patient and the therapist [2].

The expectation model implies an interruption of the pain experience at a cortical level. One could say that the patient imagines that they get relief, because that is what they expected to occur. More graciously, one could infer that a subliminal, cortical effect occurs, in which the patient is distracted from their pain by the promise of expected relief.

Since they involve cerebral mechanisms, these conjectures are difficult to test. The pathways and processes are not amenable to experimental manipulation. Another interpretation, however, is that cerebral processes may invoke spinal mechanisms.

Spinal Mechanisms

Diffuse noxious inhibitory control (DNIC) operates as a normal physiological process within the nociceptive system. Under normal conditions, its function is to discriminate incoming nociceptive information by center-surround inhibition. Under artificial conditions, however, DNIC can suppress nociception.

Suppression occurs when brainstem nuclei are stimulated globally, which sends inhibitory influences through descending pathways to all segmental levels of the spinal cord. This is one of the purported mechanisms of acupuncture, and the possible mechanism by which deep brain stimulation relieves pain. Conversely, systemic opioids work by globally inhibiting descending pathways. The resultant loss of inhibition causes any nociceptive information to be obscured by uninhibited background noise at the spinal level of the nociceptive system.

Placebos might work if subliminal cerebral processes activate the descending nociceptive systems. Under those conditions, placebo responses are not psychological in nature, but involve physiological processes in the central nervous system. Indeed those processes are similar or the same as those by which drugs and neuro-augmentative surgery achieve relief of pain. The distinction is only that the mind, rather than an exogenous agent, switches on the descending inhibition.

Circumstantial evidence to this effective arises in experiments in which placebo responses have been reversed by the administration of opioid antagonists such as naloxone [1,3,5,10]. Conversely, antagonists to cholecystokinin enhance placebo analgesia [6]. The fact that drugs, known to block analgesic pathways in the brainstem and spinal cord, also block placebo effects implies that the same physiological systems are involved.

Meaning Model

The meaning model invokes quite a different process [3]. It suggests that, in order to maximize the placebo response, the patient must feel listened to; must receive what they perceive to be a valid explanation for their illness; feels care and compassion from their treatment environment; and feels empowered.

This model does not invoke anti-nociception, nor does it invite it. Instead, it predicts that patients who exhibit a placebo response are ones who have amplified their symptoms, at the time of treatment, because of fear, ignorance, and forlornness. When these are addressed, the amplification is removed; the report of pain is less; and the treatment appears to have relieved pain. Psychic amplification can be reduced by directly addressing the patient's fears and ignorance, and having them feel understood and cared for. Alternatively, the same effects might occur circumstantially when a practitioner delivers an otherwise inactive treatment but with confidence and conviction, which implicitly relieves the patient's psychic concerns.

MAGNITUDE

Multiple studies have demonstrated that placebo effects and placebo responses are ubiquitous. Essentially every intervention for pain will have a placebo component. Either an individual will have a response that is partially due to the active treatment and partially due to a placebo effect; or within a cohort of patients, some may have an effect that is entirely due to placebo. Controlled trials reveal how often this effect occurs and its magnitude.

Placebo controlled trials of analgesics, fairly consistently have shown that the placebo effect amounts to at least 50% or up to 80% of the effect of the active agent. Whereas an analgesic might reduce pain, on the average, from 6 to 3 on a 10-point scale, placebo drugs will reduce pain from 6 to between 4 and 5. This implies that more than half the efficacy of analgesics must be attributed to placebo effects.

In other instances, the efficacy of analgesics is not significantly different from that of placebos. That implies that the apparent efficacy of these analgesics, in the 'real' world, is entirely due to placebo effects [11].

Similar proportions apply to those surgical interventions for pain that have been subjected to placebo controls. On average, sham-treated patients experience 50% as much relief of pain as do patients treated with antiradical electro thermal therapy [12]. But these average figures belie the actual situation. While some patients have no response to sham treatment, others can obtain complete relief of pain. This combination results in an average of about 50%, but that average is not shared by all patients.

The same applies to less invasive procedures. The efficacy of lumbar intra-particular injection of corticosteroids is no greater than that of intra-particular injection of saline [13], intramuscular injection of either steroids or saline [14], or of simple medial branch blocks [15].

Even diagnostic procedures are subject to placebo effects. Patients who believe that they are undergoing zygapophysial joint blocks report complete relief of pain following subcutaneous injection of normal saline [16]. Stellate ganglion blocks with normal saline relive the symptoms of complex regional pain syndrome [17]. Intravenous infusions of normal saline relieve the motor features of complex regional pain syndrome [18].

Such data warn that practitioners in conventional practice have no right to believe that the success that they achieve is due to the purported mechanism of their treatment. That is not to say that the successes are not real. The issue is one of attribution. In principle, the outcome might be due to a placebo effect. Unless and until that is excluded, claims that the outcome is wholly due to the purported active component of the treatment cannot be sustained.

Practitioners face a professional, if not ethical and moral, dilemma. It is convenient to believe that placebo effects do not occur in conventional practice. It serves the ego to believe that all interventions work because of the practitioner's ability to perform the treatment, and their knowledge of how the intervention is said to work. It is anathema to accept that it could all be a sham: that the treatments work because of non-specific factors that the practitioner does not acknowledge, and which ostensibly lessen the expertise and skill of the practitioner. Yet, to ignore placebo, amounts to creating an illusion that is perpetrated on the patient, and perpetuated in the interests of sustaining the standing of the practitioner. Therein lies the dilemma: whether to be loyal to the facts or to the reputation.

If Pain Medicine is to be accountable to science, the role of placebo must be acknowledged, measured, and accommodated. To ignore it, relegates Pain Medicine to the status of a medieval guild, whose purpose is only to exploit the suffering of patients for its own gain.

REFERENCES

1. Wall PD. The placebo effect: an unpopular topic. Pain 1992; 51:1-3.
2. Peck C, Coleman G. Implications of placebo theory for clinical research and practice in pain management. Theoretical Medicine 1991; 12:247-270.
3. Brody H. The placebo response: recent research and implications for Family Medicine. J Fam Pract 2000; 49:649-654.
4. Shapiro AK. Semantics of the placebo. Psychiatr Q 1968; 42:635-695.
5. Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning activated specific subsystems. J Neurosci 1999; 19:484-494.
6. Benedetti F, Amanzio M. The neurobiology of placebo analgesia; from endogenous opioids to cholecystokinin. Prog Neurobiol 1997; 51:109-125.
7. Lord S, Barnsley L, Wallis BJ, Bogduk N. Chronic cervical zygapophysial joint pain after whiplash: a placebo-controlled prevalence study. Spine 1996;21:1737-1745.
8. Wallis BJ, Lord SM, Bogduk N. Resolution of psychological distress of whiplash patients following treatment by radiofrequency neurotomy: a randomised, double-blind, placebo-controlled trial. Pain 1997;73:15-22.
9. Beecher HK. The powerful placebo. JAMA 1955; 159:1602-1606.
10. Ter Riet G, de Craen AJM, de Boaer A, Kessels AGH. Is placebo analgesia mediated by endogenous opioids? A systematic review. Pain 1998; 76:273-275.
11. Van Tulder MW, Scholten RJPM, Koes BW, Deyo RA. Nonsteroidal anti-inflammatory drugs for low back pain. A systematic review within the framework of the Cochrane Collaboration Back Review Group. Spine 2000; 25:2501-2513.
12. Pauza KJ, Howell S, Dreyfuss P, Peloza JH, Dawson K, Bogduk N. A randomised, placebo-controlled trial of intradiscal electrothermal therapy for the treatment of discogenic low back pain. The Spine J 2004; 4:27-35.
13. Carette S, Marcoux S, Truchon R, Grondin, Gagnon J, Allard Y, Latulippe M. A controlled trial of corticosteroid injections into facet joints for chronic low back pain. New Engl J Med 1991; 325:1002-1007.
14. Lilius G, Laasonen E M, Myllynen P, Harilainen A, Gronlund G. Lumbar facet

joint syndrome: a randomised clinical trial. J Bone Joint Surg 1989; 71B:681-684.
15. Marks RC, Houston T, Thulbourne T. Facet joint injection and facet nerve block: a randomised comparison in 86 patients with chronic low back pain. Pain 1992; 49:325-328.
16. Schwarzer AC, Wang S, Bogduk N, McNaught PJ, Laurent R. Prevalence and clinical features of lumbar zygapophysial joint pain: a study in an Australian population with chronic low back pain. Ann Rheum Dis 1995;54:100-106.
17. Price DD, Long S, Wilsey B, Rafii A. Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglion of complex regional pain syndrome patients. Clin J Pain 1998; 14:216-226.
18. Verdugo RJ, Ochoa JL. Abnormal movements in complex regional pain syndrome: assessment of their nature. Muscle & Nerve 2000; 23:198-205.