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"The Placebo Effect : Myths, Muddle and Methodology"

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"If you can believe fervently in your treatment, even though controlled studies show that it is quite useless, then your results are much better, your patients are much better, and your income is much better too. I believe this accounts for the remarkable success of some of the less gifted, but more credulous members of our profession, and for the violent dislike of statistics and controlled tests which fashionable and successful doctors are accustomed to display"

Richard Asher, 1972

The Placebo Effect: Myths, Muddle and Methodology

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The Placebo Effect

- Chapter in R. Roberts & D. Groome (eds.). (2001). *Parapsychology: The Science of Unusual Experience*. London: Arnold.
- Structure of presentation
 - Introduction
 - The Nature of Placebo Effects
 - Myths and Methodology
 - Attempts to Explain the Placebo Effect
 - Conclusion

Introduction: Derivations and Definitions

- Placebo - from the Latin, "I will please"?
- Shapiros' (1997) definition of placebo: "any therapy prescribed ... for its therapeutic effect on a symptom or disease, but which is actually ineffective or not specifically effective for the symptom or disorder being treated"
- Shapiros' (1997) definition of placebo effect: "the nonspecific, psychological, or psychophysiologic therapeutic effect produced by a placebo, or the effect of spontaneous improvement attributed to the placebo"
- Nocebo - from the Latin, "I will harm"

History of the Placebo Effect

- usnea (moss from the skull of victims of violent death), Vigo's plaster (viper's flesh, live frogs and worms), parts of the skulls of executed criminals, oil of brick, ants, spiders' webs, saliva of a fasting man, sexual organs, excreta of all kinds ...
- purging, puking, poisoning, cutting, cupping, blistering, bleeding, freezing, heating, sweating, leeching, and shocking.
- Negative attitudes to placebo effect within modern Western medicine (association with quackery; not seen as "true" therapeutic effect).

Nature of Placebo Effects

- Found in all areas of medicine, e.g., treatment of depression, anxiety, insomnia, headaches, nausea, asthma, diabetes, multiple sclerosis ...
- Much research in area of pain control.
- Although mechanisms not fully understood, patient's expectations, determined largely by the behaviour of those administering the treatment, are crucially important.

Double-Blind Randomised Clinical Trials (RCTs)

- Compare therapeutic effectiveness of active treatment with placebo treatment
- Neither patient nor therapist should be aware of treatment condition
- Placebo condition should be as similar as possible to treatment condition
- Allocation to conditions should be random
- Triple-blind studies require that those assessing outcome are also blind until analysis complete.

Types of Treatment Exempt from Requirement of RCTs

- Surgery - but note findings of Cobb et al. (1959) and Dimond et al. (1960). Sham operations were as effective in relieving symptoms of angina as real operations in which internal mammary arteries were ligated.
- Alternative therapies - practitioners and clients usually convinced of effectiveness on basis of personal experience and anecdotal evidence.
- Psychotherapies - highlight the problems of defining suitable placebo conditions which differ in terms of nothing but "active ingredient"

Myths and Methodology (1)

- Myth 1: The placebo differentiates between organic and mental disease.
 - Wall (1999): many "old-school clinicians drilled in classic theory" still subscribe to this "cruellest and most dangerous myth"

Myths and Methodology (2)

- Myth 2: The placebo is the equivalent of no therapy.
 - Most studies using placebos do not include a "no treatment" condition, making it impossible to conclude that any placebo effect has even occurred.
 - Ernst & Resch (1995) differentiate "perceived placebo effect" (response of placebo group in an RCT) and the "true placebo effect" (difference between that response and response of no-treatment group).

Myths and Methodology (3)

- Myth 2: The placebo is the equivalent of no therapy (cont.)
 - No-treatment group could improve for a variety of reasons:
 - The natural history of the disease (cf. Beecher, 1955, on the common cold)
 - Regression towards the mean
 - Other time-related effects
 - Estimates that 70% of patients treated with ineffective therapies show improvement may be true (Roberts et al., 1993) but this does not represent solely placebo effects.

Myths and Methodology (4)

- Myth 3: A fixed fraction of patients respond to placebos
 - “about a third” often quoted.
 - Beecher (1955) gave figure of 35.2% - but based on average over 11 studies with widely varying rates.
 - Rates can vary from 0% to 100%
- Myth 4: Placebo responders have a special mentality
 - Most studies show no correlations between placebo response and personality measures and the rest are contradictory (Wall, 1999).

Myths and Methodology (5)

- Myth 5: Placebos only affect subjective aspects of illness not objective measures of disease.
 - E.g., “Placebos have no effect on the progress or outcome of disease but they may exert a powerful effect upon the subjective phenomena of illness, pain, discomfort and distress. Their success is based upon this fact.” (Skrabanek & McCormick, 1989)
 - But majority opinion: “Objective variables such as the results of blood tests, postoperative tissue swelling, body temperature or the healing of wounds are also placebo-prone.” (Ernst & Abbot, 1999)

Myths and Methodology (6)

- Myth 6: Patients in double-blind trials do not know which condition they are in.
 - In fact evidence shows that patients, patients’ relatives and doctors are often able to guess which group patient is in, e.g., on basis of side-effects of active treatment

Myths and Methodology (7)

- Myth 7: In controlled trials, the placebo never has a specific therapeutic effect upon the condition being treated.
 - Kienle & Kiene (1996) cite the much-reported study by Ho et al. (1988) comparing ultrasound treatment, placebo treatment and no treatment on pain and swelling following tooth extraction. Strong placebo effect was claimed BUT both ultrasound and placebo conditions differed from no treatment condition by including application of moist, cooling cream - which may have directly affected pain and swelling.

Myths and Methodology (8)

- Myth 8: Patients will always give an honest and accurate account of their subjective well-being.
 - Kienle and Kiene (1996) refer to *experimental subordination*. “This term means that the subjects of an investigation say what they believe is expected from them without being careful to ensure that their statements are based on actual experiences or perceptions”.
 - A true placebo effect would be one in which patients genuinely felt better and were not simply saying they did in order to please their doctor or a researcher.

Attempts to Explain the Placebo Effect (1)

- Classical Conditioning
 - e.g., drug treatment = US
 - physiological responses = UR
 - eventually physiological responses become CR associated with contextual cues, e.g., pills, syringes, white coats, etc. (CS)
 - Animal research appears to show some support BUT CR (to say injection of saline following conditioning trials) is sometimes in same direction as initial UR, sometimes in opposite direction.

Attempts to Explain the Placebo Effect (2)

- Classical Conditioning (cont.)
 - Voudouris and colleagues appeared to demonstrate conditioning of placebo response in humans (e.g., Voudouris, Peck, & Coleman, 1989).
 - Participants trained to reliably report intensity of painful electric shock, with intensity levels in full view.
 - Given inert cream and told it was powerful analgesic.
 - A few showed higher thresholds, i.e., a weak placebo effect

Attempts to Explain the Placebo Effect (3)

- Classical Conditioning (cont.)
 - With different group, experimenters surreptitiously reduced shock level after cream applied, so it appeared to participants that cream was very effective.
 - On subsequent testing with original intensity levels, large proportion of participants showed higher thresholds.
 - BUT: Montgomery & Kirsch (1997) repeated study, included a group like second group above but told them that cream was inert. This group showed no placebo affect, suggesting results due to ...

Attempts to Explain the Placebo Effect (4)

- Expectancy
 - supported by wide range of evidence (see Kirsch, 1997) ...
 - ... BUT Kienle & Kiene (1996) present convincing evidence that results of Voudouris and colleagues (and, by implication, Kirsch & Montgomery) are best explained in terms of ...
- Experimental subordination effects
 - Has the placebo effect ever been convincingly demonstrated at all?

Attempts to Explain the Placebo Effect (5)

- Endorphins as an explanation of placebo analgesia
 - Although early studies (e.g., Levine et al., 1978) were open to methodological criticism, later methodologically superior studies support the notion that placebo pain reduction is indeed mediated by the release of endorphins (see review by ter Riet et al., 1998).
 - These results cannot be explained in terms of experimental subordination.

Conclusion (1)

- Although a neurochemical explanation for placebo-related pain reduction is now supported by a growing amount of convincing experimental evidence, it is fair to point out that this by no means represents the end of the story. As Anne Harrington (1997) points out, "Endorphin release, rather, became just one more placebo-generated phenomenon to be explained – and we still did not understand the processes whereby a person's belief in a sham treatment could send a message to his or her pituitary gland to release its own endogenous pharmaceuticals."

Conclusion (2)

- This presentation has hopefully illustrated the great need for further studies, employing improved methodology and clearer conceptualisations of the placebo effect itself. It will almost certainly turn out to be the case that we should speak of placebo effects, rather than of a single effect, and each effect may have a different explanation. In the future, we can hope that further research will unravel the mysteries of these effects and perhaps even render the term "placebo effect" redundant.