

05 - 4. Placebo effect

4. Placebo effect

© SPMM Course 4. Placebo effect □ Placebo is any intervention deliberately used for non-specific psychological or psychophysiological treatment effect. Placebo effect, as defined in research trials, includes any difference in outcome between a placebo-treated group and an untreated control group in an unbiased experiment (Ernst 2001). □ Placebos could be pharmacologically active or inert substances, most commonly the latter. □ An 'active placebo' has some activity inherently, but not against the treated condition. □ The term placebo literally translates in Latin meaning 'to please'. It was coined by an anaesthetist Beecher in 1955. □ When a substance administered for placebo effects produces prominent side-effects, it is known as a 'nocebo'. The term 'nocebo effect' (Latin: 'I shall harm') refers to the negative consequences, adverse reactions and intolerance resulting from the administration of a placebo. Nocebo effects are usually non-specific e.g. headache and nausea. □ Placebo sag is a term used to refer to decrease in placebo effect with repeated or chronic administration of placebo drugs. □ The placebo effect may be disproportionately large for non-blinded therapies potentially resulting in what has been called the efficacy paradox. □ Placebos work best for pain, disorders of autonomic sensation, and disorders of factors under neurohumoral control e.g. nausea, blood pressure, and bronchial asthma. □ Psychiatric disorders such as depression, anxiety and phobias show good placebo response. In depressive illness, the response rate varies from 25 to 60%, in mania it is as high as 25% and in schizophrenia it may vary from 25 to 50%, depending upon the criterion of improvement that is used and other factors. In panic disorder, placebo response rates of up to 70% are seen. More chronically ill patients show lower placebo response rates. □ Placebos fail in hereditary degenerative disorders, toxic and metabolic syndromes or vascular events. □ Placebo effects are not unique to placebo preparations; they are seen with active drugs too. e.g. a substantial proportion of patients responding to analgesics or antidepressants do so due to the placebo effect. Hence, the net effect of a given drug is thus the sum of the drug's pharmacological effects and the placebo effect. □ Physiological changes in opioids and GABA have been proposed to explain some aspects of placebo action; this neuropeptide hypothesis holds good for placebo analgesia, but not proven to operate in other conditions e.g. depression. □ Three factors are necessary for placebo action: the nature of the disease treated and the nature of the dynamic relationship between patient and doctor, patients' expectations and experience with treatment in the past. Gender, suggestibility scores, and IQ do not affect placebo effect consistently.

© SPMM Course □ Placebos are more effective for clinical than experimentally induced conditions. □ Placebos work better for severe than mild pain, but mildly depressed patients respond well than severely depressed ones. □ In studies of depression and schizophrenia the difference in improvement in the group of patients on active treatment compared with the group on placebo

increases gradually, with little difference until about 2 weeks of treatment and the full difference developing by 6 weeks and it increases progressively for several months. □ Those who respond to a placebo for one condition, when treated by one doctor, will not show same placebo response for another condition or another doctor. Hence, there are no homogeneous placebo reactors in the population. This view is furthered by the demonstration that the use of placebo 'run-in' approach in antidepressant trials, wherein 'placebo reactors' are eliminated before the trial commences, does not actually lower the placebo response rate or increase the drug-placebo difference to a great extent. But such procedures reduce generalisability and pragmatic nature of these trials as placebo responders may be most likely to benefit from a biologically active treatment, and their exclusion makes any estimate too conservative. □ A placebo can be a procedure and not a medication e.g. sham ECT, and sham surgeries with the only skin incision. □ The placebo response is higher in trials with more than 2 arms compared to those with two arms only (placebo vs. active arms). In a three-armed trial, participants are aware that they have 2 /3 chance of receiving active treatment compared to ½ chance in 2 armed study – hence there is a higher placebo response. □ People have individual traits that predispose them to be more or less responsive to certain stimuli; the interaction between the learned associations of the clinical situation and the person's particular biology produces a response. □ Placebo analgesia may be associated with decreased beta-adrenergic activity of the heart as measured by decreased heart rate and low-frequency heart rate variability □ Capsules are perceived to be stronger than tablets, producing more placebo effects. Larger pills have stronger placebo effect than smaller pills. The number of pills also influences the perception of pill strength. Multiple pills have stronger placebo effect than single pills. □ Anxiety symptoms responded better to green tablets and depressive symptoms responded better to yellow tablets. These are examples of the relative potency of medication varying with pill colour (Schapira et al. 1970). □ Injections elicit a stronger placebo effect than oral medications. Surgery is likely better than the others in terms of eliciting placebo effects. Why does a placebo work?

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1. Natural remission theory states that the disorders for which placebo works are inherently episodic (i.e. natural cycles show periods of remission and relapse). Hence even without treatment an improvement would have occurred, and placebo use is merely coincident.
2. Measurement regression: When a continuous variable is measured repeatedly in a sample, with each subsequent measurement the mean of the sample will move from extreme values and become closer to the population mean, the central value. This might explain why there is an apparent placebo response in control groups.
3. Conditioning theory: Placebo is in a way a behavioural intervention. Patients, who have learnt that receiving a medication will improve symptoms, will be showing a conditioned response of improvement when a placebo is administered. Learned associations producing placebo effects can be acquired through conditioning, especially for immune or endocrine conditions. □ According to classical conditioning models of placebo effects active medications are Unconditioned Stimuli and the vehicles in which they are delivered (i.e., the pills, capsules, syringes, etc.) are Conditioned Stimuli. The medical treatments that people experience during their lives constitute conditioning trials, during which the vehicles are paired with their active ingredients leading to the unconditioned response of therapeutic benefits initially. These repeated pairings endow the pills, capsules, and injections with the capacity to evoke therapeutic effects as Conditioned Responses later

on. □ During placebo treatment, the belief of the patient in being treated may result in selective attention to symptom improvement and expectation. The momentary experience of symptom improvement may then act as a reward and positively reinforce preceding changes of autonomic function. Thus, visceral learning due to a mechanism similar to operant conditioning may occur, in which the reward is internally provided □ Placebo responses are mediated by conditioning when unconscious physiological functions, such as hormonal secretion, are involved, whereas they are mediated by expectation when conscious physiological processes, such as pain and motor performance, come into play, although a conditioning procedure is performed.

4. The role of endogenous opioids: Endogenous opioids (e.g. endorphins) play a significant role in mediating placebo-induced analgesia. Interestingly, placebo-induced analgesia is partially reversed by administering the opioid antagonist naloxone. Dopamine reward system is being increasingly implicated in placebo effects in psychotropic research. The nature of placebo response in depression is compared with the antidepressant-induced response in depression. Placebo response starts abruptly, occurs early in treatment and is less likely to persist (Quitkin et al., 1991). But the antidepressant response is often gradual, occurs later and is more likely to persist. But the neurobiological correlates of the responses may not be truly

© SPM Course different as shown by Mayberg et al. (2002). Mayberg et al. (2002) observed that the patients in their study whose depression relented after treatment with either fluoxetine or placebo had nearly identical positron emission tomography (PET) brain scans. The ACC is an important anatomical component of the dopaminergic as well as an opioid system and has been activated during placebo analgesia.

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