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# The placebo effect: can we use it better?

*Placebos work best for pain, disorders of autonomic sensation, and disorders of factors under neurohumoral control*

See papers on p 86 and p 103

Shapiro defined a placebo as any treatment deliberately used for non-specific psychological or psychophysiological effect.[1] That the placeo effect, a classic example of the mind-body relation, is as clinically undeveloped as it is pervasive may reflect the dominance of modern chemotherapy. The placebo depends on largely subconscious interactions between the doctor, the treatment process, and the patient[1 2]; it is the form of a treatment without its substance.

In practice, placebo treatment usually consists of a dummy medication or an intervention, which ranges from surgery to history taking. Placebo medication commonly operates through the administration of a substance, either pharmacologically active (a drug) or inert. The net effect of a given drug is thus the sum of the drug's pharmacological effects and the placebo effect associated with the act of treatment.[3]

The use of placebos raises important ethical questions[3 4]; if these can be answered can we exploit the placebo effect to benefit patients? We first need to consider the neurophysiology of the placebo effect. In the psychoneurophysiology of pain the model of cognitive versus somatic pain survives.[5] In this paradigm somatic pain is linked to the source of nociception while the patient's awareness and cognition, probably residing in the thalamus,[6] determine the perceived pain.[2 7] Anxiety activates the hypothalamic-pituitary-adrenal axis and increases perceived pain; likewise, the removal of anxiety decreases pain. This two component model is supported by "negative placebo effects" such as "clinic hypertension," in which anxiety increases blood pressure in a conditioned response.[8]

In 1964 Lasagna *et al* first showed the hyperalgesic effect of the partial opioid antagonist naloxone.[9] Animal and clinical experiments later showed that a family of opioid peptides in the brain, the endorphins, mediates some types of somatic pain.[7 9 10] The endorphins originate from pro-opiomelano-corticotrophin and are thus linked, through β lipotrophin,[11] with the regulation of the hypothalamic-pituitary-adrenal axis.[12] Neither animal nor human experiments using opioid antagonists have shown the precise functional links between the opioid, anti-opioid,[7] and β lipotrophin systems of neuroendocrine peptides[13] in placebo analgesia. The neurotransmitter γ-aminobutyric acid increases the secretion of both β endorphin and β lipotrophin. The endorphins may also modulate the stimulation by γ-aminobutyric acid of secretion of endorphins in a negative feedback loop.

How endorphins interact with brain opioid receptors is poorly defined. The endorphins might behave as pure opioid μ receptor agonists, such as codeine or morphine,[14] or as μ receptor partial agonists, since they produce only limited pain relief.[5 9] A system of anti-opioid neurotransmitters seems to modulate the opioid system in the rat brain.[15] Endogenous anti-opioids may confer 'supersensitivity to endorphins by increasing the number of opioid receptors.[16]

Although an integrated model including opioids, anti-opioids, and γ-aminobutyric acid may explain some aspects of placebo action, we do not know how a thought releases neural peptides. The neuropeptide hypothesis holds for placebo analgesia, but little is known about how placebo promotes wellbeing in other ways. The placebo mechanism thus seems to be both multidimensional and selfregulating. In evolutionary terms the placebo effect might compensate for overexcitation of the hypothalamic-pituitary-adrenal axis by environmental threats. Is the placeo effect mimicked or enhanced by anxiolytic drugs such as the benzodiazepines? An unrecognised placebo response could, indeed, partly explain the success, in subjective terms, of anxiolytic drugs across cultures. Specific placebo treatment appeals both because it resonates with the holistic view and because it is unlikely to cause harm.

Can we select patients accurately for placebo treatment? Two factors are necessary for placebo action: a suitable disease and a dynamic relationship between patient and doctor. Often, however, neither patient nor doctor is aware of the placebo effect. Experience also colours the response to placebo. A placebo works in about one third of subjects.[5] Placebos are more effective for clinical than experimental pain and for severe than mild pain,[2] but mildly depressed patients respond better than severely depressed ones.[17] Gender, suggestibility, and intelligence quotients do not affect respon-siveness to placebos. "Placebo reactors" who regularly respond to placebos do not exist.[1 2 5] Selecting those patients most likely to benefit from placebo is therefore difficult.

In which diseases is a consistant response most likely? A placebo works best and most commonly in pain and

disorders of autonomic sensation, such as nausea[2 9]: psychoneuroses, phobias, and depression[2 5]; and disorders of factors under neurohumoral control, such as blood pressure[2 8] and bronchial airflow. Placebos will not work if the disease is hyperacute (for example, cardiac arrest), or when vital functions degenerate (for example, in severe metabolic acidosis). Also, the placebo effect usually fails in unremitting disease, such as hereditary syndromes.

Adjuvant placebo treatment is useful in some neuroses and mild depression and may be useful in some chronic non-cancer pain syndromes and in hypersensitivity or hyper-reactivity conditions in which psychic factors play a part (for example, dermatitis and bronchial asthma). Adjuvant placebo seems unlikely to affect the course of cancer. Could the placebo effect be boosted long term? Prolonged administration of opioids in mice inhibits the expression of cell surface markers on T lymphocytes in a dose related manner.[18] This suggests an impairment of immune function, which may outweigh the advantage of a sustained placebo effect.

What about combining placebo treatment with unorthodox techniques such as acupuncture, hypnosis, and homoeopathy? These are likely to potentiate any placebo effect only if they work through an independent mechanism. Hypnosis and acupuncture may not depend on endorphins,[19] but more information is needed. Even greater is the need to determine the placebo component of medicines—both traditional and conventional. The extent to which homoeopathy works through the placebo effect is unresolved, as discussed elsewhere in this issue (p 103).[20] Another study in this week's journal reports that an impressive number of cancer patients experienced benefit such as increased optimism from complementary treatments (p 86).[21] Interestingly, because a reduction in anxiety is a marker of placebo action, patients in this study who used complementary treatments were more anxious than those who did not.

Insights have come from recent studies of the placebo effect, but there is no easy way around the poor specificity and predictability of placebo treatment. Moreover, the self regulating nature of the placebo mechanism may limit the treatment gain. Nevertheless, in appropriate patients, doctors might consider giving a placebo when active treatment is both costly and likely to confer only marginal or transient benefit.

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# Microscopic haematuria

## *Requires investigation*

Gross haematuria is obvious to the patient and is usually followed up, appropriately, by a complete urological work up. The much commoner microscopic haematuria, however, may not always receive the attention that it deserves. Dealing with this symptom adequately in the general practitioner's surgery requires a substantial body of knowledge. Recent developments warrant a re-examination of this topic.

Microscopic haematuria is rare before the age of 50 (occurring in fewer than one in 100 people of this age); after 50 the prevalence rises sharply and varies from 2% to 18% [1 2] (with some of this variation explained by different definitions). The commonly used dipstick test gives a yes or no answer to the question of whether microscopic haematuria is present and semiquantitative information at the same time. Comparing its results with those of standard microscopic evaluation of urinary sediments, one representative study found a sensitivity of 100% and a specificity of 60%.[3] The relatively high frequency of false positive results of dipstick tests may be due to the technique's detection of normal numbers of red cells (1-2 $\times 10^{12}$/l urine). The consensus is that if the result of a dipstick test is positive then the urinary sediment should be examined; if the result of a dipstick test is negative no further investigation is needed.

The figure gives an algorithm of recommended diagnostic tests for patients with haematuria. Several explanations exist for some of the variations in the prevalence of microscopic haematuria in different populations. A dipstick test may yield a positive result in the very concentrated early morning urine whereas it may give a negative result during the day after fluid intake. Several other artefacts, especially the contamination of urine with menstrual blood or sexual trauma in men and women, must be considered. Laville *et al* evaluated risk factors in 8200 workers in the metallurgical and chemical industries