Taboos, worms and prophecies: insights into the placebo enigma

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The placebo response is a complicated and complex social, cultural, psychological and biological phenomenon that contributes to every drug effect, complicates every clinical trial and influences every interaction between healthcare professionals and patients. Researchers now have an unprecedented understanding of the biological basis for the phenomenon, although, important questions remain.

A surgeon operating near the front line in the Korean War started suffering severe abdominal pain, which he knew indicated acute appendicitis. As incoming wounded needed his help, the surgeon asked a nurse to inject him with morphine. Returning to duty after his appendectomy, the surgeon looked through the operating room records and found that ‘since he appeared distressed’ the nurse had injected saline, probably to avoid effects on cognition. The surgeon, however, expected the nurse to follow his instructions, which helped invoke placebo analgesia powerful enough to counter the pain of acute appendicitis.

The placebo response is a complicated and complex social, cultural, psychological and biological phenomenon that contributes to every drug effect, complicates every clinical trial and influences every interaction between healthcare professionals (HCP) and patients. Even worms and flies, a recent paper notes, show placebo-like effects, suggesting that the response, in part, reflects a fundamental biological process essential for survival.

A ubiquitous response
The term placebo derives from the Latin phrase meaning ‘I shall please’. By 1811, placebo had come to mean a ‘medicine adapted more to please than benefit the patient’. Indeed, doctors in the early 20th century used a variety of multicoloured sugar pills, bread pills and subcutaneous water injections as placebos, especially for patients they regarded as ‘unintelligent, neurotic or inadequate’.

Countless studies now show that the placebo response is not confined to the credulous. In randomised controlled trials (RCT), for example, the placebo response rate can range from less than 10% to more than 60%, ‘even within single clinical entities’. For example:

- In epilepsy, between 9.9% and 15.2% of patients in the placebo arm of clinical studies show at least a 50% improvement of seizures compared to baseline.
- 26% and 16% of patients with diabetic neuropathic pain and dental pain respectively reported a 50% reduction in pain.
- Placebo responses are common in fibromyalgia (45%), migraine (29%) and pancreatic pain (20%).
- Placebo response rates can reach 60% in sleep disorders assessed using polysomnography and 25% in active Crohn’s disease based on the Crohn’s Disease Activity Index or endoscopy.

Taboos and adverse events
In the mid-19th century, a Maori woman accidently ate fruit harvested from a place covered by a taboo (tapu). When, in the afternoon, she learnt that she had broken the tapu, she claimed that the chief’s spirit would kill her. She was dead by noon the following day. In a classic article, American physiologist Walter Cannon from Harvard Medical School describes the tapu as ‘a fatal power of the imagination working through unmitigated terror’.

Just as the Maori woman believed that the tapu would cause her harm, patients often believe that drugs cause adverse events. So, patients experience adverse events or non-specific effects when taking a placebo – the so-called ‘nocebo response’.

A meta-analysis of 21 RCTs, for example, assessing antidepressants found that 44.7% of patients taking placebo reported adverse events (such as headache, nausea and dizziness) compared with 40.9% of those receiving active drugs. Moreover, 4.5% and 6.9% of the placebo and active arms discontinued treatment because of adverse events. Other studies confirm the nocebo response is widespread:

- An analysis of 56 studies of multiple sclerosis found that 74.4% of patients in the placebo arm developed adverse events and 2.1% stopped treatment as a result.
• In 41 studies of Parkinson’s disease, 64.7% developed adverse events and 8.8% stopped treatment; the figures were 62.9% and 9.5% respectively in 16 fibromyalgia trials.

• An analysis of seven RCTs assessing antiepileptic drugs in paediatric refractory focal epilepsies reported a placebo response rate of 19.7%, while 81.3% experienced at least one adverse event, usually headache (11.4%), somnolence (9.6%) or ataxia (4.6%). Indeed, 3.6% of children taking placebo withdrew due to adverse events.

Researchers now have an unprecedented understanding of the biological basis for these responses, although, as we will see, important questions remain.

**Self-fulfilling prophecies**

The doctor in the Korean War expected the nurse to follow his instructions, which helped invoke potent placebo analgesia.2,9 Certainly, expectation can have a strong influence on the response to treatment: expecting a benefit or a side effect can become a self-fulfilling prophecy.

For instance, in an excellent review, Jakovljevic offers a useful list of self-fulfilling prophecies that could contribute to placebo and nocebo responses.10 To take just two examples: The ‘halo effect of uncontrolled novelty’ means that receiving a new treatment may change a person’s expectations, stimulate them to be more alert or change another behaviour.10 After all, some people embrace novelty. Others fear change. In therapeutic interactions, the HCP could subtly communicate their expectations. In turn, patients alter their behaviour to conform with the HCP’s expectations.

Indeed, the therapeutic alliance – such as the extent to which HCPs provide a meaningful explanation and express care and concern – can have an important influence on placebo responses.9 Leuchter et al. randomised 88 people with major depression to eight weeks of supportive care either alone or combined with double-blind treatment with placebo or an antidepressant. Medication or placebo were not significantly different. Both, however, were significantly more effective than supportive care alone. The ‘strength’ of the therapeutic alliance predicted the response to medication and placebo. Expectations of efficacy predicted the response to placebo only.11

Similarly, patients can learn what to expect with a certain drug, which can again become a self-fulfilling prophecy. Giving a placebo after conditioning with repeated administration of aspirin produces an aspirin-like effect. Similarly, giving a placebo after conditioning with ketorolac or morphine produces analgesic effects similar to ketorolac or morphine respectively. In the latter case, patients may also experience morphine-like adverse events.12

In other words, patients who expect adverse events may be especially prone to experience the nocebo response. So, information about adverse events provided before treatment, negative experiences, stress and anxiety also seem to increase the likelihood of a nocebo response.6

One study, which enrolled 46 healthy people, used red, yellow and green cues to alert subjects that an upcoming thermal pain would be high, medium and low intensity respectively. After a conditioning phase, the researcher kept (without the subjects’ knowledge) the pain set at ‘medium’ but changed the cues to measure placebo and nocebo effects.15

Together motivation and suggestibility accounted for the 51% of the variance in placebo responses. Anxiety, openness, extraversion and depression accounted for 49.1% of the variance in nocebo responses. The study confirmed that expectations correlated highly with placebo and nocebo effects. However, psychological factors did not influence a person’s expectation of a change in pain intensity.15

**Introducing the placebome**

Studies are clarifying the neurochemical changes evoked by these cues. For example, the ‘placebome’ refers to the various genome-related or derived molecules—such as genes, proteins, or microRNA (small non-coding RNA that regulates gene expression)—that seem to affect an individual’s placebo response.14 In a compelling review, Hall et al. ‘speculate that the placebome comprises multiple intersecting pathways that have upstream or downstream effects on dopamine and opioid function, depending on the disease or disorder being treated’.

The observations raise the prospect of developing biomarkers that indicate which people might have a propensity towards a placebo response. If confirmed, such biomarkers could have implications for clinical trial design.14

Certainly, placebo analgesia changes the activity of several CNS regions that seem to process pain, including the dorsolateral prefrontal cortex, the anterior cingulate cortex and periaqueductal grey as well as reducing nociceptive processing in the spinal cord. This suggests that ‘top-down mechanisms suppress pain processing in the central nervous system at the earliest stages’.12
In other neurological conditions, such as Parkinson’s disease, dopaminergic reward mechanisms may mediate the placebo response. One study, for example, found that placebos induced an increase in endogenous synaptic dopamine levels in the striatum of people with Parkinson’s disease. The experiment did not include a direct reward. Nevertheless, dopamine release in the nigrostriatal system may reflect the expectation of clinical benefit.6

Placebo analgesia is associated with the release of several neurotransmitters, including opioids, cholecystokinin (implicated in anxiety and hyperalgesia), oxytocin and cannabinoids. For example, naltrexone can antagonise placebo analgesia driven by an expectation of benefit. Rimonabant, a cannabinoid receptor 1 antagonist, blocks placebo analgesia conditioned by ketorolac.12

Worms and flies

Despite such advances, as Harvey and Beedie noted, ‘important questions remain’, such as whether the placebo response ‘is an evolved, and potentially ubiquitous, trait, or an unpredictable side effect of another evolved process’.5 It is of more than academic interest. Answering the question may, in the future, allow clinicians to module the physiology underlying placebo and nocebo responses to optimise outcomes with drugs and other treatments. Moreover, if the trait is ubiquitous, researchers may be able to develop animal models to investigate hypotheses that would be ethically or practically impossible in human studies.5

Studies in the nematode worm Caenorhabditis elegans and the fruit fly Drosophila melanogaster that undermine the reliability of predictable cues suggest the trait might be highly conserved. For instance, studies using C. elegans show that cold perception, rather than the effects on cellular function, are critical for the worm’s survival.3

Prolonged exposure to temperatures below 5°C kills adult C. elegans. Exposing the worms to low, but non-stressful, temperatures habituates the nematode and markedly reduces or even blocks the mortality from low temperature. Disrupting specific neurons can replicate the habituation response even when the temperature remains constant. In other words, habituation reflects temperature perception rather than the environment. In other words, Harvey and Beedie write, ‘we can observe placebo effects in worms and flies: ‘there is an expectation of something and a subsequent set of changes that (should) optimize fitness under the expected condition’.3

Of course, such traits are only one aspect of the placebo response. Communicated expectations, previous experience (learning), manipulated learning (conditioning), context – such as the ‘white coat effect’ (blood pressure rises when measured in the clinic) – emotions (including hope and anxiety, personality), health attitudes and belief systems3,11 are among the diverse factors that seem to contribute to placebo and nocebo responses. Studies assessing placebo and nocebo effects also need to account, for example, for spontaneous remission, intrinsic variations in disease severity over time and regression to the mean.5,14

Overall, however, recent studies – the examples above barely scratch the surface – show that our understanding of and investigations into these enigmatic effects are moving ‘away from vague self-reported and subjective responses towards robust and directly measured biological events’.2 Nevertheless, there is still a need for much more research into these enigmatic responses. In the meantime, placebo and nocebo responses will continue, as Jakovljevic comments, to ‘fascinate, confuse, mystify and challenge’.10

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References