Chapter 23
The Ups and Downs of Placebos

Pete C. Trimmer, Ph.D. and Prof. Alasdair I. Houston, Ph.D.

> To everyone is given the key to heaven; the same key opens the gates of hell.
>
> Ancient Proverb

Lay Summary Patients are sometimes given dummy tablets or treatments, termed placebos, that sometimes seemingly affect patients' health despite such treatments providing no direct medicinal benefit. The effect is often regarded as somewhat mysterious: why would evolution by natural selection not have resulted in individuals recovering their health as soon as possible, with or without a placebo? Despite the effect being poorly understood, it is often assumed that any 'placebo effect' will be positive. Here, we review the possible effects of placebos from an evolutionary perspective. We identify situations where evolutionary theory predicts that placebos should have positive or negative effects on patients. The outcomes will typically depend on numerous factors relating to the condition and, more specifically, beliefs of the patient. The evolutionary perspective highlights the many trade-offs involved in how the immune system can be affected by placebos, and the potential danger of confusing symptoms with an underlying ailment when considering effects.

P.C. Trimmer (✉) · A.I. Houston
School of Biological Sciences, University of Bristol, Bristol, UK
e-mail: pete.trimmer@gmail.com

A.I. Houston
e-mail: a.i.houston@bristol.ac.uk

A. Alvergne et al. (eds.), *Evolutionary Thinking in Medicine*,
Advances in the Evolutionary Analysis of Human Behaviour,
DOI 10.1007/978-3-319-29716-3_23

23.1 Introduction: The Trade-Off Between Current Health and Other Factors

It is notoriously difficult to define the term 'placebo' satisfactorily [1]. The word is most often used in the context of the 'placebo effect' (frequently regarded as the improvement in health resulting from having taken a pill containing only inert substances), and many definitions of the term assume or imply that any effect of a placebo will be positive. For instance, the on-line Google dictionary defines a placebo as, 'A *harmless* pill, medicine, or procedure prescribed more for the psychological benefit to the patient than for any physiological effect' (our italics). Further such definitions are summarised in Appendix A.

Clearly, it is best not to define a possible treatment by its intended outcomes; the decision of whether to prescribe a placebo would surely then follow from its presupposed effect. Here, we define a placebo simply as, 'a treatment which may have an effect on health only indirectly, through modifying the patient's beliefs'. The beliefs need not be conscious and may be true or false (note that our use contrasts with the anthropological lexicon, where beliefs are generally regarded as conscious [2]).

Many positive effects have been attributed to placebos, such as pain relief. Some of the positive findings are likely to be due to reporting bias. For instance, Okaïs et al. [3] find that, 'vaccinees and healthcare professionals tend to report preferentially the symptoms of the disease against which the nonlive vaccine was administered' and it has occasionally been argued that most findings of placebo effects are simply the result of reporting bias (e.g. [4]). Nevertheless, there is considerable evidence for placebos having positive effects on some conditions: pain, ulcers, etc. For reviews, see [5–9]. The effect of dummy tablets is modulated by many factors, such as the colour of the pills, their size, the regularity with which they are taken and so on. Operations seem to have more effect than tablets, and the manner of the treating physician also modulates the effect. These effects are summarised by Olshansky [8]. However, some conditions (such as cancer or schizophrenia) do not seem to be influenced by placebos.

Evans [5] suggests that placebo effects are related to the modulation of the innate immune system, rather than the acquired immune system. The hypothesis is data-driven: many placebo-responsive conditions (including pain, swelling, stomach ulcers, depression and anxiety) involve the acute phase response of the innate system. Thus, Evans argues, any condition that is not affected by the innate system will not be affected by placebos and, conversely, any condition which is affected by the innate system may be affected by placebos.

This chapter provides an evolutionary perspective on placebos, addressing the question of why an external cue can sometimes prompt individuals to get well, when they already had the capability to do so (since the placebo supplied no biologically active component). We summarise recent work that has shown how the placebo

effect could be favoured by natural selection, and identify conditions under which placebos could have deleterious effects. In each case, the effects can be understood as an evolved response to trade-offs in different requirements, as we now discuss.

Biological systems can often be understood in the context of trade-offs (e.g. [10]). From the perspective of natural selection, the fitness of an individual is not just about immediate health, but long-term reproductive success (cf. [11]). The reproductive value of an individual will depend on many factors; age, health, risks of starvation or predation, etc. Fighting off a disease as quickly as possible may reduce the body's ability to deal with other infections or diseases in the near future. Humphrey [12] draws an analogy between the immune system and a hospital administrator who must manage resources when dealing with emergencies (taking into account current resources, expected deliveries and likely future emergencies). Rather than use all the available bandages, blood, etc., it is often better to hold some back in case of future needs. Similarly, it is expected that natural selection has shaped the body to manage its resources when dealing with an illness.

We are interested in the physiological allocation 'decisions' which affect health. Such decisions need not be conscious; evolution by natural selection shapes behaviour (including taking account of the costs and benefits of physiological actions in the immune system), so whether the immune system is adjusted consciously or not does not affect the analysis (cf. [13]).

All else being equal, it is always better to be healthy than ill. But given that someone is ill, the general 'decision' is how much resource (such as energy) to devote to the immune system at the current time (see Fig. 23.1). The key logic is that because the state of the world will affect the optimal level of resource allocation in current health (i.e. effort), perceptions about the world should affect the activity of the immune system.

23.2 Research Findings

There are many ways in which altered beliefs may affect immune systems. We break these down into positive and deleterious effects.

23.2.1 Positive Properties of Placebos

23.2.1.1 Reducing the Perceived Cost of Immune Action

In some situations, a placebo may reduce the perceived cost associated with increased immune effort. For instance, a sick individual could afford to put more effort into fighting an ailment if someone were there to assist (in case food provisions ran low or there was a predation threat). This accords with Houston et al. [14], who

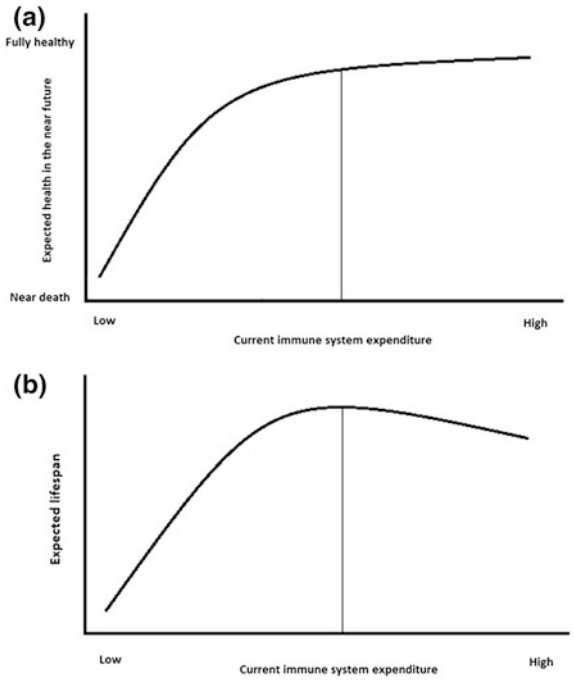

Fig. 23.1 The effect of immune system effort on current health for a particular condition. **a** Provides an example of how expected health in the near future might increase with immune system effort for a given condition. The vertical line shows a hypothetical (evolved) amount of effort typically put in by someone with that condition. To explain why they do not put more effort in (to further improve their expected health in the near future), we need to consider the consequences of increased effort. **b** Shows that for a given set of expectations (regarding current predation risk, prevalence of the disease, food supplies, weather conditions, etc.), some level of immune effort at the current time will maximise expected lifespan. This assumes that some reserves should be held back for potential emergencies in the future, such as other illnesses (this can change over time, depending on current illnesses and expectations about the future). Consequently, the optimal effort level will not maximise health in the near future, allowing beliefs (e.g. through placebos) to have an effect on health

show that the optimal allocation of energy to the immune system increases with energy reserves, when there are risks of death through disease or starvation. In the developed world, food is rarely in such short supply, but the perception of having others there to provide support may still have an effect, because we have not yet evolved to deal with the ecological features of the developed world. In this way, even the presence of someone who appears willing to support a sick patient may produce positive outcomes by increasing the amount of resource allocated to the immune system, much like a dummy tablet.

Trimmer et al. [15] consider a situation where mortality may be caused by disease or other factors. Increased immune activity may prevent the disease from gaining a foothold, or fight it off more readily. Such activity may also reduce energy levels

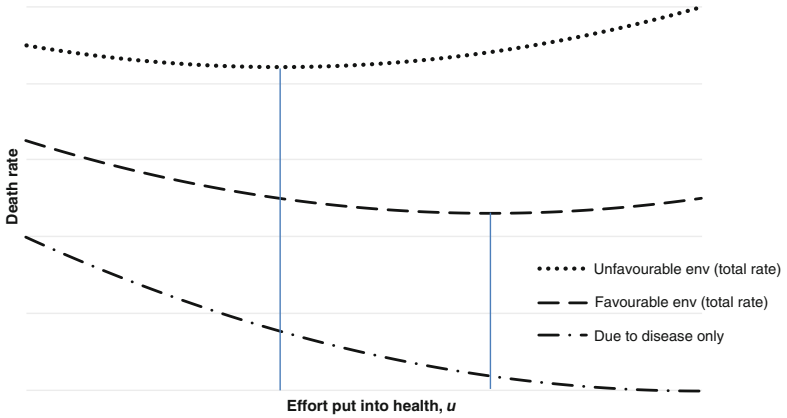

Fig. 23.2 (Reproduced from Fig. 23.1 of [15]): effort put into health should alter with environmental conditions. The death rate due to disease, D, decreases with effort put into health, u. The death rate from other sources (such as starvation or predation), M, decreases with the quality of the environment, a, and increases with u. In an unfavourable environment (where factors such as starvation or predation are more common than in the favourable environment), the optimal effort level, u^*, is low (indicated by the *vertical bar* on the *left*) because there is a high rate of mortality from other sources, so it is best not to increase that rate still further by putting much effort into health. In a favourable environment, where there is a smaller probability of death from other sources, the total mortality rate is minimised by putting more effort into health (indicated by the *right vertical bar*). $D(u) = (1 - u)^2/10$. $M(a,u) = (1 + u)/(20a)$. Unfavourable environment: $a = 0.4$, $u^* = 0.38$. Favourable environment: $a = 0.8$, $u^* = 0.69$

available for escaping predators, avoiding starvation, etc. Consequently, effort put into the immune system reduces the risk of mortality due to disease but increases the risk due to other sources. By assuming that the risk of mortality due to other sources is also dependent on the current conditions, Trimmer et al. show that in good conditions, it is optimal to put more effort into the immune system (Fig. 23.2). Consequently, if a placebo were to give an individual the perception that the world was "safe" (so the main mortality risk was through disease) then more effort should be put into the immune system, resulting in a positive placebo effect.

23.2.1.2 Reducing Perceived Effort of Overcoming Ailment

A placebo may sometimes work by reducing the perceived effort required to overcome an illness. If a dummy tablet is believed to assist recovery, then patients may (whether consciously or subconsciously) respond by increasing their immune activity so as to overcome the ailment now, rather than let it drag on. Consequently, the more powerful a placebo treatment is believed to be (enhanced by being more colourful, larger or prescribed to be taken more regularly), the greater the effect should be, as is often the case [8]. However, we shall see that, in some forms, such a belief may also be detrimental.

23.2.1.3 Reprioritisation Through Increased Urgency

So far, we have considered placebos that increase the perception that the world is currently conducive to improving health: less effort is currently required to fight off an illness, the risks of increasing the immune effort are currently low, or the risks of death through other sources are reduced. Each of these serves to reprioritise (and increase) how much effort to put into the immune system. However, it is also possible to reprioritise effort by regarding the current illness as more (or less) important. So a rather different method of inducing improvements in health would be to emphasise the importance of fighting the illness off as soon as possible. In an extreme form, this might be caused by a doctor saying, 'This is serious, it kills some people—you need to fight it off now!' but (more realistically) being told to take pills at regular intervals may be enough to highlight the importance of dealing with a condition, resulting in more effort being put into improving immediate health.

The extent to which placebos may influence health will, of course, depend strongly on the extent to which beliefs can affect the functioning of the immune system. However, we have seen that there are many ways in which beliefs should, at least in theory, have positive effects on health.

23.2.2 Deleterious Effects of Placebos

We have argued that current investment in the immune system should be traded off against other dangers. If a person's immune system was operating at the optimal level and a placebo altered the amount of effort put into immediate health, the placebo must therefore have increased some risks.

23.2.2.1 The Adjustment of Perception

Pain can be beneficial; it indicates a problem, encourages reduced use of the damaged region (e.g. a broken limb) and reduces activity, thereby giving the healing systems more chance to act. People who do not feel pain (due to a rare genetic mutation) have a low life-expectancy [16]. It is possible that a placebo which acts to reduce pain, without having any direct benefit on the ailment causing the pain, could lead to more danger.

Placebos certainly can have such an effect. By measuring how long people are able to submerge their arms in ice water, it has been shown that a placebo (even one so simple as telling the patients about the positive benefits of ice water immersion) can significantly increase the length of time that subjects are willing/able to expose themselves to such cold (e.g. [17]).

Nevertheless, the use of placebos for pain reduction carries many benefits without the pharmacological side effects of 'real' pain killers; if a placebo will

suffice, there is little or no benefit of using active drugs. The downside of placebos in this case also goes for 'real' pain killers; very occasionally, too much pain reduction may be detrimental.

In some cases, placebos seem to improve patients' symptoms (by reducing their perception of pain) while the underlying condition remains unchanged (or even deteriorates). Any placebo that reduces perceived risk may result in time being lost before useful treatment is obtained. This is arguably one of the risks of 'quackery' and alternative (but ineffective) medicines; the more convincing the treatment (i.e. the more effect they have on perception without improving the underlying cause), the more harm may be done.

23.2.2.2 The Perceived Cure-All

Too much belief in a treatment may reduce the effort put into fighting an ailment. If an individual believes that a treatment is sure to fix their ailment, then there is no need for them to put effort in themselves. Because there is nothing medically active in a placebo, and the individual could be misled into putting less effort into their immune system, they may get worse rather than better.

This 'reverse placebo effect' was identified in Trimmer et al. [15] from a theoretical perspective. However, it is difficult to know how such an effect (of strong belief in a placebo treatment leading to deterioration in health) could be shown empirically while remaining ethical.

23.2.2.3 The Dangers of Depleted Resources

Having been influenced by a placebo into putting more effort into health, an individual will have reduced resources such as energy and rare minerals. In the developed world, where food is generally plentiful (all year round), there may be less risk in prescribing placebos to people than those that are at greater risk of starvation (e.g. in low-income countries). However, with depleted resources (e.g. micronutrients such as trace minerals, which are crucial for immune function), they may be more prone to infection and disease.

23.2.2.4 Future Effects

If there is an increased perception that placebos are often prescribed, patients may become more cynical, which may have consequences:

1. Reducing the placebo effect (including that associated with 'real' treatments) in the future, with other illnesses.
2. Reducing faith in doctors—perhaps meaning that people will be less likely to visit doctors to be treated (or delay until symptoms are worse).

23.2.3 Identification of Effects

Placebos are prescribed (and taken) because a once-healthy person has an ailment that needs to be 'fixed'. If taking a placebo results in recovery, then the improvement is (often) attributed to the placebo. But if the ailment gets worse, then the expectation may be that it was going to get worse anyway. Without any expectation that a placebo may have detrimental effects, it is easy for such effects to be missed.

Testing of medicines is most often carried out on new treatments. If a new type of treatment (with both medicinal and placebo components) is having negative effects, the outcomes may be attributed to the medical properties of the treatment rather than the placebo component of the effect. The health of the patients must come first, so it is more difficult to identify deleterious placebo effects (due to discontinued trialling).

Even in 'pure' placebo settings, Mitsikostas et al. [18] note that negative consequences may be more difficult to identify. People experiencing negative outcomes are more likely to drop out of studies and the people who go in for clinical trials may not be a representative selection of the population (cf. [19]).

23.2.4 The Complexity of Causation

One of the complications when studying the effect of placebos arises through the difficulty of distinguishing between an underlying illness (improving or deteriorating) and symptoms (improving or deteriorating). Evolutionary approaches to medicine [20] highlight that there is a potential danger of just treating the symptoms rather than the disease. Symptoms are sometimes caused by the immune defences being active, so a short-term deterioration in symptoms (such as a high temperature) may be associated with a longer-term improvement in health. Repeated stress responses have long-term, deleterious effects on the immune system [21, 22]. Therefore, if a placebo seemingly 'works' by increasing stress, thereby reducing immune activity and reducing symptoms in the short term, the treatment may produce negative outcomes in the longer term.

Table 23.1 summarises the four possible outcomes of a condition that would be *improved with increased immune system activation*, depending on the placebo effects on both the underlying illness and the symptoms.

An additional complication comes through the potential for symptoms to exist without an illness being present. This is because the body's defences are often triggered on a precautionary basis, reacting to risks rather than waiting to know that such a defence is needed. For instance, when eating a group meal, if one person is sick, this can trigger others to vomit. From an evolutionary perspective, this is an understandable precautionary reaction; the benefit of those few calories needs to be

Table 23.1 The correlation between long- and short-term effects of placebos can depend on the condition being treated

		Illness itself (and thus long-term symptoms)	
Symptoms (short term)		Improvement	Deterioration
	Improvement	Symptoms are caused by illness; placebo has increased the immune response	Symptoms are caused by fighting the illness; placebo has reduced the immune response
	Deterioration	Symptoms are caused by fighting the illness; placebo has increased the immune response	Symptoms are caused by illness; placebo has reduced the immune response

weighed against the risk of illness or death [23]. Placebos may reduce the precautionary reactions; whether this is good or not will depend on the situation.

23.3 Implications for Policy and Practice

We have clarified the distinction between the lay-term 'the placebo effect' (often assumed to be positive) and 'the effect of placebos' which may, in some situations, be deleterious. It is important for medical professionals to be aware of the possibility that dummy treatments have adverse effects.

Many people would prefer a world where placebos were not necessary; where any affliction could be dealt with directly, with no need for deception. However, since this is not possible, questions arise over the extent to which it is ethical to use placebos, when placebos will help or hinder, and the associated risks. An evolutionary perspective helps to address these questions; the general effects are shown in Table 23.2.

Present theory suggests that if prescribing placebos, a doctor needs to make a judgement about whether their patient would benefit from increasing or reducing their immune activity, and tailor their message accordingly. For instance, if the

Table 23.2 Summary of the effects of a placebo component of a treatment as a function of the current state of the immune system

Effect of placebo on immunological effort			
		Increase investment	Decrease investment
Immune system currently	Overactive	Deleterious (e.g. increasing exhaustion, autoimmunity? sepsis?)	Beneficial (e.g. reducing allergies)
	Balanced	Slightly deleterious, but can look beneficial in terms of immediate health	Deleterious; more likely to get ill
	Underactive	Very beneficial (normal 'placebo effect' in public consciousness)	Very deleterious

We ignore the cases where the placebo has no effect on subsequent immunological effort

patient has an under-active system (the norm, so the aim is to encourage increased immune function), then the patient should be encouraged to believe that they have something which they need to take seriously, and that the treatment will 'help' to boost their immune system to fight off the ailment.

In terms of policy, Shiv et al. [24] identify that it may be necessary to charge for placebos if they are to have their maximum effect. But charging for something with no active ingredient means that there is a risk of law-suits. However, the finding that more expensive placebo treatments produce larger effects (e.g. for pain, see [25]) may mean that doctors and drug companies are not easily prosecuted. Although this is something which needs to have a current policy, it is also an aspect requiring more research in the future.

23.4 Future Directions

Evolutionary thinking is making progress in understanding the complex and subtle effects of placebos. Rather than prescribe placebos on the assumption that they will cause no harm, we recommend that future studies involving placebos also consider the possibility of deleterious effects.

There is already some empirical evidence that placebos produce negative effects in humans. For instance [26], a meta-analysis of many placebo studies is performed. Most studies involving placebos are carried out to study the effect of 'real' treatments, so they do not include a control case of 'no placebo'. However, by comparing options when different numbers of placebos have been taken, the study identified that those receiving more doses of placebos were more likely to report symptoms such as nausea, headaches and weakness. As Evans [5: 123] concludes, 'more research is needed'.

We regard a placebo as a treatment that can only have an effect on health by modifying expectations, so our analysis is also relevant to the potential for nocebos (typically ascribed the power to do a subject harm through negative expectations; [27]) to have positive effects. From a top-down perspective, there are many ways in which beliefs *should* affect the immune system (positively or negatively). However, more work is required to better understand the proximate mechanisms by which the brain affects the immune system, and how best to discern long-term precautionary reactions from short-term symptoms (especially in relation to [5]).

The key to progress on the placebo effect is in understanding how beliefs can affect physiology. Although there have been relatively few tests of placebos against a control of 'no treatment' for medical problems, there is a strong parallel with sports. While Humphrey talks of a 'health governor' in relation to the placebo effect on health (e.g. [28]), Noakes [29] talks of a 'central governor' in relation to how much effort an individual will put into an activity. The two are arguably closer than analogies; in each case, the brain makes use of information to modulate the body. In the case of physical activity, anticipation affects current effort level, and altering an

individual's beliefs (whether consciously or not) may affect how much effort is put into an activity. As Beedie and Foad [29] summarise,

> Findings suggest that psychological variables such as motivation, expectancy and conditioning, and the interaction of these variables with physiological variables, might be significant factors in driving both positive and negative outcomes.

Considerable further work is required to understand how beliefs affect physiology. This research is needed if we are to fully harness the power of the placebo effect to better treat patients in the future.

Acknowledgments This work was supported by the European Research Council (Evomech Advanced Grant 250209 to A.I.H.).

Appendix: Definitions of a Placebo that Presuppose Its Effect Will Be Non-negative

Google online dictionary: A harmless pill, medicine, or procedure prescribed more for the psychological benefit to the patient than for any physiological effect.
Evans [30]: A placebo is a medical treatment that works (i.e. relieves symptoms or cures disease) because the patient believes it works.
www.clarkfamilydental.com/glossary.php: Inert medication or treatment that produces psychological benefit.
en.wiktionary.org/wiki/placebo: A dummy medicine containing no active ingredients; an inert treatment; anything of no real benefit which nevertheless makes people feel better.
http://www.merriam-webster.com/dictionary/placebo: An inert or innocuous substance used especially in controlled experiments testing the efficacy of another substance (as a drug).
Kitsch [1]: A placebo is a chemically inert substance that works by virtue of its presumed psychological effect.
Humphrey [12: 256]: a treatment which, while not being effective through its direct action on the body, works when and because:

- the patient is aware that the treatment is being given;
- the patient has a certain belief in the treatment, based, for example, on prior experience or on the treatment's reputation;
- the patient's belief leads her to expect that, following the treatment, she is likely to get better;
- the expectation influences her capacity for self-cure, so as to hasten the very result that she expects.'

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