The role of placebos in family medicine

Implications of evidence and ethics for general practitioners

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Background
Placebo use is prevalent in primary care. A wealth of discourse on the ethical use of placebos in clinical contexts invariably assumes that placebos oblige practitioners to peddle in deception. However, the recent surge in empirical findings within the field of 'placebo studies' provides a very different perspective: namely, that placebos may yet prove to be both effective and ethical.

Objective
The aim of this article is to synthesise state-of-the-art scientific and bioethical research to provide up-to-date recommendations on placebo use for general practitioners.

Discussion
After disambiguating placebo concepts, this article outlines experimental studies into placebo effects and explores the ethical and evidence-based arguments for prescribing placebos. Evaluating the latest research into 'open-label placebos', it can be surmised that there are not yet persuasive grounds to incorporate these treatments into routine clinical care. Notwithstanding, the quality of physician interactions may go some way to harnessing remedial placebo effects among patients.

IN THE UK, a survey conducted in 2013 found that 77% of general practitioners (GPs) prescribed placebos at least once per week.[1] In the USA, a report published in 2008 found that approximately one in two (46–58%) internists and rheumatologists used placebos 'regularly'.[2] The results of these surveys encompassed both 'pure placebos' (eg sugar pills, saline creams) and 'impure placebos' (eg antibiotics for viral infections). Against the backdrop of the widespread use of placebos in primary care and an upsurge in scientific findings on placebo effects, the concrete implications of placebo research for GPs have received scarce attention. The aim of this article is to describe landmark empirical studies into the placebo effect and review new research endeavouring to explore the possibility of ethical clinical placebos (so-called 'open-label placebos'). Although there is currently insufficient evidence to recommend the routine use of openly prescribed placebos in clinical care, this basic research underscores the significant therapeutic potential of effective doctor–patient interactions.

Disambiguating placebo concepts

It is important to clarify what is meant by placebo terminology. Certainly, as a vast and daunting literature search makes clear, definitions of 'placebo' and 'placebo effect' have been subject to protracted disputes. Clarity about placebo concepts is of utmost importance, and philosophical contributions to these intricate discussions can justifiably be viewed as integral to science: without due attention to terminological matters, empirical research risks conceptual and methodological imprecision in terms of what is being investigated (as well as how and why).[3]

Drawing on extensive philosophical reflections, it is possible to delineate between broad but distinctive definitions for placebo concepts (Table 1).[3–6] Briefly, within the scientific community, placebo effects refer to psychobiological processes that give rise to genuine therapeutic effects for a range of conditions.[7] While there is no evidence that placebo effects can treat viral infections or shrink tumours, they may be particularly valuable in alleviating self-reported symptoms including depression, anxiety, pain, migraines and irritable bowel syndrome (IBS).[7] Placebos, on the other hand, have two distinctive but nuanced usages reflecting the separate domains in which these terms are used. First, placebos can refer to interventions (eg pills, injections) that are used in clinical contexts. Placebos in this context are variously understood as treatments that are employed with the aim of 'pleasing difficult patients', giving patients with medically unexplained illnesses hope or boosting their morale, and/or reducing patients' symptoms by harnessing placebo effects.[3,4] The second, and very distinctive, usage of placebos is as controls

in methodological contexts. Here placebos are deployed in randomised clinical trials as tools for determining the efficacy of treatments.[3,4]

The placebo effect: What do we know?

In the past 30 years, interdisciplinary scientific research has advanced our understanding of placebo effects.[7,8] Mechanisms of action are thought to include conscious and non-consciously mediated 'response expectancies', 'classical (Pavlovian) conditioning' and 'social learning'.[8] While the relationship between these mechanisms is not fully understood,[9,10] response expectancies have received the most sustained attention, evinced in a number of fascinating and important studies.[11–13]

To date, experiments show that patients' expectations about interventions may be raised via verbal suggestions (eg by the content of disclosures)[14] as well as by non-verbal and behavioural cues in the clinical encounter.[11,12] For example, in one 'open/hidden' experiment, patients were administered the same dosage of pain killer either overtly (fully aware they were receiving it) or covertly (from another room).[15] Individuals allocated to the covert condition required 50% more painkillers to obtain the same palliative effects as those in the overt condition. Similarly, in a recent study, antidepressant medication was reported to be more potent when patients were informed that the treatment was an active medication as opposed to a placebo pill.[16]

Aside from the content of information conveyed, the way in which it is disclosed, as well as expressions of socio-emotional support, appears to be highly relevant in modulating expectancy and, thereby, placebo effects. A 2008 study by Kaptchuk et al randomly allocated 262 patients with IBS into one of three groups: no treatment (the waitlist group), sham acupuncture administered in a 'businesslike manner' (the limited interaction group) or sham acupuncture with an augmented practitioner–patient interaction (the augmented group).[17] Practitioners in the second group were 'instructed not to converse with patients'; however, those in the third group were tasked with encompassing at least five behaviours into their interviews:[17]

> *... a warm, friendly manner; active listening (such as repeating patient's words, asking for clarifications); empathy (such as saying, 'I can understand how difficult IBS must be for you'); 20 seconds of thoughtful silence while feeling the pulse or pondering the treatment plan; and communication of confidence and positive expectation ('I have had much positive experience of treatment [for] IBS ...') ...*

Adequate relief was reported by 28% of patients in the waitlist group, 44% in the limited interaction group and 62% in the augmented group. Refining this research agendum, Howe and colleagues investigated the quality of provider interactions by focusing specifically on provider warmth and competence.[18] An allergic reaction was induced among healthy volunteers, and it was found that participants who had positive expectations of allergy relief when administered an inert cream, and who interacted with a practitioner perceived to be high in competence and warmth, had the largest reduction in their allergic reaction, measured by decreased weal size. Weal size decreased less in other groups; that is, patients with negative expectations and/or interactions with practitioners showing low warmth and/or low competence.[18] Taken together, these findings build on a body of research suggesting that provider behaviour, including expressions of empathy, can carry significant therapeutic effects on healthcare outcomes.[19]

Subfields of placebo research are also directed at understanding the neurobiology of placebo effects, including identifying regions of the brain implicated in these processes, and the role of neurotransmitters such as endorphins, dopamine and cholecystokinin in placebo effect–induced analgesia.[8,20,21] Meanwhile, prominent investigations have focused attention on the so-called

Table 1. Summary of placebo concepts

Placebos may refer to either:

Methodological controls in randomised controlled trials

Placebos in randomised controlled trials (RCTs) are methodological tools ('controls') to screen out the noise of clinical research (refer to 'Placebo responses').[3–5] Placebos ideally should be indiscernible from the treatment (the 'verum') by both patients and clinician–experimenters. For example, an optimally designed placebo pill should be the same colour, size and taste as the verum medication. It might be more appropriate to refer to placebos in RCTs as 'treatment controls', although the term placebo is now culturally embedded.[3,6]

or

Treatments used in patient care

Placebos in patient care are interventions that, owing to their intrinsic properties, are ineffective for a particular condition or symptom(s) but may be intentionally used in clinical settings with the aim of satisfying patients in need of a treatment and/or elicit placebo effects.[3–5] The ethical use of placebos is keenly debated by bioethicists (Box 1).[25–29]

Placebo effects

Research in placebo studies indicates that placebo effects comprise genuine psychobiological events that engage perceptual and cognitive processes to produce therapeutic effects among patients.[7,8,20,21] So far, research shows that placebo effects may be especially valuable for a range of self-reported conditions and symptoms, including (but not limited to) depression, anxiety, pain, fatigue and irritable bowel syndrome.[7,8]

Placebo responses

Placebo effects should be differentiated from the concept of 'placebo responses'; the latter encompasses the full range of outcomes (the 'noise') that may arise after the administration of placebos as 'controls' in RCTs; such factors include spontaneous remission, regression to the mean, Hawthorne effects, etc.[24] Placebo responses can also (under the certain sets of conditions) encompass placebo effects.[3,4]

'placebome' – identifying the genetic signatures associated with placebo-effect responders[22] and determining personality traits associated with response differences.[23]

Finally, and importantly, findings in placebo studies highlight two subtle points that may currently be overlooked within general medicine (perhaps owing to the opacity of terminology). First, placebo effects need not be dependent on 'placebos' to be effective; indeed, they may be elicited during routine administration of regular treatments: a sizeable percentage of the pain relief for 'genuine' analgesics is likely owed to placebo effects.[24] Second, placebos are not necessary (nor may they be sufficient) to elicit placebo effects; rather, a range of verbal and non-verbal practitioner cues appear to be implicated in the psychobiological pathways of placebo effects.[24,25]

Evidence carries ethical imperatives, both in terms of establishing the most effective treatments for patients and their possible harms or side effects, and (partly as a result of such findings) by informing decisions about what ought to be communicated to patients. The ethical discourse on placebos has not always been attentive to the value of empirical research.

The evolution of a medical dilemma

Conventional ethical debate

For most of medical history, the administration of placebos by physicians has been framed as a moral dilemma.[25–29] Placebos, it has long been assumed, necessitate deception on the part of providers to elicit beneficial effects. The fulcrum of ethical debate has therefore turned on whether such deception is ever justified (and, if so, under what circumstances), with the dispute structured as a trade-off between the potential for enhanced wellbeing ('beneficence') versus physician dishonesty with the consequence of diminished patient autonomy (Box 1). Against the backdrop of this discussion, in recent decades there has been a move away from paternalism in medicine to models of shared decision making in which both patients and physicians contribute to medical decision making.[30] Deceptive placebo use undermines this paradigm shift by excluding patients from meaningful decisions about their care.

Questioning the orthodoxy: Open-label placebos

Leading placebo researchers – and subsequently ethicists – have recently urged that it may be possible to harness placebo effects without deception via (so-called) 'open-label placebos' ('OLPs'; Box 1).[25,31,32] Over a dozen clinical trials of OLPs have been undertaken for a range of conditions including IBS,[31] chronic lower back pain,[33] episodic migraine[34] and cancer-related fatigue.[35,36] In many of these experiments, investigators appear to strive to optimise placebo effects via positive framing in disclosures; for example, in seven out of 13 OLP trials, clinician-experimenters informed participants of four discussion points related to placebos:[31,33,35–39]

1. The placebo effect is powerful.
2. The body can automatically respond to taking placebo pills, in the same way as Pavlov's dogs salivated when they heard a bell.
3. A positive attitude can be helpful.
4. Taking the pills faithfully is critical.

Results of these studies are encouraging, with authors of a recent systematic review and meta-analysis concluding that '[OLPs] appear to have positive clinical effects compared to no treatment.'[40] However, as leading placebo scholars point out, caution is advised: so far, OLP studies have been hampered by small sample sizes and short-duration studies.[40,41] More recently, researchers have also argued that shortcomings include the lack of rigorous control groups, and biases via the uncontrolled allegiance effects of clinician-experimenters.[42] For example, in several prominent studies, investigators – who were un-blinded to allocation – interacted with participants midway through the trial.[31,33,36,42] Conceivably – just as has been long-recognised in pharmacological clinical trials – such contact may have

Box 1. Summary of ethical debate about placebos

Arguments for and against deceptive placebos

Some scholars have argued that deceptive placebos are sometimes justified in the interests of therapeutic gain – for example, where no other treatment options are available.[27] Others have proposed that placebo use is ethical on the grounds that such interventions involve no serious threat to patient autonomy: the deception or omission, it is claimed, relates to a trivial feature of care – namely, how a treatment works, not that it works.[26]

Against these views, the overwhelming majority of medical ethicists have urged that lying to or deceiving patients is always harmful and threatens to derail trust in physicians.[25,28,29] Furthermore, these scholars argue that respect for patient autonomy must never be compromised in the interests of physician 'paternalism' with its underlying claim that 'doctors know best.' Rather, it is urged that honesty and transparency are necessary to support patient-centred care and to uphold the right of individuals to make their own treatment decisions. Additionally, deceptive placebos may promote the idea among patients that there is a 'pill for every ill' and contribute to antibiotic resistance via the misuse of these treatments.

A third way? Open-label placebos and practitioner behaviour

Open-label placebos ('OLPs') may provide an ethical means of eliciting therapeutic placebo effects.[32] Clinical trials into OLPs show promise for a range of self-reported conditions including irritable bowel syndrome, chronic lower back pain, episodic migraine and cancer-related fatigue.[31,33–39] Studies have been small and of short duration, and it is currently unclear whether the action of taking the pills, the rationale provided to participants and/or the quality of interaction influences the size of placebo effects in these studies.[40–42] In addition, the effects of OLP prescription on patient behaviour and help-seeking remain unknown.

Beyond the use of placebos, it remains possible that practitioners' verbal (eg confidence, affective tone) and nonverbal (eg maintaining eye contact, warm facial expressions, active listening) cues may increase placebo effects.[17,18]

boosted the outcomes of those in the OLP group. Of course, it might be argued that positive practitioner–patient interactions and confidence in treatments constitute important factors in elevating placebo effects. Curiously, however, some trialists appear to have de-emphasised these factors, focusing instead on the therapeutic importance of taking the placebo pill.[41]

While OLPs may yet prove to be effective, experimentalists must be more upfront about the particulars associated with basic empirical research that they hope to translate into clinical care: namely, whether it is the pill, rationale or quality of the interaction (or indeed some combination thereof) that is therapeutically important for placebo effects.[42] Notably, there have been instructive exceptions: for example, Locher et al theorised that the rationale may be a significant factor in eliciting placebo effects, a hypothesis confirmed by the results of a study involving application of heat pain among healthy participants.[14] Further rigorous, long-term studies are required to reap the potential clinical use of OLPs.

Conclusion

The study of placebos is a nascent but burgeoning field. While acknowledging the ethical problems raised by deceptive placebos and recognising the therapeutic potential of placebo effects, researchers have initiated enquiries into the possible benefits of OLPs. It is hypothesised that, by harnessing placebo effects for certain conditions, practitioners may help to reduce over-prescribing and unwanted side effects associated with commonly administered medications (including painkillers and antidepressants); some researchers suggest that transparently prescribed placebos may play a promising part in tackling the opioid crisis.[24,43]

Notwithstanding the potential value of this innovative research program for patients, at least three concerns must be addressed before OLPs can become routine in clinical care. First, future methodologically robust research into OLPs must identify the specific practitioner, patient and treatment factors that are relevant to eliciting placebo effects. Without greater clarity regarding the mechanisms of action of OLPs, practitioners may not know how to maximise the OLPs' potential through specific disclosures and behavioural cues, nor which patients are most likely to benefit.

Second, the long-term health impact of using OLPs among different patient groups is unknown. Some patients, especially those for whom placebo effects carry the most potential, may self-stigmatise or feel guilt, perhaps by diminishing the medical importance of their symptoms as being 'all in their heads'. This risk may be most acute among vulnerable patients, such as those who have pain, depression or medically unexplained symptoms, and for whom practitioners may consider OLPs a possible intervention, particularly if other treatment options have failed. Third, and relatedly, it is unknown how OLPs influence help-seeking. It is conceivable, for example, that as a result of being prescribed placebos, some patients may lose faith in mainstream medicine; others may erroneously believe that placebos legitimise complementary and alternative treatments.

Deceptive placebo use runs contrary to the medical ethical principles of upholding physician honesty and respect for patient autonomy. Yet, at least so far, there is insufficient evidence to ethically sanction the routine use of OLPs (Box 2). Where does this leave practitioners in harnessing the role of placebo effects in primary care? Advancements in placebo studies add to considerable evidence that practitioners can play a significant part in augmenting health outcomes and improving patient wellbeing via the quality of communication.

In summary, by engaging in attentive listening and empathic support, and via the provision of clear, honest and understandable dialogue, physicians may yet tap into the significant therapeutic power of placebo effects for the good of patients.

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Box 2. Key questions and findings

What is already known about this topic?

- Placebo use is widespread in primary care.
- A growing body of basic scientific research indicates that placebo effects may be particularly important for a range of symptoms and conditions including depression, anxiety, pain, irritable bowel syndrome (IBS) and fatigue.
- Deceptive placebos undermine physicians' ethical duties to be open and honest with patients.

What are the new findings?

- Research into honestly described open-label placebos (OLPs) studies shows some promise, but large-scale, methodologically robust studies are required before clinical translation can ensue.
- Aside from their possible effectiveness, it is unknown whether the use of OLPs among patients might lead to confusion and negative repercussions for help-seeking, including the possibility of self-stigmatisation, guilt or the diminution of symptoms as 'all in the head'. Conversely, further research is required to establish whether OLPs can help to reduce side effects, costs and over-treatment of conditions such as pain, IBS and depression.
- By engaging in empathic, supportive communication styles, there is some evidence that general practitioners may be able to augment placebo effects without the use of placebo pills.

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