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ARE OPEN-LABEL PLACEBOS ETHICAL? INFORMED CONSENT AND ETHICAL EQUIVOCATIONS

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ABSTRACT

The doctor-patient relationship is built on an implicit covenant of trust, yet it was not until the post-World War Two era that respect for patient autonomy emerged as an article of mainstream medical ethics. Unlike their medical forebears, physicians today are expected to furnish patients with adequate information about diagnoses, prognoses and treatments. Against these dicta there has been ongoing debate over whether placebos pose a threat to patient autonomy. A key premise underlying medical ethics discussion is the notion that the placebo effect necessitates patient deception. Indeed, the American Medical Association guidelines imply that placebo treatment necessary entails a form of deception. As a consequence of this assumption, the fulcrum of debate on the use of placebo treatment has hinged on whether that deception is ever justified. Recently performed experiments with open-label transparently prescribed placebos have begun to challenge the notion that deception is necessary in eliciting the placebo effect and such effects necessarily involve a binary distinction between autonomy and beneficence. In this article we focus on the content of disclosures in distinctive open-label, transparently disclosed placebo studies and inquire whether they might be said to invoke deception in clinical contexts, and if so, whether the deception is unethical. We find that open placebos may be said to involve equivocation over how placebos work. However, drawing on surveys of patient attitudes we suggest that this equivocation appears to be acceptable to patients. We conclude that open placebos fulfil current American Medical Association guidelines for placebo use, and propose future research directions for harnessing the placebo effect ethically.

INTRODUCTION

Debate over the ethical use of placebos in clinical practice is over 200 years old.[1] A key premise in this ongoing discourse is the notion that the placebo effect necessitates patients being unaware that they are being treated with a physiologically inert substance. The assumption is that placebo treatments in clinical practice involve deception. On this view, it is the doctor's *deceit* with regard to the effectiveness of the pill that is understood to elicit the placebo effect. Recent studies in the US highlight the role of deception in clinical practice and show that around every year 55% of internists and rheumatologists reported using a 'pure' or 'impure placebo' (a medication such as vitamins or analgesics that would have no effect on the illness but were prescribed for their psychological value)[2];

[1] H. Brody. The lie that heals: The ethics of giving placebos. *Ann Intern Med* 1982;97:112–118; C. E. Kerr, I. Milne, T. Kaptchuk. William Cullen and a missing mind-body link in the early history of placebos. *JRSM* 2008;101:89–92; R. Jutte. The early history of the placebo. *Complementary Therapies Medicine* 2013; 21: 94–97.

[2] J. C. Tilburt, E. J. Emanuel, T. J. Kaptchuk, F. A. Curlin, F. G. Miller. Prescribing 'placebo treatments': results of national survey of US internists and rheumatologists. *BMJ* 337, a1938.

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similarly, in the UK 97% of primary care doctors admit to using a placebo or impure placebo during their career, and 77% say they use placebos at least once per week.[3] These studies conclude that intentional placebo-related deception by doctors is widespread. As a means of circumventing deception and upholding respect for patient autonomy and informed consent, the American Medical Association (AMA) Council on Ethical and Judicial Affairs issued its own code on the ethical use of placebos in 2008.[4] We contend that its guidelines imply that some degree of sanctioned masking of placebos (or authorized deception) is required in clinical placebo use. Using the AMA guidelines as our ethical standard we investigate whether open-label placebos might be acceptable in clinical practice.

The article begins by clarifying the terms placebo, and placebo effect, and examines medical ethics guidelines for placebo use in clinical contexts. Next, given the matter of fact that doctors' are obliged to respect patient autonomy, we situate our discussion in recent duty-based arguments over the use of deceptive placebos. From this framework, we move on to examine whether the disclosures made in recent open-label placebo research studies (whereupon patients were told they were receiving a placebo) might ethically be deployed in clinical contexts. These research studies should be disambiguated from placebo-controlled clinical trials where patient treatment is concealed and patients are informed that they may or may not receive a placebo. Rather, in these studies, the patients were *explicitly* informed that they were receiving placebos, and the effects of the intervention were then measured. In the light of the success of these research studies the central questions of this article are: If these open-label placebo scenarios occurred in clinical practice, would these treatments meet AMA standards? And broadening the ethical discussion, we further enquire: Might these disclosures overcome autonomy-based objections to deceptive placebo use in clinical practice?

In answering these questions, we find that such open disclosures may yet be said to involve equivocation about the effectiveness of placebos. However, drawing on surveys of patient attitudes we suggest that this equivocation appears to be acceptable to patients (though we argue that more research may be warranted). Moreover, we conclude that should such open-label placebos disclosures occur in clinical settings they would fulfil current AMA guidelines for placebo use. We close by proposing future research directions for harnessing the placebo effect ethically.

CLARIFICATIONS: PLACEBOS, THE PLACEBO EFFECT AND MEDICAL GUIDELINES

Placebos are typically understood to be dummy or fake medications (usually microcrystalline cellulose or sugar pills) which can elicit a therapeutic benefit when administered to patients. The *placebo effect* should not be confused with the natural course of a disease, response biases, or regression to the mean: it refers to genuine psychobiological effects that result from placebos *and/or* contextual factors of care.[5] Contextual or incidental factors such as the branding and labelling of medications[6] and the treatment modality (e.g. injections or pills)[7] can influence the magnitude of the placebo effect; and socio-emotional factors relating to the therapeutic encounter, including both verbal and non-verbal cues from practitioners (signifying empathy, confidence, and their belief in the effectiveness of the treatment), can also influence the size of the placebo effect. Such contextual factors suggest that placebos are not necessary to elicit the placebo effect.[8] Multi-layered models are offered to explain placebo effects, and psychological and neurobiological mechanisms have been described in recent years.[9]

Unlike the General Medical Council (GMC) in the UK, the AMA does have explicit guidelines on clinical use of placebos, and supplies an ethical policy: 'Opinion 8.083 – Placebo Use in Clinical Practice' (2007) advises:

[3] It should be noted that the distinction between 'pure' and 'impure' placebos has been challenged; however, these surveys demonstrate that the use of placebos (understood as fake medication or medication that is not considered remedial for a particular ailments) is widespread. See: J. Howick, F. Bishop, C. Heneghan, J. Wolstenholme, S. Stevens, F. D. Richard Hobbs, G. Lewith, G. Placebo use in the United Kingdom: Results from a national survey of primary care practitioners. *PLOS ONE*, March 2013; 8(3):e58247.

[4] American Medical Association, Opinion 8.083 – Placebo use in clinical practice, *AMA Code of Medical Ethics*, http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion8083.page?, 2007. Accessed 15 April 2015.

[5] D. Finnis, T. Kaptchuk, F. Miller, F. Benedetti, Biological, clinical, and ethical advances of placebo effects. *Lancet* 2010;375:686–695.

[6] S. Kam-Hansen, M. Jakubowski, J. Kelley, I. Kirsch, D. C. Hoaglin, T. Kaptchuk, R. Burstein Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Science Translational Medicine* 2014; 6: 218ra5.

[7] T. Kaptchuk, P. Goldman, D. Stone, *et al*. Do medical devices have enhanced placebo effects? *J Clin Epidemiol* 2000;53:786–792; T. Kaptchuk, J. Kelley, L. Conboy, et al. Components of placebo effect: randomized controlled trial in patients with irritable bowel syndrome. *BMJ* 2008;336:999–1003.

[8] Ibid.

[9] D. Finnis, T. Kaptchuk, F. Miller, F. Benedetti. Biological, clinical, and ethical advances of placebo effects. *Lancet* 2010;375:686–695; I. Kirsch. Response expectancy as a determinant of experience and behaviour. *Am Psychol* 1985; 40:1189–1202; G. M Montgomery, I. Kirsch. Classical conditioning and the placebo effect. *Pain* 1997; 43:107–113; S. Stewart-Williams, J. Podd, The placebo effect: Dissolving the expectancy versus conditioning debate. *Psychol Bull* 2004; 130:324–340; L. Colloca, F. Benedetti. How prior experience shapes placebo analgesia. *Pain* 2006; 124:151–160; F. Benedetti. Placebo effects: from the neurobiological paradigm to translational implications. *Neuron* 2014; 84: 623–37; K. Hall, J. Loscalzo, T. Kaptchuk. Genetics and the placebo effect: the placebome. *Trends Mol Med* 2015; http://dx.doi.org/10.1016/j.molmed.2015.02.009.

> Physicians may use placebos for diagnosis or treatment only if the patient is informed and agrees to its use. A placebo may still be effective if the patient knows it will be used but cannot identify it and does not know the precise timing of its use. A physician should enlist the patient's cooperation by explaining that a better understanding of the medical condition could be achieved by evaluating the effects of different medications, including the placebo. The physician need neither identify the placebo nor seek specific consent before its administration. In this way, the physician respects the patient's autonomy and fosters a trusting relationship, while the patient may still benefit from the placebo effect.[10]

We interpret these guidelines as an attempt to balance the ethical norms of openness, patient autonomy and beneficence with the recommendation that placebos require some degree of 'sanctioned' deception or more precisely concealment as to their timing in order to be effective. In short, it would seem that the AMA approves the use of clinical placebos with authorized ignorance of the exact details of timing etc, which it claims is consistent with respect for patient autonomy. It should also be pointed out that the 2008 report by the AMA Council on Ethical and Judicial Affairs (aimed at clarifying these guidelines) states that 'physicians may utilize placebos within their clinical practice *without relying on the act of deception*'.[11] On a charitable reading this suggests that the AMA may not consider 'authorized deception' to be properly classified as *deception*. On a less charitable interpretation, this clarification indicates some ambivalence over the role and importance of deception in clinical placebo use (is it necessary or isn't it, and what form should it take?)[12]

We argue that an explicit definition of deception is required in order that we might efficiently evaluate the ethics of open-label placebo use in clinical contexts. Following Barnhill and Miller, we contrast deceit with lying: 'lies are false statements made with the intention of getting the listener to believe something false';[13] deception, on the other hand can involve withholding information *with the intention of misleading another* (i.e. it is not sufficient to define deception as the mere omission of information: rather, the omission must intentionally mislead the listener). Deception often involves equivocation (some form of ambiguity in the disclosure whereby it is intended that the listener interprets the utterance to arrive at a predictably false inference). It might be argued that authorized deception still constitutes deception but given that the patient has waved his or her right to receiving truthful information, it might argued that the deception is ethical.[14] However, circumventing these issues, we suggest that AMA did not envisage the possibility of clinical use open-label placebos for patients; therefore appraising such placebo interventions in light of these guidelines is a valuable task.

BACKGROUND TO THE RECENT ETHICAL DEBATE

In order to better assess the ethics of open-label placebos it is important to examine the broader duty-based debate about deceptive clinical placebo use. Central to this debate are questions about what constitutes adequate disclosure in informed consent, including clarifications about when deception might be said to apply. Beauchamp and Childress have proposed that doctors must rely on a 'reasonable person standard' in reaching decisions about what to disclose to patients (for example, what information would a reasonable person desire in respect of a particular treatment?).[15] However, and not least in respect of placebos, this still begs the question of what doctors ought to disclose to patients. Recent deontological arguments into the clinical use of placebos have asked: What form of autonomy is morally important in doctor-patient relationships?

It has variously been argued that the concept of autonomy can accommodate deceptions (in some circumstances), and therefore placebo use may be justifiable (O'Neill, 1984; Barnhill, 2011).[16] Onora O'Neill argues that medical conceptions of autonomy need to move away from naively idealistic interpretations: consent cannot encompass the attainment of patients' refusal or approval of *every* aspect of care. Rather, she contends, 'In human contexts…the most that we can ask for is consent to the more *fundamental* proposed policies, practices and actions…Respect for

[10] American Medical Association, Opinion 8.083 – Placebo use in clinical practice, *AMA Code of Medical Ethics*, http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion8083.page?, 2007. Accessed 15 April 2015.

[11] N. Bostick, R. Sade, M. Levine, D. Stewart. Placebo use in clinical practice: A report of the American Medical Association Council on Ethical and Judicial Affairs. *J Clin Ethics*, Spring 2008, 19(1):58–61.

[12] Pollo A, Amanzio M, Arslanian A, Casadio C, Maggi G, Benedetti F. Response expectancies in placebo analgesia and their clinical relevance. *Pain.* 2001 Jul;93(1):77–84.

[13] A. Barnhill, F. Miller. Placebo and deception: A commentary. *J Med Philos* 2014; doi:10.1093/jmp/jhu043.

[14] Nonetheless, one of the authors has misgivings about the effectiveness of authorized deception in those clinical contexts that involve potential nocebo responses: C. Blease, 2015 'Authorized concealment and authorized deception: Well-intended secrets are likely to induce nocebo effects'. *Am J Bioeth* 15(10): 23–25.

[15] T. Beauchamp, J. Childress. *Principles of biomedical ethics.* Oxford: Oxford University Press, 2009.

[16] O. O'Neill. Paternalism and partial autonomy. *J Med Ethics* 1984;10:173–178; A. Barnhill. What it takes to defend deceptive placebo use. *Kennedy Inst Ethics J* 2011;21:219–250. Others such as Pugh (2015) have argued that how we conceive of autonomy in medical practice needs to be overhauled. Such debates take us beyond the concerns of this paper which focuses on whether open-label placebos are commensurate with a received conceptualization of autonomy: See J. Pugh. Ravines and sugar pills: Defending deceptive placebo use. *Journal of Medicine and Philosophy*; 2015 doi:10.1093/jmp/jhu045.

autonomy requires that… consent to trivial and ancillary aspects of action and proposals be absent or impossible'.[17] O'Neill argues that placebo deception need not infringe on patient autonomy since the deceit involved need not relate to a fundamental aspect of care. In what circumstances might placebos be considered non-fundamental? Expanding on this account, Barnhill proposes that the *purpose* of a treatment may be considered fundamental (e.g. 'taking this pill will help to alleviate pain') but informing patients of the mechanism of action may be viewed as ancillary, namely, whether the pill works according to pharmacological properties or whether it works via psychological ones (i.e. placebo effects).[18] She claims that deciding what constitutes an ancillary concern for patients requires empirical investigation (via studies of patients' attitudes).

While we can see merit in Barnhill's argument we discern two significant caveats in respect of it. First, who decides what is 'fundamental' and what is 'trivial' about a treatment, and why should we rely on personal intuitions about this rather than scientific evidence? Research shows that health outcomes can be contingent on patients' (and therefore doctors') perceptions about treatments.[19] For example, studies show that patients who believe that their depression is wholly caused by a biochemical imbalance and who do not embrace a bio-psycho-social model of depression are more likely to regard themselves as 'essentially' depressives.[20] Such patients are more likely to expect a worse prognosis and to consider lifestyle changes and other interventions as irrelevant to the treatment of depression. What is currently perceived to be trivial may, in fact, have fundamental repercussions for patient health behaviour and outcome. Similarly, if the patient has knowledge that the body has endogenous ways of treating symptoms, this may have very important implications for how patients manage their illness. Second, we argue that people should be told the truth about their treatment being sugar or cellulose (if that is the case) because this information may help them later in dealing with their illness: we consider the later potential for harming trust as not worth this risk. However, the possibility of effective open-label placebos may help to circumvent these major problems with Barnhill's account.

Thus, we concur with Barnhill that deception may be acceptable (and not a breach of patient autonomy) but only in those circumstances whereupon the relevance of the information neither threatens patient health, nor does it jeopardize future trust and the relationship with the doctor. In these restricted circumstances deception may be judged to be trivial and this may best be decided by patients' attitudes. In the next section we build on this core discussion to ask whether the disclosures invoked in recent open-label placebo studies (whereby patients were explicitly informed that they are receiving a placebo) might ethically be transposed to clinical contexts. We appraise whether these disclosures can be said to involve deception, and whether such deception can be said to be trivial.

DO OPEN-LABEL PLACEBOS INVOLVE DECEPTION?

In order to evaluate whether the disclosures made in open-label placebo studies would be ethically acceptable in clinical encounters, we first need to know what is divulged to participants in the open-label studies. Clearly, disclosures and informed consent in clinical trials must be subject to different moral evaluations from those disclosures that occur in clinical contexts. What makes the recent open-label placebo studies interesting is that patients were explicitly informed that they were receiving a placebo and the effectiveness of the placebo intervention was then evaluated; this differs from standard FDA clinical trials, for example, where patients are informed that they may or may not be allocated to the placebo arm of the trial. Therefore, the purpose of this article is to enquire if such open-label placebo disclosures in these unique studies might also be ethically provided to patients in clinical contexts.

Research in the field of open-label placebos is still nascent; to our knowledge, so far there have been three randomly controlled experiments of open-labelled placebo treatment.[21] In this article we focus on the open-label placebo study for

[17] O. O'Neill. Paternalism and partial autonomy. *J Med Ethics* 1984;10:178.

[18] A. Barnhill. What it takes to defend deceptive placebo use. *Kennedy Inst Ethics J* 2011;21:219–250.

[19] C. Blease. The duty to be well-informed. *J Med Ethics* 2014;40:225–229.

[20] C. France, P. Lysaker, R. Robinson. The 'Chemical imbalance' explanation for depression: origins, lay endorsement, and clinical implications. *Prof Psychol Res Pr* 2007;28(4):411–20; B. Deacon, G. Baird. The chemical imbalance explanation of depression: reducing blame at what cost? *J Soc Clin Psychol* 2009;28(4):415–35; J. C. Phelan, L. H. Yang, R. Cruz-Rojas. Effects of attributing serious mental illness to genetic causes on orientations to treatment. *Psychiatr Serv* 2006;57:382–7.

[21] J. Kelley, T. Kapthcuk, C. Cusin, S., Lipkin, M. Fava. Open label placebo for major depressive disorder: A pilot randomized controlled trial. *Psychother Psychosom* 2012; 81:312–314; S. Kam-Hansen, M. Jakubowski, J. Kelley, I. Kirsch, D. Hoagin, T. Kaptchuk, R. Burstein. Altered placebo and drug labelling changes the outcome of episodic migraine attack. *Sci Transl Med* 8 January 2014; 6(218):218ra. T. Kaptchuk, E. Friedlander, J. Kelley, M. Sanchez, E. Kokkotou, J. Singer, M. Kowalczykowski, F. Miller, I. Kirsch, A. Lembo. Placebos without deception: A randomized controlled trial in irritable bowel syndrome. *PLOS ONE* 2010;5(12):e15591. Note also that the first open placebo study conducted in 1965 by Park and Covi [L. Park, L. Covi. Non-blind placebo trial: an exploration of neurotic patients' responses to placebo when its inert content is disclosed. *Arch Gen Psych* 1965;12:336e45] but did not contain a no-treatment control. Two studies by Sandler investigated reduced dosage of medication supplemented by an open label placebo for ADHD; see: A. D. Sandler & J. W. Bodfish, Open-label use of placebos in the treatment of ADHD: A pilot study. *Child Care Health Dev* 2008; 34(1):104–110; A. D. Sandler, C. E. Glesne, J. W. Bodfish, Conditioned placebo dose reduction: A new treatment for ADHD, *J Dev Behav Pediatr* 2010;31(5):369–375.

irritable bowel syndrome (IBS) by Kaptchuk et al.[22] There are four reasons for examining this study. First, it was the first study that randomly assigned patients to an intervention that was exclusively a placebo treatment with open disclosure and which also had a wait-list control (where participants received no treatment and which was aimed at controlling for regression-to-the mean and natural fluctuations of symptoms). Second, the IBS study has received the most attention partly because of its novelty and promising outcome: those in the open-label placebo wing experienced a clinically significant reduction in IBS symptoms compared to subjects in the no-treatment control. Third, the informational script provided to patients in the study provides an excellent starting point for investigating any limitations of ethical disclosure in respect of open-label placebos in clinical contexts. And finally, empirical research has gauged patient attitudes to open-label placebos for IBS.[23]

In the IBS study, practitioners delivered the following statement to patients: 'placebo pills made of an inert substance, like sugar pills. . .have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes.'[24] Patients were further advised of the following four scripted points: '1) the placebo effect is powerful, 2) the body can automatically respond to taking placebo pills like Pavlov's dogs who salivated when they heard a bell, 3) a positive attitude helps but is not necessary, 4) taking the pills faithfully is critical'.[25]

As we have seen (in respect of O'Neill's remarks), the notion of an ideal disclosure is elusive in clinical contexts: it is impossible for the doctor to provide exhaustive details about any given treatment (including its mechanisms of action). Moreover, even if exhaustive details were provided, not all patients would understand such information and some might consider it irrelevant to informed consent. In addition, the doctor only has a limited amount of time in the consultation. Therefore, just as in other medical interventions, there is no easily stipulated 'ideal open-label placebo' disclosure. Against this background, however, we can still attempt to answer the question: Does the open-label placebo disclosure in the IBS study present an ethically acceptable disclosure should it occur in clinical contexts? On the face of it, the response to this may seem obvious – that the disclosures are acceptable. However, we focus on two challenges to this open placebo condition (should it be clinically deployed). These criticisms are parsed according to the initial disclosure statement. The first criticism is that in clinical contexts practitioners might unethically deceive patients with respect to the evidence for the effectiveness of placebos: 'placebos. . .*have been shown in clinical studies* to produce significant improvement in IBS'. (We will broaden our analysis to include clinical studies which show the effectiveness of placebos for other conditions and in light of the statement '1) the placebo effect is powerful'.) The second challenge to autonomy is that describing placebos as healing is an unethical exaggeration: this is located in the claim that placebos work via 'mind-body *self-healing* processes'.

Disclosure 1: 'Placebos have been shown in clinical studies to produce significant improvement'

In this article we assume that clinical studies have shown that placebo effects elicit clinically significant therapeutic benefit to patients for certain conditions. Empirical evidence warrants this assumption.[26] In what sense, then, might deception occur in respect of the above disclosure should open-label placebos be deployed in clinical contexts? One potential major criticism is that the evidence for the above statement is based on an original concealment, since the use of placebos in those clinical trials aimed at assessing placebo effects have typically involved concealment (i.e. deception). Underlying this criticism is the claim that there is therefore an equivocation over how placebos work which is conveyed to the patients in the IBS open-label placebo scenario and it is this equivocation that renders such disclosures unethical should they be deployed in clinical contexts: the practitioner *intends* that the patient believes that placebos are effective but the statement is not supplemented by the *caveat emptor* that placebos are considered to be effective *because patients in previous studies were blinded to whether the pill was a drug or placebo and therefore could believe they were receiving* powerful medication. Therefore the equivocation in this open-label placebo scenario, it might be argued, is located in the intention to create an expectation that the treatment will be effective which in turn potentially elicits the placebo effect in the patient. This *might* be described as an attempt to deceive the patient into believing that deception is never relevant in eliciting the placebo effect.

In response, it might be noted that in the overwhelming majority of studies in which placebo effects are

[22] T. Kaptchuk, E. Friedlander, J. Kelley, M. Sanchez, E. Kokkotou, J. Singer, M. Kowalczykowski, F. Miller, I. Kirsch, A. Lembo. Placebos without deception: A randomized controlled trial in irritable bowel syndrome. *PLOS ONE* 2010;5(12):e15591.

[23] S. Hull, L. Colloca, A. Avins, N. Gordon, C. Somkin, T. Kaptchuk. Patients' attitudes about the use of placebo treatments: telephone survey. *BMJ* 2013;346:f3757 doi:10.1136/bmj.f3757.

[24] T. Kaptchuk, E. Friedlander, J. Kelley, M. Sanchez, E. Kokkotou, J. Singer, M. Kowalczykowski, F. Miller, I. Kirsch, A. Lembo. Placebos without deception: A randomized controlled trial in irritable bowel syndrome. *PLOS ONE* 2010;5(12):e15591.

[25] Ibid.

[26] D. Finnis, T. Kaptchuk, F. Miller, F. Benedetti. Biological, clinical, and ethical advances of placebo effects. *Lancet* 2010;375:686–695.

demonstrated, subjects are informed that they *may* be allocated to a placebo arm of the trial: yet placebo effects are still elicited among subjects in spite of this ambiguity of whether they are receiving a placebo or the active drug. Certainly, this information is potentially of interest to patients.

Furthermore, this equivocation may yet be answered (and resolved) since open-label placebos have been effectively demonstrated for some conditions (including migraines).[27] However, at this juncture we will assume that there is an equivocation in the disclosure statement. Whether this is perceived to be an ancillary concern by patients or judged a possible threat to future trust in the practitioner, or in the patients' health outcomes, are important issues that we will shortly address.

Disclosure 2: 'Placebos work via mind-body self-healing processes'

Is it an exaggeration to speak about placebos 'healing' patients? In order to assess this criticism in its strongest form let us assume that placebos are only administered in cases where they have been shown to be effective for particular conditions.

Does the statement involve the equivocation that placebos *cure* patients?[28] We argue that answers to this question depend on lay interpretations of the term 'heal'. While the dictionary definition of 'heal' is 'to restore to health or to make well'[29] this still leaves some vagueness about whether its usage, in everyday parlance, is synonymous with 'curing'. Do people typically mean by cure (or healing) something like *remission* where this is defined as the alleviation of functional impairment (whereby residual symptoms remain)? Or patients tend to understand it as the *complete alleviation of all* symptoms associated with the condition under treatment? Alternatively, the term(s) may be interpreted as meaning the *prevention of relapse* of a disease or illness.

We suggest that the meaning of the term 'heal' may vary contextually – that is, according to the condition/symptoms to which treatment refers, and also according to how a treatment elicits its effects. For example, consider the following two scenarios:

1. A doctor prescribes a common prescription painkiller and informs the patient, 'I'd like to prescribe you a painkiller called Tramadol – it should help *to heal the pain* you've been experiencing'.
2. A doctor tells a patient, 'I'd like to prescribe you a placebo pill – it works by mind-body *self-healing* mechanisms – it should help *to relieve the pain* you've been experiencing'.

In the first context 'heal' refers to the alleviation of symptoms and not the cause of those symptoms. The usage of 'heal' in this context may make us bristle – it sounds like a misnomer to speak of healing (rather than alleviating) symptoms rather than their root cause. Compare this to the use of the term 'heal' in the second context: '*self*-healing' differs from '*healing*' *simpliciter*. Arguably the prefix imparts an additional nuance of meaning – the fact that the treatment works endogenously rather than exogenously.[30] Determining whether the claim that placebos invoke 'self-healing effects' *in fact* misled patients or whether it is judged an acceptable description requires empirical investigation – to which we will now turn. We note, however, that in future studies, it may be worth proposing an alternative phrase: for example, 'placebos activate specific brain circuitry that produces relief of symptoms'.

SURVEY OF PATIENTS' ATTITUDES

Recall our earlier consideration that equivocation or deception may be acceptable if it is non-fundamental to consent, and this is in part an empirical matter as decided by patients' attitudes. Two important caveats are that this information must not pose a risk to patient health or pose a possible future risk to the doctor-patient relationship. Thus, in light of the foregoing discussion we contend that it is necessary to determine if patients consider *how placebos* work to be a fundamental aspect of disclosure and indeed patients' attitudes to placebo use have begun to be the subject of empirical research.[31] In order to

[27] It should also be noted by one of the authors in regard to the IBS study (TJ Kaptchuk) that patients were informed that scientists did not know if open-label placebo worked as all previous studies were performed 'double-blind'. However, we focus solely on the statement presented to patients as published in the paper. S. Schafer, L. Colloca, T. Wager. Conditioned placebo analgesia persists when subjects know they are receiving a placebo. *J Pain* 2015, doi:10.1016/j.jpain.2014.12.008.

[28] S. Justman. Placebo: The lie that comes true? *J Med Ethics* 2013;39:4 243–248.

[29] Mirriam-Webster's Dictionary defines heal as 'to become healthy or well again; to make someone (or something) healthy or well again'.

[30] When it comes to pain relief we now know that the placebo effect is mediated by the activation of endogenous opioids (the nervous system's pain-relieving compounds) and PET and fMRI scans show changes in the same regions of the brain in the placebo effect as with opioid medications. Research shows that the placebo effect triggers the same, downstream physiological pathways as 'orthodox' medication (J. K. Zbieta, J. A. Bueller, L. R. Jackson, et al. Placebo effects medicated by endogenous opioid neurotransmission and μ-opioid receptors. *J Neurosci* 2005;25:7754–62; T. D. Wager, J. K. Rilling, E. E. Smith, et al. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science* 2004;303:1162–66).

[31] F. Bishop, L. Aizlewood, A. Adams,. When and why placebo-prescribing is acceptable and unacceptable: A focus group study of patients' views. *PLOS ONE* 2014;9(7):e101822; S. Hull, L. Colloca, A. Avins, N. Gordon, C. Somkin, T. Kaptchuk. Patients' attitudes about the use of placebo treatments: telephone survey. *BMJ* 2013;346:f3757 doi:10.1136/bmj.f3757.

appraise patient understanding of placebos it is important to examine the most extensive quantitative study (to date) on lay attitudes to the placebo effect: a telephone survey conducted among Kaiser Permanente health insurance members (aged 18–75) in Northern California, USA. The study, published in BMJ, included a randomly chosen sample of patients who had been seen in an outpatient clinic for a chronic health problem in the previous six months. A total of 853 patients were questioned on placebo use. The survey furnished patients with the following definition of 'placebo treatments': 'A patient experiences a placebo effect when they get better after taking a treatment, not because of the treatment itself, but because the patient expected they will be benefit from the treatment'.[32] Respondents were then asked their views on a range of questions including deceptive and open placebo scenarios.

On the basis of this definition some 80% of patients believed that placebo treatments necessitated deception in order to be effective; over 95% of patients believed also that 'thinking positively can improve the physical symptoms of illness'. When presented with a range of doctor-patient scenarios, patients judged deceptive placebo use to be objectionable: 'nearly twice as many patients thought that placebo use would have a negative effect rather than positive effect on the doctor-patient relationship' (53.9% v 28.5%).[33]

However, when presented with an open-label placebo vignette the responses diverged considerably from the deceptive scenario: nearly 85% of patients considered open-label placebos acceptable. This result is particularly illuminating given that the open placebo vignette was based on an IBS open placebo disclosure with comparable content to the disclosure we have examined in this article: 'patients with *chronic abdominal pain* were told that the pills were placebos, like sugar pills, but *had been shown in clinical studies to produce relief through mind body-self healing processes*'.[34] In this scenario 61.5% of respondents reported that they would be willing to try open placebos for abdominal pain if offered them by their doctor and a similar percentage believed the placebos would be effective.

Is this sufficient evidence to show that patients deem open-label placebos to be ethical? Certainly, as the study points out there are inconsistencies in the respondents' conception of the placebo effect. If the majority of patients believe that placebos necessitate deception, do they also believe that the open placebo scenario involves deception too – especially since so many consider it likely to be effective? Or perhaps patients judge open placebos to be ethically permissible regardless. We can note that the open placebo finding is particularly interesting given that respondents were spilt in their views over whether placebos should be described as 'real medicine' (46.4% agreed; 53.5% disagreed).[35] Perhaps patients did not consider the open placebo to be a 'real medication' but expected it to be effective as a treatment nonetheless, since 95% of respondents agreed that thinking positively can improve physical symptoms. Therefore, perhaps we can infer that patients, at least in this study, deemed the descriptor 'self-healing processes' in the open scenario to be accurate and not an exaggeration even though they understood 'no medication' had been administered.

Clearly more research is needed to determine lay understanding of open-label placebos and their ethical deployment. Therefore, after being furnished with an account of mechanisms of action of the placebo effect, it would be useful to conduct surveys aimed at asking the following questions of the lay public: Do you think that open-label placebos might be effective? Similarly, in order to check lay understanding, a follow up question might enquire: If you believe that open-label placebo treatments are effective, how do you think that they work? In order to probe deeper into lay attitudes about the ethical status of open-label placebo treatments in clinical contexts, there are two additional questions that we might put to lay patients. First, one might ask participants whether they consider detailed information about: (i) how placebos are thought to work; and (ii) the evidence for the effectiveness of placebos, as relevant to their decision to assent to open-label placebos from their doctor. Second, after directly providing participants with an initial disclosure of how placebos are thought to work, one might then ask: Do you think it is accurate to describe these treatments as 'working by self-healing processes'? Such questions would help to better enable us to assess whether the disclosures provided in the IBS study are considered ethically acceptable by patients.

Finally, we argue that it is not sufficient to rely on lay attitudes in appraising the moral status of open-label placebos in clinical contexts. Long-term studies would also be required in order to assess whether the health behaviour of patients who assent to taking open-placebos differs from other patients. For example, it may be that consenting to open-label placebos independently influences how patients understand their illness and symptoms, and that this (in turn) may influence medication-seeking behaviour and attendance at the doctor. In this respect, it would be useful to investigate if patients who consent to open-label placebos are also more (or less) likely to seek out complementary and alternative medicines as a result.

[32] Hull et al., *op. cit*. note 31.

[33] Only 17.5% of patients believing that deceptive use of placebos would have 'no effect on their future relationship' with their doctor, ibid.

[34] Ibid.

[35] Ibid.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

In this article we have singularly focussed on the assumption that the placebo effect necessitates deception. On the basis of open-label placebo studies we find that, while there are some unanswered questions in respect of patients' attitudes, the empirical findings to date tentatively support the claim that patients consider open placebos to be ethical. In accordance with our understanding of a 'reasonable person standard' and given prior explanation of how placebos work, patients appear satisfied that open placebos are acceptable. Moreover, the IBS open placebo disclosure is certainly consistent with AMA guidelines: recall that the AMA advises, 'A placebo may still be effective if the patient knows it will be used but cannot identify it and does not know the precise timing of its use…The physician need neither identify the placebo nor seek specific consent before its administration.'[36] We tentatively argue that (on the basis of current patient surveys) if the disclosure in open-label placebo scenarios were transposed to clinical contexts it would surpass these requirements, since patients were informed of the timing and identification of the pills as placebos.

Harnessing the placebo effect *without placebos* may provide another ethical (and non-deceptive) means of treating patients effectively.[37] Promising results have been obtained from studies that focus on socially sanctioned ways of eliciting placebo effects via good bedside manner and empathy, practitioner confidence, and other contextual factors.[38] Clearly larger studies are needed to confirm these earlier studies. Future research into the role of other situational factors such as cues of practitioner prestige may provide new directions in ethical use of clinical placebos and placebo effects. We contend that greater efforts should also be made to ensure better understanding among patients and doctors about therapeutic benefits of the placebo effect.

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