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Placebos Without Deception: Outcomes, Mechanisms, and Ethics

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Abstract

Scientific research indicates that open-label and dose-extending placebos (that patients know are placebos) can elicit behavioral, biological, and clinical outcome changes. In this chapter, we present the state-of-the-art evidence and ethical considerations about open-label and dose-extending placebos, discussing the perspective of giving placebos with a rational, as dose extension of active drugs, or expectancy boosters. Previous comprehensive reviews of placebo use have considered how to harness placebo effects in medicine and the need to focus on elements of the clinical encounter as well as patient–clinician relations. Here, we illustrate the similarities and differences between standard (deceptive) placebos, open-label placebos and dose-extending placebos. We conclude that placebos without deception would override ethical barriers to their clinical use. This paves the way to future large-scale, pragmatic randomized trials that investigate the potential of ethical open-label and dose-extending placebos to improve patients' outcomes, and reduce side effects.

Keywords

Expectancy; Conditioning; Verbal suggestions; Learning; Dose-extending placebo

1. INTRODUCTION

Three factors are of major importance in the suffering of badly wounded men [during the Second World War]: pain; mental distress; and thirst. Therapy has been almost entirely directed to pain, and this usually limited to the administration of morphine in large dosage.

Henry Knowles Beecher, American anesthetist and
medical ethicist

Surveys from around the world consistently find that healthcare practitioners prescribe placebos quite often (Colloca, Enck, & DeGrazia, 2016; Fassler, Meissner, Schneider, &

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Linde, 2010; Howick et al., 2013). Placebo use, however, is criticized as being unethical for two reasons. First, placebos are supposedly ineffective (or less effective than “real” treatments), so the ethical requirement of beneficence (and “relative” nonmaleficence) renders their use unethical. Second, they allegedly require deception for their use, violating patient autonomy. Here, we take it as given that at least for some conditions, placebos have effects (see Howick, 2017; Howick et al., 2013 for discussion). The recent research on open-label placebos suggests that the second objection—namely the claim that placebos require unethical deception—is also invalid. If placebos can have effects even when patients are told they are placebos, then placebos do *not* require deception and ethical objections to placebo use lose their force.

2. DO PLACEBOS REQUIRE DECEPTION? THE MYSTERIOUS CASE OF OPEN-LABEL PLACEBOS

A handful of studies have shown that long-term placebo effects can also be elicited under open-label conditions, in which patients are *explicitly* informed that they will receive a placebo (Blease, Colloca, & Kaptchuk, 2016; Charlesworth et al., 2017). This is counterintuitive since placebos supposedly work because people believe they do, but (presumably) *knowing* a treatment is a mere sugar pill makes it difficult to believe they will work. In spite of the lack of intuitive appeal, numerous studies have demonstrated that deception may not be needed to elicit placebo effects and have also demonstrated potential effectiveness at improving significant clinical outcomes in patients with irritable bowel syndrome (IBS) (Kaptchuk et al., 2010), chronic low back pain (Carvalho et al., 2016), depression (Park & Covi, 1965), attention-deficit hyperactivity disorder (ADHD) (Sandler, Glesne, & Geller, 2008), rhinitis (Schaefer, Harke, & Denke, 2016), and cancer-related fatigue (Hoenemeyer, Kaptchuk, Mehta, & Fontaine, 2018).

3. CLINICAL OPEN-LABEL PLACEBO TRIALS

Park and Covi (1965) were the first to attempt we are aware of to test the apparent paradoxical effect of open-label placebos in patients suffering from a range of anxiety symptoms (Park & Covi, 1965). The patients were told that they would have received sugar pills but that they would have perceived benefits in terms of symptom relief. Despite the small number of enrolled patients (14), significant symptom improvement was reported at 1 week of taking open-labeled placebos. In pain medicine, other studies have recently shed light on the potential efficacy of open-labeled placebos without deception in patients suffering from IBS (Kaptchuk et al., 2010) and low back pain (Carvalho et al., 2016).

In a more recent trial conducted by Kaptchuk et al., 80 patients diagnosed with IBS were randomized to receive either open-label placebo pills or no treatment (Kaptchuk et al., 2010). The open-label placebo was presented as follows:

The provider clearly explained that the placebo pill was an inactive (i.e., “inert”) substance like a sugar pill that contained no medication and then explained in an approximately 15 minute a priori script the following “four discussion 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, and 4) taking the pills faithfully is critical (Kaptchuk et al., 2010).

Investigators then measured the effect of the treatment on the IBS Global Improvement Scale (IBS-GIS, stated primary outcome). Open-label placebo produced significantly higher mean global improvement scores (IBS-GIS) at both 11-day midpoint and 21-day endpoint.

In Carvalho et al.'s (2016) study, 83 patients with at least 3 months of chronic lower back pain were randomized to receive two open-label placebo tablets, taken twice daily, or treatment as usual, for 3 weeks (Carvalho et al., 2016). Patients were told that the placebo pill was an inactive substance, like a flour pill, that contained no active medication in it. Patients were also taught about placebo effects using four "discussion points." These were: (1) the placebo effect can be powerful, (2) the body automatically can respond to taking placebo pills like Pavlov dogs that salivated when they heard a bell, (3) a positive attitude can be helpful but is not necessary, and (4) taking the pills faithfully for 21 days is critical. All participants were also shown a video clip (1 min and 25 s) of a television news report, in which participants in an OLP trial of IBS were interviewed (excerpted from <http://www.nbcnews.com/video/nightly-news/40787382#40787382>). Primary outcomes were mean weekly retrospective pain assessments (0–10) and the Roland–Morris Disability Questionnaire (RMDQ) assessed at 3 weeks. The open-label placebo demonstrated a statistically significant benefit over treatment as usual (TAU).

Gathering all these studies together, a recent meta-analysis found that open-label placebos can lead to positive therapeutic effects when compared to no-treatment. The clinical conditions were IBS, depression, allergic rhinitis, back pain, and ADHD (Charlesworth et al., 2017). However, the meta-analysis involves only five trials that were small, had different control groups (TAU vs waiting-list group), often included positive suggestions alongside the open-label placebos, one involved elements of partial conditioning (ADHD amphetamine treatment and placebos) and were rated as having a moderate risk of bias. Importantly, all these trials are characterized by the lack of blinding that can be achieved by comparing open placebos vs hidden placebos and the comparison with the best available treatment to estimate the relevance of open placebo potential effectiveness. Recently, open label placebos have been tested in 74 cancer survivors in a 21-day assessor blinded, randomized-controlled trial that compared an open-label placebo to TAU for fatigue (Hoenemeyer et al., 2018). Two placebo pills taken twice induced a 29% improvement in fatigue severity, and a 39% improvement in fatigue-disrupted quality of life. Open label placebos were tested in 74 cancer survivors ($N=74$) in a 21-day assessor blinded, randomized-controlled trial that compared an open-label placebo to TAU for fatigue (Hoenemeyer et al., 2018). Two placebo pills taken twice induced a 29% improvement in fatigue severity, and a 39% improvement in fatigue-disrupted quality of life (Table 1). These and the provocative studies on dose-extending placebos (see Section 6) may open up new research avenues with a focus on translational and mechanistic approaches.

4. LABORATORY (OPEN-LABEL) PLACEBO STUDIES

Placebo (conditioned) hypoalgesic effects persisted after revealing that the cream used to reduce the experimental heat pain was merely Vaseline (Schafer, Colloca, & Wager, 2015). Participants were told that the study aimed “to compare the analgesic effects of a topical cream with an active analgesic component (placebo cream) to a topical cream with no active ingredients (control cream).” An initial calibration phase, either long or short conditioning, and a test phase were performed. Placebo analgesia was tested before and after participants were told the treatment was a vaseline cream. Placebo analgesia was defined as the difference in pain reports between placebo and control stimulations at identical heat temperatures. Schafer and colleagues demonstrated that experiencing multiple conditioning sessions leads to robust placebo analgesia that persist even when the true nature of the placebo treatment is convincingly revealed to study participants (Schafer et al., 2015). Additionally, this study provided evidence that experienced placebo analgesia can be uncorrelated with expected analgesia. Conditioned placebo analgesia can be mediated by processes not accessible by reportable expectancy, and that there is a transition from expectancy-mediated processes to more involuntary analgesic processes as those initial expectancies are reinforced through repeated experience. These results parallel emerging evidence from other studies, suggesting that placebo analgesia might sometimes occur in the absence of belief (Charlesworth et al., 2017). Therefore, informing study participants about the realm of the placebo phenomenon and its mechanisms presents no negative reactions or negative consequences and may help engage potential factors that favor outcome improvements.

Open-label placebos have also been explored in healthy participants in a standardized experimental heat pain modulation paradigm and research has shown that they are as effective as deceptive placebos when accompanied by a rationale (Locher et al., 2017). Locher et al. (2017) explored the effectiveness of open-label placebo given with a rationale (Locher et al., 2017) as compared to open-label placebo without a rationale, deceptive placebo, and no-intervention in 160 participants who were randomly assigned to the experimental groups. All groups received an application of a placebo cream except the no-intervention group. Baseline and posttreatment measurements of pain tolerance, pain intensity, and pain unpleasantness ratings were assessed as primary outcomes. Those who received the placebo given with a rationale and the deceptive placebo compared with those who received the placebo treatment without a rationale reported significantly less pain intensity and unpleasantness ratings. These changes in pain experience were independent from the individual level of pain tolerance. A rationale given along with the placebo was as efficacious as the deceptive placebo (Locher et al., 2017) in an experimental setting.

Locher et al. findings are in contrast with other results obtained in a clinical context. Placebo analgesic effects appeared to be larger when full deceptive disclosures are given to patients with postoperative pain (Colloca, 2017; Pollo et al., 2001). The authors compared clinical pain outcomes in acute pain patients who received saline solution and were told nothing about the analgesic effect (natural history) of a basal infusion in the postoperative setting; were told that the treatment could have been either a potent pain-killer or a placebo (similar to a double-blind clinical trial); or were told that the basal infusion was a potent painkiller

(full-deceptive administration) (Pollo et al., 2001). Operationally, the placebo effect was defined as the change in the amount of requested doses of buprenorphine over the 3-day postoperative pain treatment when a continuous saline infusion was added to the active buprenorphine treatment. Overall the buprenorphine requests decreased by 20.8% in the double-blind group, and by 33.8% in the deceptive group in comparison to the natural history, respectively, leading to a significant reduction of the buprenorphine opioid intake (Pollo et al., 2001). A genuine placebo-induced analgesic effect was observed with the more transparent disclosures although the deceptive group elicited the larger reduction of buprenorphine requests.

5. DOSE-EXTENDING (OPEN-LABEL) PLACEBOS

Placebos have been given as “dose extenders” to prone the brain–body systems to create conditioned responses (CR) that are similar to the effects of the treatments (US) when deliberate conditioning stimuli (CSs) are paired with the US.

For example, Goebel et al. administered cyclosporine A (2.5 mg/kg, US) along with a green-colored, strawberry-flavored milk drink (CS) in healthy participants to test the hypothesis that cyclosporine-like effects can be detected when placebos are given with the CS in place of the cyclosporine (Goebel et al., 2002). Placebos administered with the flavored drink significantly suppressed immune functions in terms of interleukin-2 (IL-2) and interferon gamma (IFN-gamma) mRNA expression, in vitro release of IL-2 and IFN-gamma, as well as lymphocyte proliferation, suggesting that placebos can act as “dose extenders” of the cyclosporine action (Goebel et al., 2002). The duration of such a conditioned effect (e.g., suppression of T-cell function) extinguished after 14 unreinforced exposures to the CS drink. However, administering subtherapeutic dosages of cyclosporine A (0.25 mg/kg) along with the CS drink prevented the extinction of the conditioned immunosuppression (Albring et al., 2014). The intrinsic action of dose-extending placebos is illustrated in human research that demonstrated that pharmacological conditioning is effective in extending the response to morphine (Amanzio & Benedetti, 1999; Benedetti, Pollo, & Colloca, 2007; Guo, Wang, & Luo, 2010). Robust analgesic responses were documented when the administration of morphine for two consecutive days was replaced by a placebo on the third day (Amanzio & Benedetti, 1999). Importantly, different schedules of pharmacological conditioning worked in eliciting morphine-mimic effects, at least in the range of days and weeks (Benedetti et al., 2007). These observations suggest that a pharmacological conditioning procedure creates a learned response that can be reevoked. Similar results have been found in mice using pharmacological opioid and nonopioid conditioning (Guo et al., 2010).

Clinically speaking, a recent study demonstrated the effectiveness of dose-extending placebo in patients with psoriasis treated with corticosteroids (Ader et al., 2010). Patients were treated under a partial schedule of pharmacological (corticosteroid) reinforcement in which a full dose was given 25%–50% of the time and substituted by placebos the other times as compared to a dose control group, in which patients received the full dose 25%–50% of the time but not placebos, and a group receiving the full dose of active corticosteroids (100%). The frequency of relapse under partial reinforcement was lower (26.7%) than in the control group (61.5%) and clinically comparable to the reduction in symptoms induced by a full

dose of corticosteroids (22.2%). Thus, dose-extending placebos given with the partial schedule of pharmacotherapeutic reinforcement (Ader et al., 2010) with corticosteroids given one quarter or half as frequently as currently prescribed along with dose-extending placebos were sufficient to mitigate psoriasis relapses.

Importantly, a study in children with ADHD (Sandler & Bodfish, 2008) used a methodological twist in which open placebos and partial reinforcement were merged. In fact, placebo use was described to both parents and children transparently. Following a model for preauthorized placebo use, patients and parents were explicitly informed that placebos (e.g., lactose or talc pills) will be given to extend medication effects (amphetamines). Children were assigned to three arms. Those in arm 1 received a placebo pill paired with a 50%-reduced dose of amphetamine. The same reduction of treatment was performed in arm 2 but without a controlled conditioned cue (control group). Children in arm 3 received a full dose of amphetamine treatment. Pairing a conditioned stimulus (CS) with amphetamines produced placebo-conditioned responses that allowed children with ADHD to be treated effectively with a lower dose of stimulant medication. Moreover, Perlis and colleagues randomized patients with chronic insomnia to distinct regimes of 10mg zolpidem including nightly treatment with 10 or 5mg, intermittent treatment with 10mg, or partial reinforcement treatment with placebos and 10mg for 12 weeks (Perlis et al., 2015). The partial reinforcement group maintained treatment response that were similar to the full treatment groups and better than the outcomes observed in those patients assigned to the intermittent treatment who exhibited poorer sleep quality. These pioneering clinical trials could potentially merge open-label placebos, authorized deception, and (evidence-based) rationale for using placebos, clinically.

6. POTENTIAL MECHANISMS

6.1 Pharmacological Memory

The mechanisms by which open-label placebos given without a formal conditioning are complex and remain to be confirmed (see Fig. 1 and 2). It is possible that sugar pills labeled as placebos work because they retrieve a pharmacological memory, therefore acting as a conditioned cue that elicits previously learned responses in line with the learning theories including classical and nonclassical forms of conditioning (Colloca & Miller, 2011a, 2011c).

In addition to (subconscious) conditioning, conscious expectancy could play a role in how open-label placebos work. Often, the open-label placebos were delivered in addition to the TAUs and importantly with explicit positive suggestions (Carvalho et al., 2016; Hoenemeyer et al., 2018; Kaptchuk et al., 2010; Schaefer et al., 2016) proving a rationale (e.g., “Pavlovian conditioning”) and instilling some hope of improvement. The only study that lacked any positive framing and instruction sets had the smallest effect size (Kelley et al., 2012). It is known that the expectation of pain relief has been found to modulate the central regulation of pain through, in particular, the dopamine reward system and the endogenous opioid system (Price, Finniss, & Benedetti, 2008). There is also a growing body of evidence that in addition to what practitioners say, the way in which they deliver these messages (for example, with more or less empathy) can also affect health outcomes (Annoni & Miller, 2016; Caspi & Bootzin, 2002; Friedman, Sedler, Myers, & Benson, 1997).

6.2 Partial Reinforcement and Classical Conditioning

Dose-extending placebos rely on the ability of a nonhuman and human being to acquire a physiological reflex via associative learning processes (e.g., classical conditioning and partial reinforcement learning paradigms) (Ader, 1989, 1990; Colloca & Miller, 2011a). Classical conditioning experiments demonstrated that dogs would salivate (CR) in response to a bell (CS) that had previously been paired with the administration of food (unconditioned stimulus, US), Fig. 1. For dogs conditioned in this way, a ringing bell implied food, causing such automatic physiological responses as salivation (Pavlov, 1927). Similarly, visual, tactile, and gustatory cues can be associated with the US of active medication, through repeated pairing, to elicit responses (Colloca & Miller, 2011a; Enck, Bingel, Schedlowski, & Rief, 2013). As described earlier, these learning mechanisms can account for responses elicited using dose-extending placebos. Although the CS–US pairing mechanisms can explain most of the conditioned responses described in Section 5, further studies are needed to understand how adaptive responses that compensate for the primary drug effect can develop. Opposite conditioned responses (e.g., tachycardia) can occur when tolerance, a decreased response to a drug within the course of administrations, develops (Siegel, Baptista, Kim, McDonald, & Weise-Kelly, 2000). Dogs treated with epinephrine every few days presented *tachycardic* responses but when epinephrine was replaced by placebo, *bradycardic* response was observed (Subkov & Zilov, 1937). Despite potential limitations, dose-extending placebos work by means of learning effects and can enhance treatment outcomes with transparent use of placebos give as adjunct treatments Fig. 2A. In the real-world setting of health care, these putative placebo mechanisms are likely to operate in unison. Therefore, it is reasonable to assume that these proposed mechanisms are combined, to differing degrees depending on the individual and their disease, to demonstrate effectiveness.

6.3 Embodied Cognition

“Embodied cognition” is a relatively new theory that beginning to help explain how open-label placebos might work but is currently at the speculative stage. According to this theory (Shapiro, 2014) our physical interaction with the world influences or even determines our cognitions (Kemmerer, Miller, Macpherson, Huber, & Tranel, 2013). For example, the sound of the dentist’s drill might trigger a specific bodily sensation (Thompson, Ritenbaugh, & Nichter, 2009). Hence, sensory signals could evoke different reactions including those involved in positive and negative healing experiences (Fuchs & Schlimme, 2009). Embodied cognition is related to conditioning because it operates at a subconscious level and is automatic. However, it also differs in important respects. For one, it does not require a specific conditioning procedure (such as the learned pairing of a bell ringing with food). Relatedly, the cognitions arise directly from bodily experiences that are not mediated by the brain Fig. 2A. Some healthcare settings in which open-label placebos are delivered could induce the body to react in a way that subsequently leads to cognitions, which, in turn, induce the brain to produce endogenous substances such as analgesic endorphins. Further work is warranted to investigate the role of embodied condition in explaining how open-label placebos work.

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7. CLINICAL IMPLICATIONS

Whether placebos can be prescribed to achieve similar or better outcomes compared with usual medical care, whether and how physicians may recommend treatments that lack any specific efficacy remains controversial (Colloca, 2014; Comaroff, 1976; Henriksen & Hansen, 2004).

A number of studies reported that placebos are indeed used by clinicians across different countries (Fassler, Meissner, Schneider, & Linde, 2010; Kermen, Hickner, Brody, & Hasham, 2010; Louhiala, 2012; Meissner, Hofner, Fassler, & Linde, 2012; Nizan, Barash, Valinsky, Lichter, & Manulis, 1997; Tilburt, Emanuel, Kaptchuk, Curlin, & Miller, 2008) including United States (Kermen et al., 2010; Sherman & Hickner, 2008; Tilburt et al., 2008), Canada (Harris & Raz, 2012; Raz et al., 2011), Germany (Linde et al., 2013; Meissner, 2005), Switzerland (Fassler, Gnadinger, Rosemann, & Biller-Andorno, 2009), Denmark (Hrobjartsson & Norup, 2003), United Kingdom (Howick et al., 2013), Israel (Nitzan & Lichtenberg, 2004), India (Shah, Panchal, Vyas, & Patel, 2009), Saudi Arabia (Hassan, Fauzi, & Hasan, 2011), and New Zealand (Holt & Gilbey, 2009). A systematic review of 22 studies from 12 different countries reported that between 17% and 80% of interviewed clinicians administered sugar pills or saline injections during their careers (Fassler et al., 2010). Still physicians feel that there is a lack of harm and even a potential benefit associated with placebo use but that deception is essential to elicit placebo effects (Bishop et al., 2014). Interestingly, patients feel that potential benefit outweighs the importance of transparency in use. In the United States patients viewed deceptive placebo use acceptable (70%), and approximately 79% would prefer transparency over deception (Hull et al., 2013).

Other factors are also likely to play a role, including biopsychosocial forces arising from contact with a healthcare practitioner (Holt-Lunstad, Smith, & Layton, 2010), and lowered patient anxiety due to a positive expectation of recovery (Benedetti, Carlino, & Pollo, 2011; Darragh et al., 2016).

7.1 Patients' Perspective

Information regarding the views of patients, especially surrounding the concept of deception, would help inform the clinical use of placebos (Bishop et al., 2014; Cohen & Shapiro, 2013; Gold & Lichtenberg, 2014; Hull et al., 2013; Justman, 2013). Ortiz and colleagues performed a qualitative analysis of part of a US national survey to uncover underlying patient attitudes about the use of placebo in the face of deception or transparency. A total of 853 participants participated in a telephone survey (Hull et al., 2013). Adults seen in an outpatient clinic for a chronic health problem at least once in the prior 6 months were invited to participate in the survey. Respondents were women (61%) and men (39%), with an average age of 45 years. 58% were white and 42% were nonwhite. 44% had at least an

undergraduate college education. Given the large size of this survey, relative frequencies of patients' attitudes and how demographic characteristics (e.g., sex, age, race, and level education) influence such attitudes were explored. Lack of harm and potential benefit are the most common themes to justify acceptability of placebo use. Of the minority of respondents who judged it never acceptable for doctors to recommend placebo treatments, the majority referred to the doctors' obligation to do further clinical tests. The demographic characteristics that emerged as relevant were the level of education and age. Those participants with higher education mentioned potential benefit as a reason for using placebos clinically. Older age was associated with likelihood to identify overall physician–patient relationships, as opposed to treatments as relevant factors for optimal care.

Moreover, participants were asked their opinions about disclosing the use of a placebo. The majority of participants thought that physicians should not lie to patients when actively asked by the patient, a view that was based on the *patient's right to know*, the value of *honesty*, and the chance to harness the *power of the mind*. Only a minority of participants felt the patient should not be informed of the use of placebos for reasons related to *potential harm*, *obligation to do more*, and potential *lack of benefit* in being told about the use of a placebo.

8. ETHICAL IMPLICATIONS

8.1 Authorized Deception and Placebo Use

Despite the common belief that placebo research has to involve elements of deception consisting of deliberately communicating misleading information about the goal of the research study and the nature of experimental procedures, theoretical and experimental research is advocating the possibility of obtaining authorization to use placebos (Miller & Kaptchuk, 2008; Miller, Wendler, & Swartzman, 2005; O'Neil & Miller, 2009). Importantly several authors have created elegant normative work as well as empirical results on the use of deception in placebo research and pain. For example, Martin and Katz (2010) tested the inclusion of authorized deception in the informed consent process by randomly assigning participants to an authorized deception group or a deception group without authorized deception. Interestingly, the authors found that authorized deception did not influence the size of placebo-induced placebo analgesia, recruitment, and retention of participants. Martin and Katz found that informing participants about the nature of the placebo manipulation does not cause distress and lack of trust in research (Martin & Katz, 2010). More recently, Corsi and Colloca (2017) and Colloca, Pine, Ernst, Miller, and Grillon (2016) published findings that have been obtained with a preauthorization to use deceptive information. Namely the study participants were told that the research would have involved deception during the informed consent process with a verbal and written section that describes deception in the consent form as follows:

“Use of Deception - At some point during the study, we will provide you with misleading information. After the study is completed we will give you a written explanation on how the information was not true and why. We will also answer any questions that you have about the procedure and the use of any misleading information.”

Participants had been informed about the deceptive component of this study (why and when the reduced dose was used) and had the opportunity to withdraw the data after they are done participating. The so-called authorized deception approach did not impact the possibility to observe robust placebo and nocebo effects in behavioral and pharmacological research with healthy participants. Importantly, the same approach had been recently used in fibromyalgia pain patients. Perceptions about participation in an authorized deception study were examined in fibromyalgia patients and healthy controls. The majority of participants expressed little or no concern about the deception, still trusted the scientific process, and found the debriefing procedure helpful and worthwhile (personal communication).

8.2 Ethics of Open Label Placebos

Since open-label placebos do *not* require deception, their existence and effectiveness undermine the ethical objections to placebo use. The blooming research in this area warrants an investigation and perhaps revision of ethical standards surrounding placebo use. There are, however, a few notes of caution that must be issued about the ethics of open-label placebos.

First, the arguments that placebos can be ethical since they do not require deception apply to *open-label* placebos and not deceptive placebos. (Recall that deceptive placebos may be ethical but the objection that they violate autonomy is hard to eradicate altogether.) Second, up to half of patients in clinical trials do not recall or understand what they consented to (Tam et al., 2015). If not, then perhaps patients who consent to taking an “open-label placebo” might actually believe it is a real treatment. In two open-label placebo trials investigating this possibility, patients did indeed appear to understand that they were taking placebos (Carvalho et al., 2016; Kaptchuk et al., 2010). Third, the positive suggestions often delivered alongside open-label placebos could involve an element of deception, depending on their wording. This is, strictly speaking, a distinct issue and we leave a discussion of the ethics of therapeutic communication to another study (Annoni & Miller, 2016). In short, the research demonstrating the effects and mechanisms of open-label placebos demands a reanalysis of ethical strictures on placebo use, and further discussion on how open-label placebos might be implemented is warranted.

8.3 Ethics of Dose-Extending Placebos

An area where dose-extending placebo use could be particularly interesting and ethical is in comparison with standard full regimens of medication. Dose-extending placebos—wherever effective—have several benefits. First, extending the effects of a medication through the use of dose-extending placebos—rather than using only medication for a treatment of equal duration—may reduce the side effects associated with the medicine, a speculation that has been confirmed in some studies in which side effects were monitored (Sandler & Bodfish, 2008; Sandler et al., 2008). However, side effects (nocebo effects) may respond to conditioning and learning mechanisms (Colloca & Miller, 2011b), so there is a risk of conditioned side effects instead of conditioning drug efficacy when dose-extending placebos are paired with active treatments. Second, dose-extending placebos may decrease physiological or psychological dependence to medication and habit-forming behaviors toward medication. Third, using dose-extending placebos for part of the therapeutic strategy

rather than using medication for the entire treatment will lower costs by reducing the total intake of the required medication. Last but not least, dose-extending use of placebos provided with patients' education will raise awareness about the body's capacity for self-healing. Finally, by including the primary therapy alongside the dose-extending placebo, the benefits of conditioning could boost the placebo effect.

An obvious area where placebo use could improve patient outcomes is the treatment of pain, where opioid overuse has become a crisis (Belcher, Ferré, Martinez, & Colloca, 2017; Colloca, 2017). Using open-label placebos, perhaps as dose extenders, could reduce the harms caused by the opioid epidemics (Colloca, Enck, & DeGrazia, 2016). Although animal studies can be used to inform clinical studies, further human studies are needed to determine in which diseases and conditions the use of dose-extending placebos can be effective and safe. Methodologically, the ideal study protocol should include three arms: (1) an arm with a partial schedule of pharmacological reinforcement in which the full dose is given 25%–50% of the time and substituted by placebos at other times; (2) a control arm in which the full dose is given 25%–50% of the time and no placebos are administered; and (3) a comparator arm in which full dose of medication. Whenever feasible, this study design would help circumscribe changes in the efficacy outcome measures due to spontaneous remission, regression to the mean, and natural history of the disease.

Some factors stand in the way of using dose-extending placebos. These include the irreversibility of a disease, clinical contraindication to introduce treatment reductions, and the pharmacokinetic properties of the agent (e.g., US–CS pairings). Safety, optimization, and feasibility studies will help obtain a meaningful investigation of dose-extending placebos.

9. CONCLUSIONS

In conclusion, the recent flourishing of open-label and dose-extending placebo research shows that placebo effects do not necessarily require deception to produce their effects bypassing at least some of the conventional ethical barriers to their clinical use. Future large scale, pragmatic randomized trials should investigate the potential of open-label and dose-extending placebos to improve outcomes and reduce side effects. A parallel body of evidence is needed to inform us about the mechanisms underpinning how open-label and dose-extending open placebos work. Open label placebo research demands a reanalysis of ethical barriers to clinical placebo use.

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Fig. 1.
Pharmacological conditioning and evoked drug memory.

Fig. 2.
Potential mechanisms for dose-extending and open-label placebos.

Table 1

Clinical Studies With Open Label Placebos

Study	Country	Condition	No. Participants	Control Treatment	Intervention Timing	Primary Outcome Measure	Outcome Estimation (Pooled Effect Size, and 95% CI)
Carvalho et al. (2016)	Portugal	Chronic low back pain	83	Treatment as usual	21 days	Roland–Morris Disability Questionnaire	0.75 [0.31, 1.20]
Hoenemeyer et al. (2018)	United States	Cancer related fatigue	73	Treatment as usual	21 days	Fatigue Symptom Inventory (FSI-14)	0.32 [30.14, 0.79]
Kapchuk et al. (2010)	United States	IBS	80	No treatment	21 days	IBS Global improvement	0.78 [0.32, 1.24]
Kelley, Kapchuk, Cusin, Lipkin, and Fava (2012)	United States	Major Depressive Disorder	20	Waitlist	14 days	17-item Hamilton Scale for Depression	0.51 [−0.38, 1.41]
Schaefer et al. (2016)	Germany	Allergic Rhinitis	25	No treatment	14 days	Allergy symptoms	1.12 [0.26, 1.97]