Published in final edited form as:

Pain. 2016 August ; 157(8): 1590–1598. doi:10.1097/j.pain.0000000000000566.

Relieving Pain using Dose-Extending Placebos: A Scoping Review

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Abstract

Placebos are often used by clinicians, usually deceptively and with little rationale or evidence of benefit, making their use ethically problematic. In contrast with their typical current use, a provocative line of research suggests that placebos can be intentionally exploited to extend analgesic therapeutic effects. Is it possible to extend the effects of drug treatments by interspersing placebos? We reviewed a database of placebo studies, searching for studies that indicate that placebos given after repeated administration of active treatments acquire medication-like effects. We found a total of 22 studies in both animals and humans hinting of evidence that placebos may work as a sort of dose extender of active painkillers. Wherever effective in relieving clinical pain, such placebo use would offer several advantages. First, extending the effects of a painkiller through the use of placebos may reduce total drug intake and side effects. Second, dose-extending placebos may decrease patient dependence. Third, using placebos along with active medication, for part of the course of treatment, should limit dose escalation and lower costs. Importantly, provided that nondisclosure is pre-authorized in the informed consent process and that robust evidence indicates therapeutic benefit comparable to that of standard full-dose therapeutic regimens, introducing dose-extending placebos into the clinical arsenal should be considered. This novel prospect of placebo use has the potential to change our general thinking about painkiller treatments, the typical regimens of painkiller applications, and the ways in which treatments are evaluated.

Keywords

Clinical outcomes; Enhancement; Expectancy; Learning; Pain; Placebo effects Partial reinforcement; Pharmacological conditioning; Opioids

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Conflict of interest: Luana Colloca is a consultant for Emmi Solution and received an annual lecture honorarium from Georgetown University, Washington, DC, USA. There are no additional conflicts of interest to claim for the other authors.

Introduction

The history of medicine is replete with unintentional placebo and nocebo effects in medical practice. [22; 62]. Only in recent in the 20th century have physicians been able to offer drugs and treatments with specific mechanisms of action. Despite this advance, extensive use of treatments with no proven efficacy and inadvertent use of placebos persist in the present day.

Intentional use of placebos has been recently documented in survey studies spanning different countries including USA [76; 80; 51], Canada [69; 44], Germany [59; 57], Switzerland [30], Denmark [48], UK [47], Israel [63], India [75], Saudi Arabia [45], and New Zealand [46] (see also Table 1). A systematic review of 22 studies from 12 different countries reported that between 17 and 80% of clinicians interviewed have administered such placebo treatments as sugar pills or saline injections during their careers [32]. Placebos are usually administered with little, yet unclear, rationale or evidence of benefit, and without consent or pre-authorization, making their use scientifically, clinically, and ethically questionable.

In comparison with standard regimens of medication, dose-extending placebos - placebos and/or subclinical dose of painkillers that are blended with treatments in accordance with reinforcement learning principles may, where effective, offer several benefits. First, extending the effects of a medication by interspersing placebos rather than using only medication for a treatment of equal duration may reduce the overall intake of painkillers. Side effects associated with the medicine are likely to be reduced as well [70; 71], although there is some the risk of conditioned side effects [25]. Second, in cases in which the medicine is habit-forming, dose-extending placebo use may decrease physiological or psychological dependence on medication. Third, using dose-extending placebos for part of the course of treatment rather than using medication for the entire course will presumably lower costs. Dose-extending placebos in pain medicine catalyze the body's capacity for endogenous pain modulatory systems [19]. Any attempt to target placebo effects via learning mechanisms--whether there is or not active drug (e.g. subclinical doses) in the placebo--will fall under the dose-extending placebo category.

In this scoping review, we map salient concepts underlying conditioning and placebo-induced analgesia, comprehensively review available evidence about dose-extending placebos, and discuss the requirements for a clinical use of dose-extending placebos, indicating potential clinical benefits while acknowledging possible limitations. Where ethical concerns surrounding such an application of placebos are adequately addressed along the lines we recommend, introducing pre-authorized dose-extending placebos represents an innovative approach to pain management.

The rationale beyond the prospect of dose-extending placebos

Previous comprehensive reviews of placebo use have touched on such themes as the possibility of harnessing placebo effects in pain medicine, the need to focus on elements of the clinical encounter, as well as patient-clinician relations [14; 16; 52]. Herein, we focus specifically on placebos as vehicles to boost placebo effects. While the mechanisms of

learned placebo effects have been described elsewhere[20], we selected pain and no-pain related studies, which pave the way to intentionally using conditioning principles and placebos for therapeutic purposes. This timely, innovative approach can potentially help reduce the burden of opioid misuse in pain medicine and opioid-related addiction while improving the satisfaction of chronic pain patient.

Opioids are often prescribed for the management of any type of pain despite the lack of high-quality evidence demonstrating efficacy, effectiveness and safety of long-term opioid therapy for the management of chronic noncancer pain [36; 74; 79]. Long-term opioid use is associated with great risks and likely results in greater harm than good [79]. The per capita use of opioids in North America is double that of the United Kingdom, three times of that in the Netherlands, and 26 times of that in Japan [81; 27]. Opioids can induce drug tolerance (and the need for escalating doses), hyperalgesia (increased pain sensitivity), and addiction [81; 54].

Extensive research on placebo analgesia over the past several decades has expanded knowledge of a fascinating psycho-neurobiological phenomenon underlying endogenous pain reduction [23; 52]. This provocative line of research involves the use of placebos to enhance therapeutic outcomes through learning paradigms that produce behavioral and biological responses mirroring those induced by active drugs [24; 28; 29]. In particular, studies indicate that placebos given after repeated administration of active treatments (e.g. morphine) acquire a drug-like effect (e.g. pain reduction) in both animals and humans. Moreover, it is apparent that the effect of this modality is greater than that obtainable through the use of placebo alone [4; 21; 53; 33; 34]. Based on research on placebo effects derived from pharmacological and non-pharmacological conditioning, here we present the first systematic analysis of dose-extending use of placebos and factors that need to be considered before incorporating such use into clinical practice. Some of this research uses the term “partial reinforcement” instead of “dose-extension” based on Pavlovian and non-Pavlovian learning principles, but subtle differences are unheeded here due to the fact that conceptual [24; 28; 73] and empirical [6] research on partial reinforcement has been previously published.

Search methods

We searched PUBMED for articles using the search term “placebo” to select papers dealing with the placebo effect. For the approximately 100,000 citations retrieved in 2004, we screened their titles and abstracts retrospectively and excluded papers describing placebo-controlled trials of individual drugs and other medical interventions that “only” assessed differences between drug and placebo for evaluation of therapeutic benefits of the therapy. We also excluded meta-analyses of placebo-controlled trials and reviews. After exclusion of letters and editorials, we were left with approximately 1,000 papers (or approximately 1% of all papers screened) that discussed different aspects of the placebo response and/or placebo effects in different medical and psychological subspecialties. These were predominantly experimental data (exploring the different mechanisms of the placebo response) and reviews, systematic reviews, re-analyses and meta-analyses of RCT data. For 2004 until 2015, this search was repeated weekly for updates. This database currently (Dec 31, 2015) contains

3,023 papers addressing various aspects of the placebo and nocebo responses in medicine and beyond. For this review, this database was searched using the terms “Pharmacological conditioning” (22 hits) and “conditioning” (225 hits) (Fig. 1). All the papers were hand-searched for studies using drug-like effects’ as a means to extend pharmacological effects via the placebo effect. We also hand-searched the reference lists of these papers to check for further citations not occurring in our database. This way, we identified 22 experimental studies that fulfilled selection criteria including pain- (10) and no-pain-related (12) studies, Fig 1. Herein, we review the identified pivotal studies that provide the scientific rationale for placebos to be administered in a learning-based way so that they can act as booster agents mimicking the action of active drugs.

Pain studies

Animal research on dose-extending placebos and pain—Learning from prior positive experience can create strong memory-based analgesic responses, and likewise prior negative experiences can elicit nocebo effects. We designed a study in which one group received a treatment perceived as efficacious (actually, the intensity of painful stimulations was surreptitiously decreased) and a second group received a treatment perceived as ineffective (verbal suggestions with no manipulation of the intensity of painful stimulation). When tested for placebo analgesia the first group reported significant reduction of pain (49.3%), while the second group reported a smaller pain reduction (9.7%) [21]. After four to seven days, both groups were retested for placebo analgesia. We found that the placebo responses following the effective procedure were significantly higher than that observed after the ineffective treatment (29% versus 18% pain reduction). Therefore, placebo and nocebo effects are shaped by learning (either positive or negative prior experience), and the effect of initial treatment exposure influences the response to subsequent placebo responses with obvious clinical implications [21]. These sorts of conditioned analgesic effects can be induced with pharmacological conditioning, which is effective in extending the analgesic response to opioids and nonopioids in animals and humans [4; 11; 41].

Similar results have been found in mice using a hot-plate test pharmacological opioid and non-opioid conditioning [41]. Conditioned cues were paired with either the opioid agonist morphine hydrochloride or non-opioid aspirin, and opioid and non-opioid-like responses that were either naloxone-reversible or naloxone-insensitive, depending on the drug used in conditioning procedure, were observed. Guo et al. performed a 4-day drug conditioning experiment in female Imprinting Control Region (ICR) mice. A hot-plate test was used to measure response latencies according to the method described by Hargraves and Hentall [43] and target the involvement of supraspinal mechanisms [55]. After conditioning with morphine, mice were treated with saline solution, exposed to the conditioned cue cage and then tested for pain tolerance [41]. Saline solution induced enhanced pain tolerance compared with control levels, indicating that the previous morphine conditioning was sufficient to evoke a morphine-like analgesic effect. A pre-treatment with naloxone blocked the placebo-induced analgesia. The same procedure described above was repeated after pharmacological conditioning with aspirin. Interestingly, similar placebo responses were observed except that the pre-treatment with naloxone did not block the conditioned analgesic response established by prior conditioning with the non-opioid aspirin. Morphine

conditioned analgesic responses also affects the behavioral despair tests and hormonal secretions in mice[42]. Male Sprague-Dawley rats were also trained with 10 mg/kg morphine for 4 days to establish the placebo analgesia model. Animals were microinjected with D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH(2), a selective μ -opioid receptor antagonist, or naltrindole, a highly selective δ -opioid receptor antagonist, or nor-binaltorphimine, a highly selective κ -opioid receptor antagonist, in the rostral anterior cingulate cortex. Only the μ -opioid receptor antagonist, but not κ -opioid or δ -opioid receptor antagonists, reduced the pain threshold in conditioned placebo analgesic responses, indicating a modulatory role of μ -opioid receptors [82].

Similar results have been shown in a rat model of conditioned analgesia in an operant pain assay. Specifically, rats were conditioned to associate a placebo manipulation with the analgesic effect of 1mg/kg morphine on facial thermal pain. Conditioned (placebo) responsiveness was characterized by three aspects that have been reported in human research: (1) inter-animal variability in the response, (2) suppression by the opiate antagonist naloxone (5mg/kg), and (3) a positive predictive relationship between the unconditioned analgesic effect and the conditioned (placebo) effect [64].

Although negative results have been reported [58], this research suggested that animals learn to associate contextual cues with elevated pain tolerance producing conditioned analgesia.

Human pain research—Robust analgesic responses have been documented in humans as well. Amanzio and Benedetti performed a complex experiment in which pharmacological conditioning was done in humans. Either morphine or ketorolac was administered for two consecutive days and then replaced by a placebo on the third day. Naloxone was also given to study to what extent the conditioned effects were antagonizable. All drugs were administered 10 min before inflating a sphygmomanometer cuff to induce ischemic pain. The time interval from cuff inflation to the last squeeze was 1 min and the time interval from drug administration to last squeeze was the same in all subjects (11 min). The pharmacological conditioning was induced by means of either the opioid agonist morphine hydrochloride or the nonopioid ketorolac tromethamine. Conditioning with morphine induced robust placebo analgesic responses that were naloxone-reversible. By contrast, ketorolac conditioning elicited smaller placebo effects that were naloxone-insensitive [4]. Opioid-related placebo analgesic responses can be antagonized by cholecystokinin-2 receptor agonist pentagastrin, indicating a fine balance between cholecystokinin and opioid systems in conditioned placebo analgesic effects [7; 8].

Different schedules of pharmacological conditioning worked in eliciting morphine-mimicking effects, at least in the range of days and weeks (Fig 2). Benedetti and colleagues also performed pharmacological conditioning with two morphine administrations that were given one week apart. Despite the long interval, strong placebo analgesic effects were elicited, indicating that the morphine conditioning has long-lasting effects [11]. Therefore opioid-mediated placebo analgesic responses can be re-evoked and learned analgesic effects have practical implications and applications. Using learning principles and pharmacological agents elicits responses that are mediated by opioidergic and non-opioid systems. Notably,

these laboratory studies designed to explore the possibility of eliciting beneficial effects by giving placebos after pharmacological conditioning may change therapeutic regimes.

No-pain related studies

Robert Ader was one of the first scientists to introduce pivotal concepts and a pilot clinical trial in support of the idea that placebos may be specific therapeutics when combined with learning principles. In the field of neuroimmunology, Ader and Cohen performed pioneering animal and human studies to explore the link between learned responses and therapeutic effects. For example, they observed that merely giving a placebo such as saccharine solution following the administration of cyclophosphamide can induce immunosuppression in rats in a dose-response manner [1]; rats that received two doses of cyclophosphamide during the conditioning phase had greater conditioned immunosuppression responses than those that received one dose of cyclophosphamide. Thus the stronger the US, the more robust the CR [1].

Similar studies have been recently performed in Schedlowski's lab. Pacheco-López et al. conditioned rats with 0.2% saccharin administered just before the immunosuppressive drug cyclosporine A, which inhibits calcineurin [65]. Cyclosporine A's pharmacological effects were then elicited by the neutral stimulus. The observed effects were not limited to animal behaviors but impacted activity at the level of splenocytes such as a change in the production of Th1-cytokine when the rats were re-exposed to the saccharin alone. Therefore, the calcineurin activity in CD4(+) T lymphocytes was identified as the intracellular target for inducing placebo immunosuppression after cyclosporin A exposure, suggesting that the use of placebos after pharmacological conditioning triggers specific neurobiological pathways [65].

Human research on pharmacological conditioning and dose-extending

placebos—Pharmacological conditioning has been used to study the mechanisms underlying placebo effects in the context of motor [9] and endocrine [12] systems. However, there are interesting studies in which conditioning is considered a viable strategy to harness therapeutic conditioned effects. One of the first studies adopting dose-extending placebos explored decrements in peripheral leukocyte counts in 10 patients treated for multiple sclerosis with four intravenous cyclophosphamide treatments paired with a conditioned stimulus. Eight of 10 patients showed a decreased peripheral leukocyte count when a placebo was given after cyclophosphamide [37].

In a pre-clinical trial, Goebel et al. gave healthy subjects cyclosporine A (2.5 mg/Kg) along with a green-colored, strawberry-flavored milk drink (CS) [40]. The effects of conditioned immunosuppression were assessed by measuring interleukin-2 (IL-2) and interferon gamma (IFN-gamma) mRNA expression, in vitro release of IL-2 and IFN-gamma, and lymphocyte proliferation. A placebo given 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, revealing for the first time the mechanisms underlying conditioned immune responses [40]. More recently, a study explored the duration of such a conditioned response, observing that

the suppression of T-cell function extinguished after 14 unreinforced exposures to the CS drink. Notably, administering sub-therapeutic dosages of cyclosporine A (0.25 mg/Kg) along with the CS drink prevented the extinction of the conditioned immunosuppression[3]. A similar approach was used to produce antihistamine-like effects in patients with allergic rhinitis [39] and condition behaviorally the acute response to interferon (IFN)beta-1a [38].

Notably, Ader and colleagues demonstrated that placebos given in a certain context to elicit conditioned responses can be used with corticosteroids in patients to reduce the symptoms of psoriasis [2]. Patients were treated under a partial schedule of pharmacologic (corticosteroid) reinforcement in which a full dose was given 25% to 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 active corticosteroids every time. The partial schedule of pharmacotherapeutic reinforcement with corticosteroid administration given one quarter or half as frequently as currently prescribed along with dose-extending placebos was sufficient to treat psoriasis. Indeed, the frequency of relapse under partial reinforcement (26.7%) was lower than in the control group (61.5%) and clinically comparable to the reduction in symptoms induced by a full-dose of corticosteroids (22.2%) [2].

More recently, Perlis and colleagues applied a similar therapeutic schedule to medically manage chronic insomnia in the long term using a partial reinforcement strategy with nightly dosing strategies including 10 mg zolpidem pill use with 50% active medication and 50% placebos for 12 weeks. The partial reinforcement group showed the same clinical benefit as the other three groups randomized to 10 mg or 5 mg or intermittent 10 mg nightly dosing [67].

A recent study in children with Attention Deficit Hyperactivity Disorder (ADHD) indicates further therapeutic potential [71]. Children were randomly assigned to 1 of 3 schedules of 8-week treatments. Children 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 with amphetamines produced placebo conditioned responses that allowed children with ADHD to be treated effectively with a lower dose of stimulant medication. In a novel methodological twist, use of placebos was described to both parents and children transparently, thus offering a model for pre-authorized placebo use in which patients are explicitly informed that placebos (e.g. lactose or talc pills) will be given to extend medication effects. Although open label versus concealed placebos may produce different degrees of effect, pre-authorized placebos would avoid the ethical problems associated with deception and satisfy requirements of informed consent [70; 71]. We elaborate this point in the following section.

Together, the aforementioned (and other) studies in humans and animals suggest that pharmacological conditioning of the immune system might impact the time course and severity of symptoms by harnessing placebo effects.

Clinical requirements

As just discussed, there is significant evidence of the dose-extending power of placebos. Although this evidence is by no means conclusive, it motivates the following important question: If further studies confirm these initial findings, should we consider the possibility of introducing dose-extending placebo use into the clinical arsenal? Might such placebo use eventually become a component of clinical medicine? In addressing this question against the background of the scientific rationale provided in the previous section, we will consider several possible advantages of using dose-extending placebos in clinical practice, several limitations, and leading ethical considerations. If placebos administered in a learning-based way can act as *booster agents* and mimic the action of active drugs, they might be administered to modulate pain and other symptoms, possibly limiting side effects and other disadvantages associated with continued administration of active drugs. After providing scientific background, the present section defends three theses about the use of dose-extending placebos: (a) Such placebo use may be understood as a form of medical enhancement, but not in a sense that generates ethical concerns; (b) *Pre-authorized* use of placebos avoids the ethical difficulties associated with deception and is consistent with professional norms governing disclosure and informed consent; and (c) Where robust evidence indicates therapeutic benefit comparable to that of standard treatment, we should consider the prospect of introducing pre-authorized, dose-extending placebo use into the clinical arsenal.

By critically reviewing the studies above, the authors agreed that further human studies are necessary to define when use of dose-extending placebos is effective and in addressing which specific medical conditions. Methodologically, the study protocol should include three arms: 1) a comparator arm in which full-dose of medication is given; 2) an arm with a partial schedule of pharmacologic reinforcement in which the full dose is given 25% to 50% of the time and substituted by placebos at other times; 3) a control arm in which the full dose is given 25% to 50% of the time and no placebos are administered. When feasible, this kind of study design would rule out confounding changes in the efficacy outcome measures (e.g. spontaneous remission, regression to the mean).

At the same time, the effective use of dose-extending placebos might be limited by such factors as the irreversibility of a disease, inability to adjust or optimize treatment reduction, and the pharmacokinetic properties of the relevant agent. Safety, optimization, and feasibility studies are needed to obtain a meaningful assessment of dose-extending placebos in chronic pain diseases (Box 1).

Box 1

Considerations for using dose-extending placebos to relieve pain

Running Initial safety, feasibility, and optimization studies

Points to consider:

- Is the rationale for the study design scientifically and ethically sound?

- Is there sufficient evidence to justify the inclusion of placebos in the therapeutic regimens (safety, feasibility, primary and secondary outcomes, and sample size)?

Performing confirmatory efficacy studies

Points to consider:

- Have safety, feasibility, and dose optimization been confirmed for the clinical condition under evaluation?
- Have all potential biases been minimized? Specifically, are investigators, assessors and participants blinded about the treatment administration time? Are treatments as usual (TAU) control groups included? Are open label placebos as effective as phase IV post-marketing treatments?
- Does the informed consent form address the issue of pre-authorized use of dose-extending placebos and post-treatment debriefing? Have health practitioners been trained to prepare consents forms that are clear and understandable to any patients?

If the above criteria are satisfied, then it is clinically and ethically appropriate to include dose-extending placebos in the therapeutic regimen.

There is a need to address specific questions. For example, little is known about how long placebos can be used to supplement long-term medication use and whether, and if so when, the effectiveness of the placebo use will diminish or disappear. Also, it is necessary to determine the following: 1) whether conditioning with short-term acting agents (short half-time) is more effective than conditioning with long-term acting agents; 2) whether such a paradigm is more effective where reactions to the drugs are consciously perceivable; and 3) which physiological systems are more easily subject to conditioning mechanisms. Caution is also needed in generalizing learning effects. Conditioned compensatory responses that are opposite to those induced by the medication can occur as a result of tolerance, a decreased response to a drug within the course of administrations [77]. For example, Subka and Zilov demonstrated that dogs treated with epinephrine every few days developed tolerance, presenting *tachycardic* responses that decreased over time. When epinephrine was replaced by placebo (e.g., an inert solution), an opposite *bradycardic* response was observed [78]. Further studies are needed to understand whether pre-drug cues elicit paradoxical responses because pharmacological stimulations initiate adaptive responses that compensate for the primary drug effect.

Another point to be considered is the possibility of carryover effects from drug to drug. A recent study used pharmacological conditioning with oxygen and aspirin in a model of high-altitude headache [10]. Both sham oxygen and sham aspirin were given after three administrations of real drugs. The placebo oxygen given after the conditioning with oxygen induced pain relief along with a reduction in ventilation, blood alkalosis, and salivary prostaglandin (PG)E₂. By contrast, the post-conditioning placebo aspirin induced pain relief and inhibition of the cyclooxygenase products (e.g. PGD₂, PGE₂, PGF₂, PGI₂, thromboxane (TX)A₂), without affecting either ventilation or blood alkalosis. Interestingly,

a third group received sham aspirin after conditioning with real oxygen. None of the above physiological changes were observed, suggesting the unlikelihood of carryover effects from drug to drug..

Last but not least, we expect that study participants and patients suffering from pain vary in their response to painkillers and therefore in their conditioned placebo analgesic effects. In order to justify enrollment in a protocol with dose-extending placebos, effective USs should be identified to guide health practitioners and patients towards such a mechanistic-based, personalized therapeutic approach.

Ethical considerations

Is dose-extending placebo use a form of medical enhancement?—An additional possible source of concern regarding the prospect of dose-extending placebos pertains to the concept of medical enhancement. Although a great deal has been written about placebo use in clinical practice, and placebo use in relation to deception, it has not been previously appreciated that certain types of placebo use might represent a form of medical enhancement. Here we explain why concerns associated with medical enhancement are easily allayed.

A substantial literature on medical enhancement has emerged in recent decades. In most of this literature, enhancement has been conceptualized by contrasting it with medical treatment [50; 66; 17; 72]. According to this mainstream conception, while medical treatment or therapy attempts to cure or ameliorate some medical illness or condition, enhancement goes *beyond therapy* and attempts through medical means to achieve improvements in patients who are already healthy or “normal.” Some commentators have expressed concerns that enhancement lies beyond the appropriate purview of medical practice and is therefore ethically problematic. Importantly, this line of critique presupposes that medical treatment and medical enhancement are mutually exclusive, a claim we reject.

Enhancement, whether medical or nonmedical, can be defined as *any deliberate intervention that aims to (1) improve an existing capacity, (2) select for a desired capacity, or (3) create a new capacity in a human being* [26]. This definition offers at least two advantages. First, unlike more traditional definitions of enhancement in medical contexts, which contrast enhancement with therapy, this definition is not tethered to any claim about what should count as therapy and what as “beyond therapy” (a discrimination that can be highly arbitrary and difficult in practice); the same intervention can be both therapy and enhancement. Second, the present conceptualization is closer to the ordinary meaning of “enhancement,” according to which enhancement involves some sort of improvement or growth of capacities, whether it occurs in someone who is healthy or unhealthy [18].

Dose-extending placebo use is a type of enhancement in the present sense of the term. That is because, by activating healing mechanisms that would otherwise be “silent,” such placebo use either improves or creates a patient’s capacity for self-healing. For example, a child with ADHD, who benefits from a stimulant plus a placebo that extends the stimulant’s effects, will have decreased symptoms of ADHD. An adult who suffers from psoriasis and benefits from the use of corticosteroids in combination with a placebo that extends their effects is

better able to reverse the symptoms of this medical condition. Even if neither of these patients is able to “self-heal” except in the context of dose-extending placebo use, both patients benefit from *an enhanced capacity to ameliorate the effects of their medical condition*—and very possibly with less of some of the disadvantages associated with a full course of treatment, such as side effects. The effective use of placebos in these instances lies at the intersection of medical treatment and medical enhancement. Precisely because this form of enhancement is also a form a therapy, commonly advanced ethical concerns about medical enhancement are avoided since these concerns presuppose that enhancement is “beyond therapy” [68].

Avoiding deception—From an ethical perspective, concerns arise whenever use of dose-extending placebos is deceptive. Historically, placebo use has almost always involved deception, provoking ethical problems associated with lying to or misleading patients: disrespect of the patient’s autonomy, threats to a clinician’s integrity, and potential damage to societal trust in the medical profession [13; 61; 15]. For this reason, non-deceptive (*open-label*) use of placebos is especially important—and especially promising from an ethical standpoint. Contrary to the common belief that effective placebo administration requires deception, dose-extending placebos can be given with patients’ and doctors’ agreement. A recent study along with a survey study exploring patients’ attitudes towards placebos suggested that placebos can be given in a nondeceptive manner [31; 49]. Neither studies involved pharmacological conditioning (dose-extension), thus, leaving somewhat unclear implications for the approach we are advocating in this article. Nevertheless the use of dose-extending placebos might be clinically feasible and can be acceptable by patients and health practitioners.

Although a benevolent use of deception to invoke a placebo effect in clinical practice has been the subject of philosophical analysis [56; 35], and the open-label use of placebos is still under scrutiny, we maintain that avoiding deception is ethically paramount [60]. This judgment concurs with the opinion of the American Medical Association: “Physicians may use placebos for diagnosis or treatment only if the patient is informed of 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” [5].

A physician who believes it would be advisable to use a placebo to extend the effects of medication should explicitly request *pre-authorization* for doing so, incorporating in the informed-consent process a statement such as the following: “If you agree to this arrangement, then you will be given a blister pack of painkillers and placebos and at some point during the course of treatment you will receive placebo rather than medicine, but you won’t know when” (Fig. 3). Patients might also be informed about the role of learning principles and how it can shape physiological processes and therefore clinical pain outcomes. Such a statement should be made in the context of an appropriately full and unpressured informed-consent discussion with ample opportunity for the patient to ask questions, receive answers, and consider alternatives; following the course of treatment, patients should have the option of being debriefed about the timing of placebo administration. If the patient gives informed consent to the proposed use of placebos, and the

physician goes on to administer a placebo during the course of treatment, concerns about deception would be eliminated.

This point merits elaboration. Neither the physician's communications nor his or her later behavior involves a lie (an intentional telling of what one believes to be false so as to make the listener believe it) or any other type of deception (a statement or action that intentionally directs the listener to believe what one believes to be false). The administration of the placebo does involve nondisclosure of the fact that a placebo is being given *at that time*, but the patient had earlier consented to this arrangement; thus, the administration is not misleading in any morally significant sense. Moreover, because the informed consent process (we have assumed) met appropriate ethical standards and health practitioners have been appropriately trained, the patient gave *valid* consent to the possibility of the physician's nondisclosure that he or she was giving a placebo at a particular time. Thus, in our view, such pre-authorized placebo use represents an ethical option—if there is adequate scientific confirmation that such dose-extending placebo use is comparable in expected benefits to standard use of the relevant medication.

Concluding remarks

Taken together, the studies discussed in this article suggest that dose-extending placebo use is a distinct and significant way of harnessing endogenous pain modulatory processes. Moreover, as mentioned at the outset, evidence supports the assumption that this type of placebo use has greater therapeutic value than that of ordinary administration of placebos. With sufficient understanding of the underlying placebo mechanisms, these responses can be strategically elicited on the basis of a planned sequence of medication and conditioned cues—with potential relevance to clinical practice. These effects could be therapeutically exploited in routine clinical practice by integrating placebos in schedules of reinforcement, so that conditioned stimuli acquire properties and characteristics of USs. Thus, dose-extending placebo use could become part of the pharmacotherapeutic arsenal, preserving therapeutic benefits while reducing costs, quite possibly side effects, and perhaps dependence and tolerance as well. Substantial use of this treatment modality over time could offer the additional benefit of greater insight into the human capacity for self-healing.

In sum, our proposal to consider the possibility of using dose-extending placebos in routine clinical practice is based on evidence that a) placebo effects exist whenever an active medicine is given, b) conditioning in replacing an active medicine with a placebo can target and boost endogenous placebo mechanisms (beyond what a placebo alone can do) and, finally, c) it may be possible in this way to reduce the overall dose of active analgesics, costs, and potentially side effects and tolerance—all in an ethically acceptable manner. As in any development process, confirmatory studies focusing on safety, feasibility, and dose reduction optimization are essential before pre-authorized dose-extending placebos could potentially be introduced in therapeutic pain management plans.

Acknowledgments

This research was supported by funds from the National Institute of Dental and Craniofacial Research (LC) and the Clinical Center at the National Institutes of Health (DD). The funding agencies have no roles in the study. The

views expressed here are the authors' own and do not reflect the position or policy of the National Institutes of Health or any other part of the federal government.

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Flow diagram

Figure 1.
CONSORT flow chart.

Figure 2.

Pharmacological conditioning. Morphine was given in two different schedules of reinforcement in the range of days (A) and weeks (B) and ischemic pain endurance was measured (min). A natural history group was also included to exclude biases and long-lasting effects of morphine. Placebo administered after morphine elicited morphine-like effects suggesting that a pharmacological conditioning procedure creates a learned response that can be intentionally re-evoked. Data from [8] and [11].

Figure 3.

Representation of a blister pack. Active painkillers are intermixed with identical shape/smell placebo pills. The randomization is set at 1:3 to achieve a reinforcement rate of 25% based on previous preclinical studies. Patients are informed about the fact that they will receive both treatments but they will not know the exact time.

Table 1

Survey studies from 2003 to 2015 across different countries. A set of survey studies across different countries indicates that placebos have been commonly used in daily clinical practice.

Survey study	Country	Number of respondents	% of respondents using placebos
Tilburt JC, et al. <i>BMJ</i> . 2008;23;337:a1938.	USA	679	46–58% used on a regular basis
Sherman R, et al. <i>J Gen Intern Med</i> . 2008;23(1):7–10.	USA	231	45% used placebos, 8% more than 10 times in past year
Kermen R, et al. <i>Fam Med</i> . 2010;42(9):636–42.	USA	412	56% used placebos in their clinical practice
Raz A, et al. <i>Can J Psych</i> . 2011;56(4):198–208.	Canada	606	20% used placebos regularly
Meissner K, et al. <i>Fam Pract</i> 2012;29:79–85.	Germany	208	88% used a placebo at least once in their practice
Fässler M, et al. <i>BMC Health Serv Res</i> . 2009;9:144.	Switzerland	233	72% used placebos in their clinical practice
Hróbjartsson A et al. <i>Eval Health Prof</i> . 2003;26(2):153–65.	Denmark	503	86% used placebos at least once in last year
Howick J, et al. <i>PLoS One</i> . 2013;8(3):e58247.	UK	783	97% used placebo at least once in their career
Nitzan U, et al. <i>BMJ</i> . 2004;23;329(7472):944–6.	Israel	89	49–70% used placebos in their clinical practice
Shah KN, et al. <i>Indian J Med Sci</i> . 2009;63(10):472–3.	India	90	86% used placebos in the last year. 48% more than 10 times
Hassan T, et al. <i>Int J Health Sci (Qassim)</i> . 2011;5(1):45–9.	Saudi Arabia	90	68.8% used placebos in their clinical practice
Holt S, et al. <i>NZME</i> . 2009, Vol 122 No 1298	New Zealand	157	34.4% used placebos 1–10 times in last year

Placebo use included active treatments (e.g. antibiotics, analgesics, sedatives, vitamins) and inert substances (e.g. sugar pills, sterile lotions, saline injections).