Relieving pain using dose-extending placebos

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Relieving pain using dose-extending placebos: a scoping review

Luana Colloca[a,b,c,*], Paul Enck[d], David DeGrazia[e,f]

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. Provided that nondisclosure is preauthorized 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

1. Introduction

The history of medicine is replete with unintentional placebo and nocebo effects in medical practice.[22,62] Only 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,[51,76,80] Canada,[44,69] Germany,[57,59] Switzerland,[30] Denmark,[48] United Kingdom,[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 preauthorization, making their use scientifically, clinically, and ethically questionable.

In comparison with standard regimens of medication, dose-extending placebos—placebos and/or subclinical doses 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 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 through learning mechanisms—whether or not there is active drug (that is, 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 preauthorized dose-extending placebos represents an innovative approach to pain management.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Table 1

Survey studies from 2003 to 2015 across different countries.

Survey study	Country	Number of respondents	% of respondents using placebos
Tilburt et al.[80]	USA	679	46%-58% used placebos on a regular basis
Sherman et al.[76]	USA	231	45% used placebos, 8% more than 10 times in the past year
Kermen et al.[51]	USA	412	56% used placebos in their clinical practice
Raz et al.[69]	Canada	606	20% used placebos regularly
Meissner K, et al.[59]	Germany	208	88% used a placebo at least once in their practice
Fässler et al.[30]	Switzerland	233	72% used placebos in their clinical practice
Hróbjartsson et al.[48]	Denmark	503	86% used placebos at least once in the last year
Howick et al.[47]	United Kingdom	783	97% used placebo at least once in their career
Nitzan et al.[63]	Israel	89	49%-70% used placebos in their clinical practice
Shah et al.[75]	India	90	86% used placebos in the last year, 48% more than 10 times
Hassan et al.[45]	Saudi Arabia	90	68.8% used placebos in their clinical practice
Holt et al.[46]	New Zealand	157	34.4% used placebos 1-10 times in the last year

Placebo use included active treatments (eg, antibiotics, analgesics, sedatives, vitamins) and inert substances (eg, sugar pills, sterile lotions, saline injections). A set of survey studies across different countries indicates that placebos have been commonly used in daily clinical practice.

1.1. The rationale beyond the prospect of dose-extending placebos

Previous comprehensive reviews of placebo use have touched on themes such 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 relationships.[14,16,52] In this study, 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 patient with chronic pain.

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, 3 times that in the Netherlands, and 26 times 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 psychoneurobiological 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 (eg, morphine) acquire a drug-like effect (eg, 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.[4,21,33,34,53] Based on research on placebo effects derived from pharmacological and nonpharmacological conditioning, in this study, 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 because conceptual[24,28,73] and empirical[6] research on partial reinforcement has been previously published.

2. Search methods

We searched PubMed for articles using the search term "placebo" to select articles dealing with the placebo effect. For the approximately 100,000 citations retrieved in 2004, we screened their titles and abstracts retrospectively and excluded articles 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 1000 articles (or approximately 1% of all articles 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 randomized controlled trial data. From 2004 until 2015, this search was repeated weekly for updates. This database currently (December 30, 2015) contains 3023 articles 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 articles were hand-searched for studies using drug-like effects as a means to extend pharmacological effects by the placebo effect. We also hand-searched the reference lists of these articles to check for further citations not occurring in our database. In this way, we identified 22 experimental studies that fulfilled the selection criteria including pain- (10) and no pain-related (12) studies, **Figure 1**. In this study, we review the identified pivotal studies that provide the scientific rationale for placebos to be administrated in a learning-based way so that they can act as booster agents mimicking the action of active drugs.

2.1. Pain studies

2.1.1. Animal research on dose-extending placebos and pain

Learning from previous positive experience can create strong memory-based analgesic responses, and similarly, previous negative experiences can elicit nocebo effects. We designed

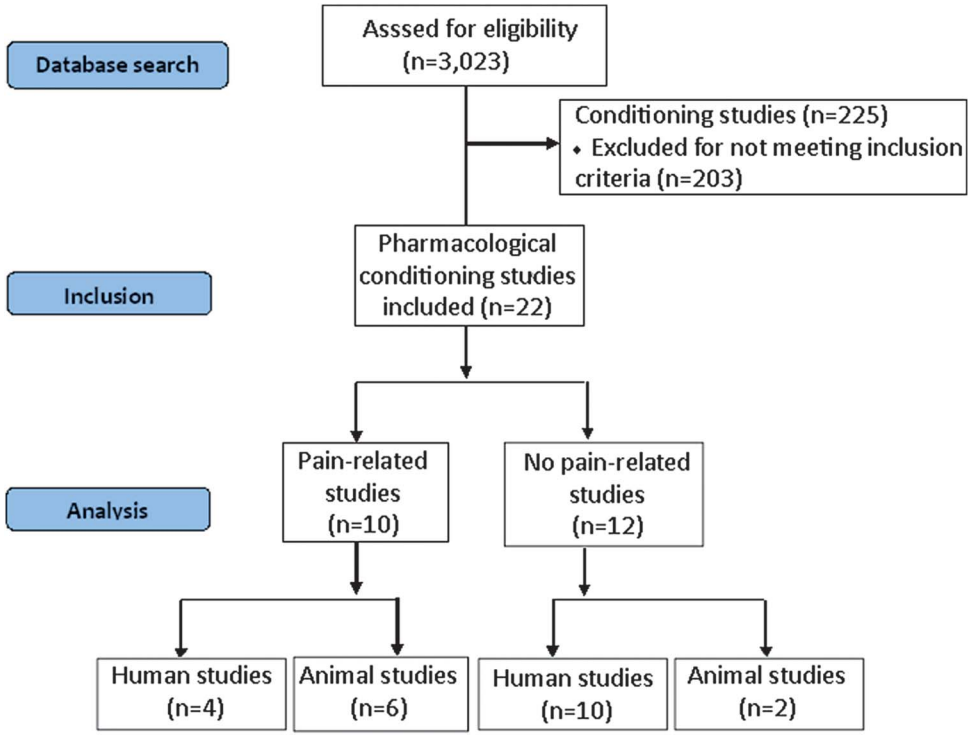

Figure 1. CONSORT flow chart.

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%), whereas the second group reported a smaller pain reduction (9.7%).[21] After 4 to 7 days, both groups were retested for placebo analgesia. We found that the placebo responses after the effective procedure were significantly higher than those observed after the ineffective treatment (29% vs 18% pain reduction). Therefore, placebo and nocebo effects are shaped by learning (either positive or negative previous 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 nonopioid conditioning.[41] Conditioned cues were paired with either the opioid agonist morphine hydrochloride or nonopioid aspirin, and opioid and nonopioid-like responses that were either naloxone-reversible or naloxone-insensitive, depending on the drug used in the conditioning procedure, were observed. Guo et al. performed a 4-day drug conditioning experiment in female-imprinting control region 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 pretreatment 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 pretreatment with naloxone did not block the conditioned analgesic response established by previous conditioning with the nonopioid aspirin. Morphine conditioned analgesic responses also affect 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, naltrindole, a highly selective δ-opioid receptor antagonist, or norbinaltorphimine, 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 1-mg/kg morphine on facial thermal pain. Conditioned (placebo) responsiveness was characterized by 3 aspects that have been reported in human research: (1) inter-animal variability in the response, (2) suppression by the opiate antagonist naloxone (5 mg/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.

2.1.2. 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 performed in humans. Either morphine or ketorolac was administered for 2 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 minutes before inflating a sphygmomanometer cuff to induce ischemic pain. The time interval from cuff inflation to the last squeeze was 1 minutes, and the time interval from drug administration to the last squeeze was the same in all subjects (11 minutes). 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 2 morphine administrations that were given 1 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 nonopioid systems. Notably, these laboratory studies designed to explore the possibility of eliciting beneficial effects by giving placebos after pharmacological conditioning may change therapeutic regimes.

2.2. Animal 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 after the administration of cyclophosphamide can induce immunosuppression in rats in a dose–response manner[1]: rats that received 2 doses of cyclophosphamide during the conditioning phase had greater conditioned immunosuppression responses than those that received one dose of cyclophosphamide. Thus, the stronger the unconditioned stimulus (US) the more robust the conditioned response (*CR*).[1]

Similar studies have been recently performed in Schedlowski's laboratory. 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]

2.2.1. 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 4 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 preclinical trial, Goebel et al. gave cyclosporine A (2.5 mg/Kg) along with a green-colored, strawberry-flavored milk drink (CS) for healthy subjects.[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 IL-2 and 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

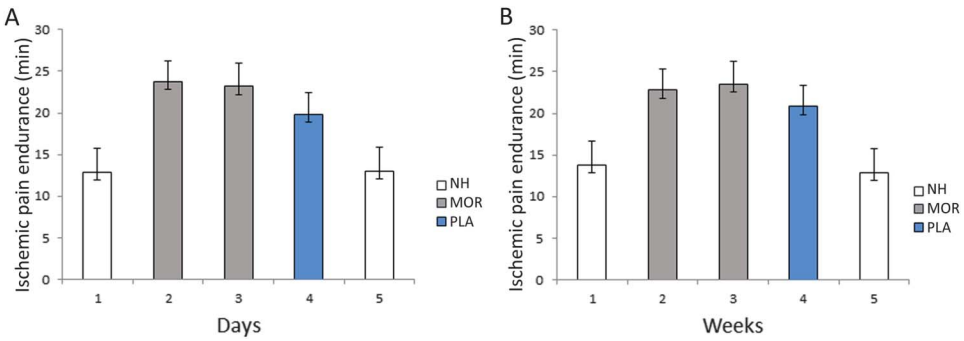

Figure 2. Pharmacological conditioning. Morphine was given in 2 different schedules of reinforcement in the range of days (A) and weeks (B), and ischemic pain endurance was measured (in minutes). A natural history group was also included to exclude biases and long-lasting effects of morphine. Placebo 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 Refs. 8,11).

function extinguished after 14 unreinforced exposures to the CS drink. Notably, administering subtherapeutic 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)β-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% to 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 zolpidempill use with 50% active medication and 50% placebos for 12 weeks. The partial reinforcement group showed the same clinical benefit as the other 3 groups randomized to 10 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, the use of placebos was described to both parents and children transparently, thus offering a model for preauthorized placebo use in which patients are explicitly informed that placebos (eg, lactose or talc pills) will be given to extend medication effects. Although open label vs concealed placebos may produce different degrees of effect, preauthorized 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.

3. 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 administrated 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 3 theses about the use of dose-extending placebos: (1) such placebo use may be understood as a form of medical enhancement, but not in a sense that generates ethical concerns; (2) *preauthorized* use of placebos avoids the ethical difficulties associated with deception and is consistent with professional norms governing disclosure and informed consent; and (3) where robust evidence indicates therapeutic benefit comparable to that of standard treatment, we should consider the prospect of introducing preauthorized, dose-extending placebo use into the clinical arsenal.

By critically reviewing the studies mentioned above, the authors agreed that further human studies are necessary to define when the use of dose-extending placebos is effective and in which specific medical conditions. Methodologically, the study protocol should include 3 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 administrated. When feasible, this kind of study design would rule out confounding changes in the efficacy outcome measures (eg, spontaneous remission, regression to the mean).

At the same time, the effective use of dose-extending placebos might be limited by factors such 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:

(1) Is the rationale for the study design scientifically and ethically sound?
(2) 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:

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

If the above criteria are met, dose-extending placebos are beneficial and ethically acceptable are part of therapeutic regimens.

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 (eg, an inert solution), an opposite *bradycardic* response was observed.[78] Further studies are needed to understand whether predrug 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 3 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 postconditioning placebo aspirin induced pain relief and inhibition of the cyclooxygenase products (eg, 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.

4. Ethical considerations

4.1. 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. In this study, 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.[17,50,66,72] 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 2 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]

4.2. Avoiding deception

From an ethical perspective, concerns arise whenever the 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.[13,15,61] For this reason, nondeceptive (*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[35,56] 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 that it will be used but they cannot identify it and do not know the precise timing of its use."[5]

A physician who believes that it would be advisable to use a placebo to extend the effects of medication should explicitly request *preauthorization* 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; after 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 who 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 preauthorized 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.

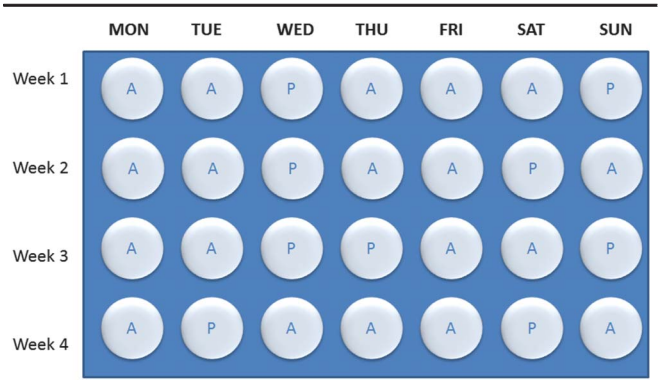

Figure 3. Representation of a blister pack. Active painkillers are intermixed with identical shape/smell placebo pills. The randomization is set at 1:3 to achieve a reinforcement rate of 25% based on previous preclinical studies. Patients are informed about the fact that they will receive both treatments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

5. 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 benefits 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 (1) placebo effects exist whenever an active medicine is given, (2) 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, (3) 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 preauthorized dose-extending placebos could potentially be introduced in therapeutic pain management plans.

Conflict of interest statement

L. Colloca is a consultant for Emmi Solution and received an annual lecture honorarium from Georgetown University, Washington, DC, USA. The remaining authors have no conflicts of interest to declare.

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References

[1] Ader R, Cohen N. Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. Science 1982;215:1534–6.

[2] Ader R, Mercurio MG, Walton J, James D, Davis M, Ojha V, Kimball AB, Fiorentino D. Conditioned pharmacotherapeutic effects: a preliminary study. Psychosom Med 2010;72:192–7.
[3] Albring A, Wendt L, Benson S, Nissen S, Yavuz Z, Engler H, Witzke O, Schedlowski M. Preserving learned immunosuppressive placebo response: perspectives for clinical application. Clin Pharmacol Ther 2014;96:247–55.
[4] Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. J Neurosci 1999;19:484–94.
[5] American Medical Association. AMA Code of Medical Ethics; Opinion 8.083: placebo use in clinical practice. Available at: http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion8083.shtml.
[6] Au Yeung ST, Colagiuri B, Lovibond PF, Colloca L. Partial reinforcement, extinction, and placebo analgesia. PAIN 2014;155:1110–17.
[7] Benedetti F, Amanzio M, Rosato R, Blanchard C. Nonopioid placebo analgesia is mediated by CB1 cannabinoid receptors. Nat Med 2011;17:1228–30.
[8] Benedetti F, Amanzio M, Thoen W. Disruption of opioid-induced placebo responses by activation of cholecystokinin type-2 receptors. Psychopharmacology (Berl) 2011;213:791–7.
[9] Benedetti F, Colloca L, Torre E, Lanotte M, Melcarne A, Pesare M, Bergamasco B, Lopiano L. Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus. Nat Neurosci 2004;7:587–8.
[10] Benedetti F, Dogue S. Different placebos, different mechanisms, different outcomes: lessons for clinical trials. PLoS One 2015;10:e0140967.
[11] Benedetti F, Pollo A, Colloca L. Opioid-mediated placebo responses boost pain endurance and physical performance: is it doping in sport competitions? J Neurosci 2007;27:11934–9.
[12] Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. J Neurosci 2003;23:4315–23.
[13] Bok S. The ethics of giving placebos. Sci Am 1974;231:17–23.
[14] Brody H. Placebo response, sustained partnership, and emotional resilience in practice. J Am Board Fam Pract 1997;10:72–4.
[15] Brody H, Colloca L, Miller FG. The placebo phenomenon: implications for the ethics of shared decision-making. J Gen Intern Med 2012;27:739–42.
[16] Brody HB, Brody D. Placebo and health–II. Three perspectives on the placebo response: expectancy, conditioning, and meaning. Adv Mind Body Med 2000;16:216–32.
[17] Buchanan A, Brock D, Daniels N, Wikler D. From chance to choice: genetics and justice. New York: Cambridge University Press, 2000.
[18] Buchanan AE. Beyond humanity: the ethics of biomedical enhancement. New York: Oxford University Press, 2011.
[19] Colagiuri B, Schenk LA, Kessler MD, Dorsey SG, Colloca L. The placebo effect: from concepts to genes. Neuroscience 2015;307:171–90.
[20] Colloca L. Placebo, nocebo, and learning mechanisms. Handb Exp Pharmacol 2014;225:17–35.
[21] Colloca L, Benedetti F. How prior experience shapes placebo analgesia. PAIN 2006;124:126–33.
[22] Colloca L, Flaten MA, Meissner K. Placebo and pain: from bench to bedside. Oxford: UK Elsevier, 2013.
[23] Colloca L, Klinger R, Flor H, Bingel U. Placebo analgesia: psychological and neurobiological mechanisms. PAIN 2013;154:511–14.
[24] Colloca L, Miller FG. Harnessing the placebo effect: the need for translational research. Philos Trans R Soc Lond B Biol Sci 2011;366:1922–30.
[25] Colloca L, Miller FG. The nocebo effect and its relevance for clinical practice. Psychosom Med 2011;73:598–603.
[26] DeGrazia D. Moral enhancement, freedom, and what we (should) value in moral behaviour. J Med Ethics 2014;40(6):361–8.
[27] Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain. BMJ 2015;350:g6380.
[28] Doering BK, Rief W. Utilizing placebo mechanisms for dose reduction in pharmacotherapy. Trends Pharmacological Sciences 2012;33:165–72.
[29] Enck P, Bingel U, Schedlowski M, Rief W. The placebo response in medicine: minimize, maximize or personalize? Nat Rev Drug Discov 2013;12:191–204.
[30] Fassler M, Gnadinger M, Rosemann T, Biller-Andorno N. Use of placebo interventions among Swiss primary care providers. BMC Health Serv Res 2009;9:144.
[31] Fassler M, Gnadinger M, Rosemann T, Biller-Andorno N. Placebo interventions in practice: a questionnaire survey on the attitudes of patients and physicians. Br J Gen Pract 2011;61:101–7.
[32] Fassler M, Meissner K, Schneider A, Linde K. Frequency and circumstances of placebo use in clinical practice–a systematic review of empirical studies. BMC Med 2010;8:15.
[33] Fiorio M, Recchia S, Corra F, Simonetto S, Garcia-Larrea L, Tinazzi M. Enhancing non-noxious perception: behavioural and neurophysiological correlates of a placebo-like manipulation. Neuroscience 2012;217:96–104.
[34] Fiorio M, Recchia S, Corra F, Tinazzi M. Behavioural and neurophysiological investigation of the influence of verbal suggestion on tactile perception. Neuroscience 2014;258:332–9.
[35] Foddy B. A duty to deceive: placebos in clinical practice. Am J Bioeth 2009;9:4–12.
[36] Furlan A, Chaparro LE, Irvin E, Mailis-Gagnon A. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. Pain Res Manag 2011;16:337–51.
[37] Giang DW, Goodman AD, Schiffer RB, Mattson DH, Petrie M, Cohen N, Ader R. Conditioning of cyclophosphamide-induced leukopenia in humans. J Neuropsychiatry Clin Neurosci 1996;8:194–201.
[38] Goebel MU, Hubell D, Kou W, Janssen OE, Katsarava Z, Limmroth V, Schedlowski M. Behavioral conditioning with interferon beta-1a in humans. Physiol Behav 2005;84:807–14.
[39] Goebel MU, Meykadeh N, Kou W, Schedlowski M, Hengge UR. Behavioral conditioning of antihistamine effects in patients with allergic rhinitis. Psychother Psychosom 2008;77:227–34.
[40] Goebel MU, Trebst AE, Steiner J, Xie YF, Exton MS, Frede S, Canbay AE, Michel MC, Heemann U, Schedlowski M. Behavioral conditioning of immunosuppression is possible in humans. FASEB J 2002;16:1869–73.
[41] Guo JY, Wang JY, Luo F. Dissection of placebo analgesia in mice: the conditions for activation of opioid and non-opioid systems. J Psychopharmacol 2010;24:1561–7.
[42] Guo JY, Yuan XY, Sui F, Zhang WC, Wang JY, Luo F, Luo J. Placebo analgesia affects the behavioral despair tests and hormonal secretions in mice. Psychopharmacology (Berl) 2011;217:83–90.
[43] Hargraves WA, Hentall ID. Analgesic effects of dietary caloric restriction in adult mice. PAIN 2005;114:455–61.
[44] Harris CS, Raz A. Deliberate use of placebos in clinical practice: what we really know. J Med Ethics 2012;38:406–7.
[45] Hassan T, Fauzi M, Hasan D. Perceptions of placebo therapy among health practitioners in jazan region of saudi arabia. Int J Health Sci (Qassim) 2011;5:45–9.
[46] Holt S, Gilbey A. Use of placebos by New Zealand doctors. N Z Med J 2009;122:84–6.
[47] Howick J, Bishop FL, Heneghan C, Wolstenholme J, Stevens S, Hobbs FD, Lewith G. Placebo use in the United kingdom: results from a national survey of primary care practitioners. PLoS One 2013;8:e58247.
[48] Hrobjartsson A, Norup M. The use of placebo interventions in medical practice–a national questionnaire survey of Danish clinicians. Eval Health Prof 2003;26:153–65.
[49] Hull SC, Colloca L, Avins A, Gordon NP, Somkin CP, Kaptchuk TJ, Miller FG. Patients' attitudes about the use of placebo treatments: telephone survey. BMJ 2013;347:f3757.
[50] Juengst ET. What Does "Enhancement" Mean? In: Parens E, editor. Enhancing human traits. Washington, DC: Georgetown University Press, 1998. pp. 25–43.
[51] Kermen R, Hickner J, Brody H, Hasham I. Family physicians believe the placebo effect is therapeutic but often use real drugs as placebos. Fam Med 2010;42:636–42.
[52] Klinger R, Colloca L, Bingel U, Flor H. Placebo analgesia: clinical applications. PAIN 2014;155:1055–8.
[53] Klinger R, Soost S, Flor H, Worm M. Classical conditioning and expectancy in placebo hypoalgesia: a randomized controlled study in patients with atopic dermatitis and persons with healthy skin. PAIN 2007;128:31–9.
[54] Kroenke K, Krebs EE, Bair MJ. Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. Gen Hosp Psychiatry 2009;31:206–19.
[55] Le Bars D, Gozariu M, Cadden SW. Animal models of nociception. Pharmacol Rev 2001;53:597–652.
[56] Lichtenberg P, Heresco-Levy U, Nitzan U. The ethics of the placebo in clinical practice. J Med Ethics 2004;30:551–4.
[57] Linde K, Friedrichs C, Alscher A, Blank WA, Schneider A, Fassler M, Meissner K. Use of placebos and nonspecific and complementary treatments by German physicians–rationale and development of a questionnaire for a nationwide survey. Forsch Komplementmed 2013;20:361–7.
[58] McNabb CT, White MM, Harris AL, Fuchs PN. The elusive rat model of conditioned placebo analgesia. PAIN 2014;155:2022–32.

[59] Meissner K, Höfner L, Fässler M, Linde K. Widespread use of pure and impure placebo interventions by GPs in Germany. Fam Pract 2012;29:79–85.
[60] Miller FG, Colloca L. The legitimacy of placebo treatments in clinical practice: evidence and ethics. Am J Bioeth 2009;9:39–47.
[61] Miller FG, Colloca L. The placebo phenomenon and medical ethics: rethinking the relationship between informed consent and risk-benefit assessment. Theor Med Bioeth 2011;32:229–43.
[62] Miller FG, Colloca L, Crouch RA, Kaptchuk TJ. Placebo: a reader. Baltimore: Johns Hopkins University Press, 2013.
[63] Nitzan U, Lichtenberg P. Questionnaire survey on use of placebo. BMJ 2004;329:944–6.
[64] Nolan TA, Price DD, Caudle RM, Murphy NP, Neubert JK. Placebo-induced analgesia in an operant pain model in rats. PAIN 2012;153:2009–16.
[65] Pacheco-Lopez G, Riether C, Doenlen R, Engler H, Niemi MB, Engler A, Kavelaars A, Heijnen CJ, Schedlowski M. Calcineurin inhibition in splenocytes induced by pavlovian conditioning. FASEB J 2009;23:1161–7.
[66] Parens E. Enhancing human traits: ethical and social implications. Washington, DC: Georgetown University Press, 1998.
[67] Perlis M, Grandner M, Zee J, Bremer E, Whinnery J, Barilla H, Andalia P, Gehrman P, Morales K, Thase M, Bootzin R, Ader R. Durability of treatment response to zolpidem with three different maintenance regimens: a preliminary study. Sleep Med 2015;16:1160–8.
[68] President's Commission on Bioethics. Beyond Therapy Book Beyond Therapy City, 2003.
[69] Raz A, Campbell N, Guindi D, Holcroft C, Dery C, Cukier O. Placebos in clinical practice: comparing attitudes, beliefs, and patterns of use between academic psychiatrists and nonpsychiatrists. Can J Psychiatry 2011;56:198–208.
[70] Sandler A, Glesne C, Geller G. Children's and parents' perspectives on open-label use of placebos in the treatment of ADHD. Child Care Health Dev 2008;34:111–20.
[71] Sandler AD, Bodfish JW. Open-label use of placebos in the treatment of ADHD: a pilot study. Child Care Health Dev 2008;34:104–10.
[72] Savulescu J, Bostrom N. Human enhancement. Oxford: Oxford Univerity Press, 2009.
[73] Schedlowski M, Enck P, Rief W, Bingel U. Neuro-Bio-Behavioral mechanisms of placebo and nocebo responses: implications for Clinical Trials and Clinical Practice. Pharmacol Rev 2015;67:697–730.
[74] Sehgal N, Colson J, Smith HS. Chronic pain treatment with opioid analgesics: benefits versus harms of long-term therapy. Expert Rev Neurother 2013;13:1201–20.
[75] Shah KN, Panchal DJ, Vyas BM, Patel VJ. Use of placebo: knowledge, attitude and practice among medical practitioners. Indian J Med Sci 2009;63:472–3.
[76] Sherman R, Hickner J. Academic physicians use placebos in clinical practice and believe in the mind-body connection. J Gen Intern Med 2008;23:7–10.
[77] Siegel S, Baptista MA, Kim JA, McDonald RV, Weise-Kelly L. Pavlovian psychopharmacology: the associative basis of tolerance. Exp Clin Psychopharmacol 2000;8:276–93.
[78] Subkov AA, Zilov GN. The role of conditioned reflex adaption in the origin of hyperergic reactions. Bull Biol Med Exp 1937;4:294–6.
[79] Sullivan MD, Howe CQ. Opioid therapy for chronic pain in the United States: promises and perils. PAIN 2013;154(suppl 1):S94–100.
[80] Tilburt JC, Emanuel EJ, Kaptchuk TJ, Curlin FA, Miller FG. Prescribing "placebo treatments": results of national survey of US internists and rheumatologists. BMJ 2008;337:1938.
[81] Zerzan JT, Morden NE, Soumerai S, Ross-Degnan D, Roughead E, Zhang F, Simoni-Wastila L, Sullivan SD. Trends and geographic variation of opiate medication use in state Medicaid fee-for-service programs, 1996 to 2002. Med Care 2006;44:1005–10.
[82] Zhang RR, Zhang WC, Wang JY, Guo JY. The opioid placebo analgesia is mediated exclusively through mu-opioid receptor in rat. Int J Neuropsychopharmacol 2013;16:849–56.