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REVIEW

Placebo: a brief updated review

Alfredo Jose Pardo-Cabello[1] · Victoria Manzano-Gamero[2] · Emilio Puche-Cañas[3]

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Abstract
Our aims were to provide updated information on placebo/nocebo effect and the potential use of placebo in clinical practice. This article can only provide a rough overview on the placebo and nocebo effect and is intended to serve as a starting point for the reader to go deeper into the corresponding literature. The placebo effect has been observed in multiple medical conditions, after oral administration, with manual therapies as well as with surgery and invasive procedures. The use of placebo in clinical trials is fundamental, although the ethics of its use is under discussion. The placebo may behave like a drug from the pharmacokinetic and pharmacodynamic point of view and can also be associated with adverse events (nocebo effect). Placebo can modify treatment by increasing or decreasing the effects of drugs. The factors associated with the occurrence of placebo effect are multiple, but in addition to those that depend on the placebo itself, the doctor-patient relationship would be the most important. As a result of findings that were published in the last two decades, the psycho-neurobiological basis of placebo is becoming better understood, although further studies are needed. In conclusion, the placebo effect in the clinic exhibits weak to moderate intensity. Placebo, in addition to its use in the clinical trial, should be considered another therapeutic remedy either as stand alone or in association with treatment, and could be useful in certain circumstances. The use of placebo should be regulated by the European health authorities through a guide in clinical practice that will improve patient care.

Keywords History of medicine · Neuropsychiatry · Nocebo effect · Pain · Placebo effect

Introduction

Placebo is an issue of renewed interest in medicine because of its effects on various diseases and its involvement in clinical trials. The term "placebo" comes from the Latin *placere* meaning to please. Its use in clinical practice is common as it is estimated that approximately 40% of prescriptions function as a placebo, sometimes with the physician being aware of this and sometimes not (Tilburt et al. 2008; Fässler et al. 2010; Kradin 2011; Kaptchuk and Miller 2015; Chavarria et al. 2017; Evers et al. 2018; Blease 2019; Colloca and Barsky 2020). There are two types of placebo: "pure" placebo refers to an inert substance such as starch, dextromaltose, lactose, talc, mentholated water and saline; and "impure" placebo refers to substances with a known pharmacological activity such as vitamins, minerals, antibacterials and psychotropic substances used in subtherapeutic doses or wrong indication, for example using antibacterials in uncomplicated viral infections. Conceptual differences have been established between placebo, placebo effect and placebo response (Mitsikostas et al. 2020). According to some authors (Mitsikostas et al. 2020), "substances and interventions are considered placebos when they lead to a beneficial outcome after administration or application, although their active ingredients lack this potential. Active ingredients include pharmacologically active compounds, properties, psychological intervention, physical manipulations and other (e.g. sham surgery, sham stimulation, etc.)". On one hand, "the placebo response consists of any favourable health change occurring from before to after a placebo administration or application" while "a placebo effect refers to those particular beneficial health changes that are observed after a placebo administration or application, which are attributed to the

✉ Alfredo Jose Pardo-Cabello
alfredoj.pardo.sspa@juntadeandalucia.es

[1] Department of Internal Medicine, Hospital Universitario San Cecilio, Avda. de La Innovación, s/n, 18016 Granada, Spain

[2] Department of Internal Medicine, Hospital Universitario Virgen de Las Nieves, Granada, Spain

[3] Department of Pharmacology, School of Medicine, University of Granada, Granada, Spain

placebo mechanisms exclusively, e.g. expectation, conditioning, observational learning" (Mitsikostas et al. 2020).

A Cochrane review study covering 158 trials and 10,525 patients showed a mild to moderate evidence for a placebo effect that was mainly observed for the conditions pain and nausea (Hróbjartsson and Gøtzsche 2010). However, other authors (Maher et al. 2021) consider that the use of placebo, outside of clinical trials, has little to contribute to clinical care. For this reason, and in view of the disparity of criteria, we will present in this review the main findings reported on the clinical and research use of placebo. Another observational study using a questionnaire showed that 77% of the surveyed physicians prescribed placebo at least once a week, with impure placebos accounting for more than 90% (Howick et al. 2013). Subsequently, a meta-analysis of observational studies on the use of placebo in Primary Care showed an average of 63% of physicians using it, with the majority of them also using impure placebos (Linde et al. 2018). Findings over the last two decades have shown that placebo, as an inactive substance, triggers a series of neurohormonal responses in the brains of patients and healthy subjects that could be the anatomic-physiological basis for its effects. Some authors consider placebo to be a useful tool for neuroscience research because neuroscientists use the placebo response as a model to understand how our brain works, and indeed, it is emerging as an excellent approach to understand several higher brain functions, such as expectation and reward (Benedetti 2013).

The aims of this brief review are to provide up-to-date information on placebo in a way that is comprehensible to the physician, as the literature on the subject is extensive and sometimes difficult to understand for non-specialists, and its potential for use in clinical practice. However, this article can only provide a rough overview on the placebo and nocebo effect and is intended to serve as a starting point for the reader to go deeper into the corresponding literature.

Pharmacodynamics and pharmacokinetics of placebo

The mechanism of action of placebo is explained by non-specific, non-receptor-mediated mechanisms. In some instances, placebos behave like normal drugs in that they have a latency time and a maximal effect as shown in time-effect curves for lactose, aspirin, codeine and aspirin plus codeine in patients with pain due to cancer (Weiner and Weiner 1996) or in time-effect curves for placebo or aspirin in patients suffering from postpartum pain (Lasagna et al. 1958). Besides, it may sometimes, but not always, have a dose–response relationship (Weiner and Weiner 1996); sometimes the placebo follows the law of "all or nothing", either the effect appears or it does not. The placebo exhibits tolerance and addiction, even when the patient is knowingly taking an inert substance, and it is capable of causing adverse effects (nocebo effect) (Barsky et al. 2002). Similarly, placebo can reinforce or reduce the effect produced by pharmacotherapy or other therapies (Evers et al. 2018); for example, the patient's positive expectations on certain drugs (remifentanil, caffeine) have been shown to increase the effect (analgesic effect and physiological variables respectively) of these drugs as previously described (Bingel et al. 2011; Walach and Schneider 2009) while negative treatment expectancy abolished remifentanil analgesia (Bingel et al. 2011).

The parameters used in the kinetic study of drugs such as maximum peak (Cmax), half-life (t1/2), clearance (Cl) and area under the curve (AUC) can also be applied to the placebo study, provided it is a substance detectable in organic fluids, as in the case of lactose (Weiner and Weiner 1996). However, other authors consider that there is little if any literature on the kinetics and dynamics of the placebo effect and, at present, the lack of knowledge about the pharmacokinetic and pharmacodynamics of the placebo effect is a possible confounding factor (Eccles 2020). It should also be borne in mind that the placebo response may follow a non-linear model (Kradin 2011).

The mechanism of action of the placebo effect involves what is known as the empathy brain (Benedetti 2013), activating various nuclei in the prefrontal cortex and their connections with the cerebral amygdalae, the limbic system, the thalamus and the hippocampus, as shown by functional neuroimaging studies in patients and healthy volunteers (Scott et al. 2007; Bingel et al. 2011; Benedetti 2013). The involvement of the frontal and parieto-temporal cortex is so important that any impairment leading to its destruction, or the disruption of cortico-cortical and subcortical pathways, results in an absence or reduction of the placebo effect. An example of this is the lower percentage of placebo response in schizophrenia versus neurosis or depression (20% vs 70%) (Benedetti 2013; Wager and Atlas 2015). Another example is the repetitive low-frequency transcranial magnetic stimulation of the dorsolateral prefontal cortex which overrides placebo analgesia in healthy volunteers (Krummenacher et al. 2010).

Similarly, an increase in dopamine release in the nucleus accumbens, related to learning and feelings of pleasure, has been described to be involved in the neurophysiological mechanism of the placebo in humans (Scott et al. 2007). Recently published findings from a neuroimaging study in healthy volunteers corroborated the involvement of brainstem nuclei that modulate nociceptive sensation (Crawford et al. 2021).

Psycho-social stimuli that reach the brain via the sensory pathway can induce non-conscious learning, Pavlovian conditioning or expectations of healing. Participating in this activation as neuromodulators are oxytocin, the so-called love hormone and its concentration in the cerebral amygdala,

vasopressin, dopamine (D1–D2 receptors), serotonin (5HT2A receptor), endorphins (mu receptor) and endocannabinoids (CB1 receptor). The neurohormonal response to these brain stimuli reaches peripheral tissues via the autonomic nervous system (Meissner 2011). In addition to pain, homeostatic systems, immunity and inflammatory response have been shown to be targets of placebo (Zion and Crum 2018).

The characteristics of the placebo effect in responders include being effective only on symptomatology and therefore lacking curative power; having a short duration, although in rare cases it may persist for days after discontinuation (Colloca and Benedetti 2006; Benedetti et al. 2007); an intensity of effect that may vary from mild to moderate (Lasagna et al. 1958; Weiner and Weiner 1996); and inducing adverse reactions (nocebo effect), among others.

Factors associated with the occurrence of the placebo effect

There are multiple factors involved in the occurrence of the placebo effect. In order for the reader to understand them better, we have divided them into three groups.

The first group is related to the placebo itself, such as its presentation, size, colour, flavour and galenic formulation (Meissner 2018; Buckalew 1982). However, other authors, like Maher et al., consider that "the notion that placebo pill appearance is important is based on a very small and weak evidence base" because "the effect of the physical appearance of a placebo pill has been tested in a few clinical studies, but the studies are small and have yielded inconsistent results" (Maher 2019). The placebo can be administered in solid, liquid, gaseous and topical forms (creams and ointments); the least common is the suppository, perhaps because it is the least accepted form. Part of the placebo effect is the well-known "halo effect" (Andrade 2012) derived from the positive or negative hype that precedes any medicine, or whether or not it has been recently introduced on the market (Lachaux and Lemoine 1989). The price of the product and whether or not it is generic also play a role in the placebo effect (Andrade 2015).

A second group is patient-dependent (Anderson and Stebbins 2020). There are placebo-responders and non-responders, with response not being associated with age, gender or cultural level, and ethnicity is under discussion (Anderson and Stebbins 2020). It seems that there might be a personality profile prone to the placebo effect in the optimistic versus the pessimistic subject (Geers et al. 2005). Factors associated with the placebo effect also include prior conditioning; the environment and place where it is administered; the patient's positive expectations about the treatment to be received, by whom and where it is carried out; and that the patient is conscious, as the placebo effect does not appear in subjects in coma or with severe dementia (Benedetti et al. 2016). In relation to expectations, as previously mentioned, the patient's positive expectations on certain drugs (remifentanil, caffeine) have been shown to increase their effect (Bingel et al. 2011; Walach and Schneider 2009) while negative treatment expectancy abolished remifentanil effect (Bingel et al. 2011). In relation to prior conditioning, pre-administration of opioid analgesics promotes the onset of analgesia in patients who are subsequently given a placebo as reported in an experiment where, after repeated administrations of morphine in the pre-competition training phase, its replacement with a placebo on the day of competition induced an opioid-mediated increase of pain endurance and physical performance, although no analgesic drug was administered (Benedetti et al. 2007). In relation to observational learning, Colloca et al. found that "the placebo effect is a learning phenomenon in which many factors come into play and may explain the large variability of the placebo responses that is found in many studies" (Colloca and Benedetti 2006).

The third group depends on the doctor-patient relationship together with the medical history, the performance of complementary tests or special explorations, such as ECG or X-ray, and the informed prescription that facilitates adherence to treatment and increases trust of the patient. It is also where oral reinforcement/suggestion is very important (Anderson and Stebbins 2020; Benedetti 2002). An empathic doctor-patient interview triggers a series of complex psycho-neuro-endocrine mechanisms in the brain developed over the course of human evolution and related to trust, pleasure and positive expectations (Anderson and Stebbins 2020; Wager and Atlas 2015; Colloca and Barsky 2020).

Genetics and placebo

Recently, genetic analysis is being applied in placebo-responders and non-responders. Polymorphisms in different genes expressing monoamine oxidase (MAO) A; COMT (catecholmetyltransferase), dopamine receptors (D2–D3) and opioid receptors (mu) are associated with a conditioning of the placebo response (Furmark et al. 2008; Leuchter et al. 2009; Hall et al. 2012; Peciña et al. 2015). Since these polymorphisms, e.g. tyrosine hydroxylase, MAO, COMT and dopamine receptors (D2–D3) belong to the dopaminergic system, these findings illustrate the important role of dopamine in the placebo effect. Experimentally, the involvement of the gene expressing tyrosine hydroxylase, the limiting enzyme that initiates catecholamine biosynthesis in tissues, has been demonstrated in placebo-induced analgesia (Lee et al. 2015). At present, genetic analysis can only provide indicative information and does not predict whether or not a subject will respond to a placebo. But it is likely that the results obtained in the coming years with the development

of genetic techniques will be important in clinical research (Hall et al. 2015).

Assessment of the placebo effect

The placebo effect can only be correctly assessed, when a placebo group is compared to an untreated group. This is required due to confounding factors that may "mimic" the placebo effect, e.g. natural evolution of the disease, Hawthorne effect and regression to the mean. Only with an untreated control group these confounding effects can be subtracted from the effect of the placebo-treated group to obtain the "pure" placebo effect. However, in a serious disease, a placebo group or a "no-treatment" group would be unethical. On the other hand, if ethically acceptable, a no-treatment group is always required to quantify the placebo effect. In the assessment of the placebo effect, a number of errors can occur that can lead to false interpretations of the results, among others: the *natural evolution of the disease*, which tends towards improvement or cure; the statistical phenomenon of *regression toward the mean*, whereby the signs and symptoms of a specific pathology tend to adjust over time to the average of the patients suffering from it; the *Pygmalion effect* (also known as *Rosenthal* or *expectancy effect*); and the *Hawthorne effect*. In the *Rosenthal effect*, the observers give less importance to symptoms reported some time ago because they expect patients to get better later what results in a false impression of improvement (Andrade 2012). The *Hawthorne effect* occurs when the act of measurement influences the value of what is being measured (Andrade 2012), e.g. the participants who can modify the results if they know they are being observed.

Medical situations where the placebo effect is potent

A remarkable placebo effect has been observed in many symptoms typical of psychosomatic medicine, in psychiatry and in both surgical and non-surgical pain (Khan et al. 2005).

Placebo and pain

This is the situation where the placebo effect has been studied most and best. Let us recall Beecher's observations in the Second World War when he injected wounded soldiers with physiological saline solution in the absence of morphine (Beecher 1946). Although Henry Beecher did not include the required untreated control group in many of his studies and Maher et al (2021) wrote "The key limitation of Beecher's work is that his measure of the placebo effect was within-group change in the placebo group. This effect estimate is biased and means that Beecher substantially overestimated the size of the placebo effect", we consider the historical value of the Beecher's research despite its flaws. The prevalence of the placebo effect in pain ranges from 39 to 56%, estimating that intravenous administration of 1 ml of saline is equivalent to the analgesia obtained with 6–8 mg of intravenous morphine (Benedetti 2013). Preconditioning with opioids augments placebo analgesia. The use of naloxone, a mu receptor opioid antagonist, reverses the placebo analgesic effect, implying the involvement of endorphins in this response. The same mechanism has been shown to explain the analgesic effect of acupuncture on painful muscles, bones and joints. Placebo analgesia is also obtained after preconditioning with non-opioid drugs such as metamizole, ketorolac and tramadol, although the latter could well be classed as an opioid, where pre-conditioning also increases the analgesic response to placebo. Placebo-induced analgesia in subjects conditioned with NSAIDs is not affected by naloxone but is affected by rimonabant, a neuronal cannabinoid CB1 receptor antagonist that blocks the effect. These findings have been observed in both humans and experimental animals using various pain models (Benedetti 2013; Keller et al. 2018; Colloca 2019). In addition to the prefrontal cortex, limbic system and hippocampus, the brainstem nuclei that modulate nociceptive sensation, the ventromedial nucleus and the periaqueductal grey matter are involved in placebo analgesia (Crawford et al. 2021). The aforementioned findings from pre-conditioning studies illustrate that the endorphin and endocannabinoid system are important neurotransmitter systems in placebo analgesia.

Placebo and neuropsychiatry

There are numerous publications reviewing placebo in psychiatry that show a significant response for some situations (Weimer et al. 2015). One of the paradigms of the placebo effect in psychiatry is the treatment of both major depression and depressive episodes (Peciña et al. 2015; Haas et al. 2022a, b; Jones et al. 2021). In bipolar depression, the placebo effect is not consistent (Gourion and Mouchabac 2016). It is suspected that 50% of the response to antidepressant drugs is due probably to the placebo effect itself (Kirsch 2019). Although its mechanism of action is unknown, some authors argue that the placebo effect in depression is related to spontaneous improvement of the depressive episode and regression to the mean (Rutherford et al. 2012; Hengartner 2020). On the other hand, a dose-dependent increase in glucose metabolism in the brain of subjects on placebo and fluoxetine after 6 weeks of treatment with both has been observed following PET scanning (Mayberg et al. 2002). Both the placebo and fluoxetine group showed regional metabolic increases in the prefrontal, anterior cingulate, premotor, parietal, posterior insula and posterior cingulate, and metabolic decreases in the subgenual, para-hippocampus

and thalamus, with larger responses to fluoxetine compared with placebo (Mayberg et al. 2002).

Besides, it has been observed that the placebo effect occurs in neuroses but not in obsessive–compulsive disorders (Khan et al. 2005; Kirsch 2019). In insomnia, a prevalent disease in European population for which benzodiazepine and non-benzodiazepine hypnotics (Z-drugs) are prescribed with a high risk of inducing serious adverse reactions, the placebo effect is powerful. Some studies, including a meta-analysis (Huedo-Medina et al. 2012) and a clinical practice guideline on insomnia (Riemann et al. 2017), reported that 50% of the hypnotic effect induced by Z-drugs (zoplicone, zolpidem and zaleplon) was associated with a placebo response.

Another paradigmatic example of placebo response is schizophrenia. A classic observational and descriptive study was conducted in the 1960s by French psychiatrists in a group of hospitalised chronic schizophrenics ($n=39$) who were secretly replaced by chlorpromazine with placebo for 9 months, observing improvement in 22 patients, no change in 15 and only two patients who worsened (Lachaux and Lemoine 1989). Today this trial would have had serious ethical problems for its conduct. It is estimated that the placebo effect in this psychiatric disease reaches 20% of patients (Khan et al. 2005).

In neurology, the results of studies in Parkinson's patients given a placebo show an improvement in tremor, rigidity and bradykinesia because of the increase dopamine synthesis in the striatum. For the placebo response to occur, it is essential that the cortex and its connections are unaffected or only slightly affected, because in Parkinson's patients with an interruption of these pathways, the response does not occur. The same happens in dementias where a large number of frontal pole neurons are destroyed (Benedetti et al. 2016). It has also been observed in attention-deficit hyperactive children that placebo reduces amphetamine treatment (Sandler et al. 2010). Recently, a positive response to placebo has also been observed in the treatment of traumatic brain injury and its complications (Polich et al. 2018).

Other medical situations sensitive to the placebo effect

In Cardiology, angina, paroxysmal atrial fibrillation and dyspnoea caused by congestive heart failure are sensitive to placebo (Sheldon and Opie-Moran 2017; Sohaib et al. 2013). Exact quantification is difficult because of the many secondary factors involved in heart disease such as personality type and the close stress-heart relationship (Olshansky 2007; Sheldon and Opie-Moran 2017). The placebo effect also occurs in hypertension, although it is mild and transient, and is related to an improvement in the subject's stress (Olshansky 2007). In Dermatology, a meta-analysis that investigated the effect of placebo on chronic itch (due to atopic dermatitis, psoriasis and chronic idiopathic urticaria) showed that itch was significantly reduced by 24% from baseline (van Laarhoven et al. 2015). In Gastroenterology, the placebo response has been reported to be also relevant in irritable bowel syndrome, in gastro-oesophageal reflux disease, in ulcerative colitis and in Crohn's disease (Bernstein 2006; Finniss et al. 2010). In Pneumology, and more specifically in bronchial asthma, the percentage of subjects responding to placebo is low, although the improvement is more subjective than objective, as no substantial changes were found in respiratory function parameters (Kemeny et al. 2007; Dutile et al. 2014). A review based on 8 studies, in patients with acute cough or upper respiratory tract infection, reported that the magnitude of the perceived placebo response has been shown to be up to 85% in terms of cough measure (subjective cough frequency, cough frequency or cough bouts) (Eccles 2002).

In Urology, placebo improves incontinence and symptoms caused by benign prostatic hypertrophy, with alpha-blockers being more effective in severe cases of prostatism (van Leeuwen et al. 2006). In fibromyalgia, a meta-analysis reported that placebo accounted for 45% of the response, in terms of pain, in the drug groups in fibromyalgia syndrome (Häuser et al. 2011).

A placebo effect has also been observed on blood glucose levels (Lin et al. 2020), on immune response (Hadamitzky et al. 2018) and in the treatment of addiction to pharmaceuticals and drugs of abuse, legal or illicit (Evers et al. 2018; Galindo et al. 2020). Finally, in Sports Medicine, the use of placebo during training improves performance in a low percentage of athletes in a moderate and significant way (Hurst et al. 2020). Although most of the results presented here come from more or less extensive literature reviews of observational studies that require confirmation, they are certainly interesting to know. Table 1 shows some medical situations in which the placebo effect occurs.

Placebo and surgery

In every medical act, there is a more or less important part of the placebo effect, and surgery is no exception (Johnson 1994). This involves expectations of healing from the intervention and trust in the surgeon (Haryalchi et al. 2017; Wartolowska 2019). Classical examples of the placebo effect in surgery are ligation of the internal mammary artery in the treatment of angina in the 1950s (Dimond et al. 1960) and the freezing of the duodenal ulcer via endoscopy in the 1960s (Ruffin et al. 1969).

The percentage corresponding to the placebo effect in surgery is not easy to estimate due to the paucity of published trials with the placebo group and randomised sample. In a meta-analysis of 39 publications with randomised sample versus placebo (sham surgery), covering traditional surgery

Table 1 Some medical situations in which a role of the placebo effect/placebo response has been reported

Clinical area	Disease	References
Cardiology	Hypertension	Patel et al. (2015)
	Heart failure	Sohaib et al. (2013)
	Cardiovascular mortality	Yue et al. (2014)
Dermatology	Chronic itch (atopic dermatitis, psoriasis, chronic idiopathic urticaria)	van Laarhoven (2015)
	Atopic dermatitis	Sölle et al. (2021)
Gastroenterology	Irritable bowel syndrome	Kaptchuk (2008)
	Ulcerative colitis	Schmid et al. (2015)
	Gastro-oesophageal reflux disease	Cremonini et al. (2010)
Gynaecology	Menopausal hot flushes	Pan et al. (2020)
Pneumology	Asthma	Dutile et al. (2014)
	Cough	Eccles (2002)
Urology	Lower urinary tract symptoms (including urinary incontinence, overactive bladder and benign prostatic hyperplasia)	van Leeuwen et al. (2006)
	Erectile dysfunction	Cocco (2009)
Others	Fibromyalgia syndrome	Häuser et al. 2011, Chen et al. (2017)
	Painful peripheral diabetic neuropathy	Häuser et al. (2011)
	Migraine	Antonaci et al. (2007)
	Insomnia	Huedo-Medina (2012)
	Depression and anxiety disorders	Kirsch 2019
	Pain	Beecher (1946); Benedetti (2013); Forsberg et al. (2017); Colloca (2019)

($n=5$) and invasive procedures ($n=34$) such as endoscopy and percutaneous technique, in cases of back pain, abdominal pain (endometriosis; colic; gastro-oesophageal reflux) and introduction of a gastric balloon in obesity, the results showed that surgery had a non-significant greater therapeutic benefit versus the placebo group (sham surgery) with a higher percentage of adverse events (34–42%). Among the invasive procedures, only endoscopy for gastro-oesophageal reflux showed a significant benefit over placebo; for the other procedures, there were inconclusive results (Jonas et al. 2015). Further trials in traditional and invasive surgery with randomised, placebo group sampling are required to reach conclusive results (Cousins et al. 2020).

Open-label placebo

The use of an inert substance in the clinical trial as well as in the clinic is currently under discussion, with the use of placebo with deception being discussed. In recent years, the concept of open-label placebo, where the patient knows that he or she is taking an inert substance and consents to it, has emerged, with varying acceptance by doctors and patients (El Brihi et al. 2019; von Wernsdorff et al. 2021; Haas et al. 2022a, b). A trial in surgery patients showed that placebo improved somatic symptoms such as pain, discomfort or insomnia but did not intervene in the time or healing process of the surgical wound (Mathur et al. 2018). Despite the increasing number of non-deceptive placebo trials, methodological issues, as ethical concerns, the role of placebo with deception vs. open-label placebo, etc., remains to be defined and are the subject of ongoing studies (Druart et al. 2020).

Nocebo effect

The term "nocebo" comes from the Latin "nocere", meaning to harm or damage, and refers to all adverse events following the administration of a placebo. In clinical practice, we do not know the incidence of the nocebo effect because the symptomatology it usually presents is of mild-moderate prognosis and usually goes unnoticed by physicians and nurses. There are known studies where the placebo effect manifested itself as hyperalgesia (nocebo) instead of analgesia after a tooth extraction (Gracely et al. 1985) or as a hypertensive crisis in an adult participant in a clinical trial on antidepressants who took an overdose of pills for suicidal purposes believing them to be antidepressants, requiring treatment (Reeves et al. 2007). In controlled trials with healthy volunteers, the nocebo effect had a prevalence of 19%, while in clinical trials it was estimated at 10% (Ferreres et al. 2004; Planès et al. 2016). In this line, a study that analysed data from randomised, placebo-controlled trials of statin drugs with sample sizes larger than 100 subjects showed that 4 to 26% of patients in the control groups discontinued

placebo use because of perceived adverse effects (Rief et al. 2006).

The most common symptoms of the nocebo effect are nausea, dry mouth, drowsiness, anxiety, nervousness, headache, dizziness, asthenia, flushing, flatulence, low blood pressure and a feeling of heaviness. They vary in intensity and disappear without sequelae when the nocebo is withdrawn (Ferreres et al. 2004; Rief et al. 2006; Planès et al. 2016). They are generally reminiscent of adverse reactions caused by psychotropic drugs. There are strong suspicions that drug-induced non-specific toxicity (intermittent adverse events, idiosyncrasy, non-dose-dependent effect and non-reproducible) could be attributed to the nocebo effect (Barsky et al. 2002; Colloca and Barsky 2020). Two studies have recently been published: SAMSON demonstrating that part of the adverse effects induced by statins is due to the nocebo effect (Howard et al. 2021), and another in a large sample of people vaccinated against COVID-19 where two-thirds of the mild-moderate discomfort suffered by the participating subjects was due to the nocebo effect (Haas et al. 2022a, b).

Factors associated with the occurrence of the nocebo effect include pessimistic personalities; those with a tendency to somatise their emotions (Geers et al. 2005); information on adverse reactions in pharmaceutical package leaflets (Vernia et al. 2010; Faasse et al. 2019); information disseminated by the media (Faasse et al. 2017; Nelson et al. 2020); and female gender (Wartolowska 2019). We do not yet know why women are more prone to the nocebo effect than men.

The pharmacodynamics of the nocebo effect is mediated by non-specific mechanisms or triggered by negative psychological stimuli (expectations, conditioning, observational learning). Among the neurobiological mechanisms involved in the nocebo effect that we are beginning to understand is the activation of the hypothalamic–pituitary–adrenal axis (HPAA) (Benedetti et al. 2016).

The occurrence of the nocebo effect is associated with anticipatory anxiety and negative expectations aroused in the subject in relation to the doctor, prescription or other therapeutic procedure. In addition, negative psychosocial stimuli may contribute; for example, the COVID-19 pandemic has generated stress in people, which favours the appearance of somatic symptoms accompanying states of anxiety (Amanzio et al. 2020). These situations generate negative emotions such as stress, fear and anxiety by activating the HPAA with adrenaline and cortisol secretion, which reduces the activity of the dopaminergic system and the release of endorphins. The administration of benzodiazepines overrides or reduces the activation of the HPAA (Wartolowska 2019). On the other hand, in stress, cholecystokinin (CKK) is released via the enteric route and its presence in the brain as a neurotransmitter produces hyperalgesia by blocking endogenous opioids. Furthermore, CKK has been shown to be an anxiogenic hormone per se when administered intravenously in animal neurophysiology studies and in humans (Andre et al. 2005; Lovick 2008; Planès et al. 2016; Benedetti et al. 2020).

Placebo/nocebo effect and clinical trials

The participation of a placebo group in the clinical trial (phase III) has been the subject of debate for several reasons: The first reason is ethical for using a deceptive placebo. The presence of a placebo group in the clinical trial (phase III) continues to be important when interpreting the results on the real capacity of a therapeutic procedure and is considered the gold standard for the pharmaceutical industry in the study of new drugs (European Medicines Agency 2001). However, the use of placebo may influence the outcome of clinical trials as reported in a systematic review that showed that response rate was on average smaller and dropouts higher for the same antidepressants in placebo-controlled trials compared with head-to-head trials (Salanti et al. 2018). The use of placebo in the control group of a clinical trial is generally allowed according to the Declaration of Helsinki under certain circumstances, including absence of specific treatment; placebo treatment is for a short period of time; placebo does not add risk to the individual; and informed consent of the participating subjects. The second reason is the nocebo effect in clinical trials, a problem to be solved for several reasons: first, there are few clinical trials where the nocebo effect is specifically studied because it is ethically very debatable; second, because in randomised controlled clinical trials themselves, possible nocebo effects are counted as adverse effects indistinctly; and third, because the appearance of intolerance leads to participant dropout, which modifies the power of the study (Mitsikostas et al. 2014). The nocebo effect is often underestimated in clinical trials. This underestimation makes it difficult to know its actual prevalence and could introduce bias in the results of the trial (Planès et al. 2016; Wartolowska 2019). Finally, to deal with the placebo effect, several statistical studies designs have been proposed, such as crossover study design, placebo run-in and randomised withdrawal designs and sequential parallel comparison designs (Raman 2020). Applying an appropriate design and statistical method facilitates the interpretation of results in placebo studies (Raman 2020).

Embodiment theory

In addition to the psychological and neurobiological contributions that have been proposed to explain the placebo/nocebo effect, there is another theory known as embodiment. According to this theory, our experiences are not only stored in our memory consciously but also through non-conscious processes from sensorimotor stimuli generated in previous

experiences. Accordingly, placebo/nocebo effects could represent the positive/negative effects of such an embodiment (Thompson et al. 2009). The embodiment is part of the cognitive learning processes in humans (Riskind 1983).

Discussion

The medical use of placebos is under permanent debate, as it is considered an inert substance with no effect, and when a placebo effect occurs, it is thought to be an illusory perception. It has always been under suspicion as to whether or not it is ethically acceptable for clinical use outside of medical research (Bernstein et al. 2020; Bayoumy et al. 2020). There are authors (Maher et al. 2021) who do not recommend the use of placebo in clinical practice because it does not provide any clear benefit, as well as being weak and erratic (as in case of pain and nausea) as reported in the aforementioned Cochrane review (Hróbjartsson and Gøtzsche 2010). However, although it has not demonstrated clinical benefit, other authors (Benedetti 2013; Colloca and Barsky 2020) advocate its use in clinical practice as its effects are based on neurobiological mechanisms demonstrated by functional neuroimaging studies and its use could improve therapeutic outcomes and minimise unintentional symptom exacerbation in clinical practice. In our modest opinion, although it is true that no study has demonstrated its clinical benefit in a conclusive and statistically significant way and it is probably not possible due to the very nature of the placebo, we do consider that, in view of the many recent studies that have demonstrated a real neurobiological effect, research into the placebo and nocebo effect should continue in order to try to explore and exploit its possible clinical utility.

It is a topic that has been taken up with great interest in medicine due to the findings of the last decade, so much so that there is even a *Journal Interdisciplinary Placebo Studies* (https://jips.online) devoted exclusively to the subject.

Due to the mistrust of prescribing an inert substance, placebo is not well accepted by doctors and nurses (Bernstein et al. 2020; Haas et al. 2022a, b). A recent study conducted with medical and nursing students showed that more than 80% of participants either were unaware of it or believed it was unethical to use on patients (Bayoumy et al. 2020). However, the reality is that placebo also encompasses substances with and without pharmacological activity, the so-called impure placebo, which are frequently prescribed in the clinic (Linde et al. 2018).

Sometimes, doctors are not aware of prescribing a placebo when they prescribe medicines at doses lower than those recommended, antibiotics for uncomplicated flu, antibacterials for clean skin wounds for which an antiseptic would suffice, when they prescribe joint cartilage regenerators for osteoarthritis, vitamin complexes to stimulate appetite, phlebotonics, cerebral vasodilators, psychotropic drugs and anti-ageing substances, among others (Linde et al. 2018), or when prescribing homeopathic remedies whose effects are difficult to explain outside the placebo effect (Shang et al. 2005; Antonelli and Donelli 2019). Despite the efforts made by EU health authorities, products of dubious efficacy or unknown mechanism of action continue to exist in practice.

The use of a placebo may be useful in situations where the physician does not know what to do when all therapeutic resources have been exhausted, in the absence of an effective drug, in cases of patients who periodically and insistently demand a prescription for ailments that are difficult to justify or in helping to reduce the dosage of chronically prescribed drugs by reducing the incidence of serious adverse reactions.

In addition to adults, the placebo effect can occur in paediatrics directly in children or through their parents and relatives, the latter being called *placebo by proxy* (Sandler et al. 2010; Schnadower et al. 2018; Fanti-Oren et al. 2019; Czerniak et al. 2020). The *placebo (effect) by proxy* concept "describes a positive effect of a patient's treatment on persons in their surrounding such as family members or healthcare providers, who feel better because the patient is being treated" (Czerniak et al. 2020). According to Grelotti and Kaptchuk (2011), "the different mechanisms that underlie the placebo effect are likely to shape placebo by proxy also; these processes may include seeing other patients respond to the same drug, associative learning such as conditioning, a supportive physician–patient relationship, and reduced anxiety" (Grelotti and Kaptchuk (2011),). Some authors find the placebo response more potent and longer lasting in paediatric vs. adult patients, while others find no difference (Janiaud et al. 2017). Whether placebo is more potent in paediatrics is an issue that requires further study as the results are inconclusive.

The reasonable use of placebo in some chronic treatments would be of benefit to the national health system and to the patient. An increased dose of analgesics after elimination of the placebo effect (open/hidden paradigm) has been reported (Finniss et al. 2010).

On the other hand, placebo is not only used to treat ailments in patients; it has also been used to improve creativity according to the results of a trial in healthy volunteers (Rozenkrantz et al. 2017) or to improve performance in athletes (Hurst et al. 2020).

A fundamental and controversial aspect of placebo is the ethics of its use in patients, which consists of not giving misleading information that generates false hope in the patient or applying placebo deceitfully. This is a difficult issue to implement in practice because not all doctors would be willing to prescribe a placebo and persuade patients of its goodness. One way to partially solve the ethical problem is the use of placebo without deception, the so-called open-label placebo where the patient knows and consents

to the prescription of an inert substance. The administration of placebo without deception has a variable acceptance by physicians and patients (El Brihi et al. 2019; Bernstein et al. 2020), but at the moment this issue is not fully resolved and more information is needed as the available information is under discussion. We believe that the use of placebo without deception would entail a Hawthorne effect, among others, which would add difficulty to the interpretation of results.

The participation of a placebo group in the clinical trial (phase III) is necessary today, not only in pharmacotherapy but also in surgery and invasive procedures. In the case of surgery, the small number of trials with a placebo group and randomisation of the sample raises the question of whether certain surgical procedures whose efficacy is unknown and which subject patients to unnecessary surgical risk (Jonas et al. 2015; Vase and Wartolowska 2019) should continue to be performed as they have been up to now.

On the other hand, unlike the placebo effect, the nocebo effect has not been systematically studied in dedicated trials. In clinical trials, nocebo effects are not recorded as such, as they are included in the group of adverse events without specifying their nature, and this, together with the withdrawal of participants due to the appearance of intolerance, poses difficulties when interpreting the results of a trial (Planès et al. 2016). There is a meta-analysis on the nocebo effect and dropout in clinical trials with antidepressants whose results showed a dropout rate of 4.5% due to intolerance in the placebo group (3255 patients), a group of people who all received an inert substance (Mitsikostas et al. 2014).

The psycho-neurological mechanisms of the placebo/nocebo response are not yet fully understood, although the contributions of the last two decades are providing data that suggest a biological basis for it. This is also valid for the whole mixture of psycho-social stimuli involved in the process, which are related to human learning and survival, developed during the course of evolution. As for negative psycho-social stimuli that generate a nocebo effect, we have a good current example in the states of anxiety caused by the COVID-19 pandemic (Amanzio et al. 2020) that have triggered the consumption of anxiolytics, antidepressants and hypnosedatives in Europe, probably in many cases unnecessarily (Jacob et al. 2021; Sánchez Díaz et al. 2021; Estrela et al. 2022).

There are strategies to minimise nocebo effect and increase the placebo effect, such as clear information to the patient about the diagnosis of their disease, the treatment and the inconveniences it might cause, anticipating positive expectations about the effectiveness of the treatment, and an empathic doctor-patient relationship that increases trust in the patient by reducing negative thoughts about the treatment in general clinical practice (Evers et al. 2018) and in neurological clinical practice (Mariani and Corvol 2020).

Although substantial progress has been made in the understanding of placebo/nocebo and its effects, more experimental and clinical studies are still needed to provide data to improve knowledge and clinical application.

Conclusion

In conclusion, we believe that the placebo effect is not imaginary. It is real as its neurophysiological basis is becoming known. Although the intensity and frequency of the placebo effect are difficult to determine in clinical practice, placebo should be taken into account by doctors and nurses as another therapeutic option that, alone or associated with other treatment, could be useful in certain circumstances. On the other hand, nocebo effects can occur during placebo through either clinical practice or clinical trial. In the light of the above, we believe that information on the indications, limitations and contraindications of placebo should be included in medical and nursing *curricula*. Finally, the use of placebo should be regulated by the European health authorities through a guide on the use of placebo in clinical practice that will improve patient care.

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Data availability Data were derived from previously published studies.

Declarations

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