

## A history of the placebo

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### ABSTRACT

**Background.** A placebo is a treatment designed to simulate a medical intervention, but which does not exert a biological effect on the disease in question. The term originates from the Latin for “I shall please”. Centuries of medical practice provide many examples that lead us to ponder whether the history of treatment is actually equivalent to the history of the placebo effect. The main question is whether the total effect of any substance is equal to the sum of the effect of its active ingredient (specific effect) and its placebo effect.

**Methods and development.** This study examines different treatments that have been applied throughout the history of medicine. In contrast with the medicine employed by primitive societies, which is based on magic and religion, modern pharmaceutical treatments always include an active ingredient.

**Conclusions.** The placebo effect is very important in clinical trials, considering that the placebo is the gold standard against which treatments are compared in these studies.

Guidelines are needed for both alternative medicine and evidence-based medicine so that the placebo effect can be measured in both cases.

### KEYWORDS

Placebo effect, history of medicine, clinical trials, alternative treatments

### Introduction

A placebo is a treatment designed to simulate a medical intervention, but which does not exert a biological effect on the disease in question. Deriving from Latin, ‘placebo’ means “I shall please”. Medicine provides many examples that raise the question of whether the history of medical treatment might be considered the history of the placebo effect. The Catholic Church popularised the use of placebos in the sixteenth century, to discredit those who performed exorcisms for profit. The Church’s intent was to show imitations of sacred relics to those said to be possessed by the devil; if their possession seemed to abate, this was proof that it had been simulated. The idea spread throughout the medical community, and widespread use of harmless substances began to be seen in the eighteenth century. The concept of the placebo effect only became officially recognised

once regulations for clinical trials were approved after World War II.

This review presents a summary of the numerous treatments used throughout the history of medicine to support my conviction that the history of medicine and the history of the placebo are one and the same. I place particular emphasis on the placebo effect in clinical trials, given that the placebo is the gold standard against which treatments are compared in this type of study. And while many specific drugs are available, numerous treatments are also used as placebos; here, the medicinal effect is provided by doctors, since our mere presence is enough to exert a placebo effect on patients. In the context of the rise of alternative medicine, and given the lack of scientific studies that prove their efficacy in most cases, doctors need guidelines to help measure the magnitude of the placebo effect in both alternative and evidence-based medicine.

## Development

### Mechanisms of the placebo effect

It is important to distinguish between placebos themselves and the placebo effect.<sup>1</sup> Any type of treatment may act as a placebo, and the placebo effect is the patient's response to that treatment. It is defined as any effect produced by the act of taking a treatment, but not by the properties inherent to that treatment.<sup>2</sup> The specificity of the placebo effect depends on the information the patient receives and the patient's resulting expectations for the intervention. Certain effects associated with treatment, such as quality of care from doctors or nurses and the doctor-patient relationship, may increase the benefits of the treatment.<sup>3</sup>

The placebo effect derives from psychological and neurobiological mechanisms. Among other psychological mechanisms, patient expectations play a key role.<sup>4</sup> Recent studies have begun to shed light on some of the biochemical bases of the placebo effect. For example, whereas placebo-induced analgesia has been linked to the release of endogenous opioids, placebo-induced release of dopamine gives rise to motor improvements in Parkinson's disease. One theory proposes that the placebo effect is mediated by the activation of reward circuits.<sup>5</sup> These biochemical findings indicate that the placebo effect is real, and they suggest that many of the arguments and ethical debates revolving around placebo use should be reconsidered. Although minimising the placebo effect may be recommendable for clinical trials, in which the goal is to measure the pure effect of the active ingredient and act in the patient's best interest, the placebo effect is habitually exaggerated in clinical settings.<sup>6</sup> We know that administration of a placebo stimulates the prefrontal, orbitofrontal, and anterior cingulate cortices, the nucleus accumbens, amygdala, periaqueductal grey, and the spinal cord. The placebo effect may translate to physiological changes, such as pain reduction due to endorphin release, increases in endogenous dopamine in patients with Parkinson's disease, and changes in bronchial muscle tone and maximum peak flow in patients with asthma.<sup>5</sup> In fact, studies with positron emission tomography (PET) have shown that the placebo effect is similar to that of opioids, and can be reversed with naloxone.

Evaluations of the placebo effect of different drugs have shown that, generally speaking, warm colours work better as stimulants and cold colours as anxiolytics.<sup>7</sup>

Furthermore, the effect increases with pill size and number.<sup>8,9</sup> We also know that the placebo effect depends on the cultural context, and that a name-brand placebo is more effective than a generic.<sup>10</sup> Similarly, expensive placebos are more effective than inexpensive ones.<sup>11</sup> Other studies have established that injections and acupuncture are more effective than pills against pain, whereas pills are more effective as hypnotics.<sup>12</sup> Furthermore, good adherence to a placebo regimen decreases mortality due to the healthy adherer effect.<sup>13</sup> We also know that prior experiences modulate the placebo effect,<sup>4</sup> and that the composition of placebos is often not indicated in clinical trials that may contain biases for<sup>14</sup> or against<sup>15</sup> active treatment.

### Medicine in primitive societies

The common denominator for medicinal practices in primitive societies is that illness was interpreted as divine punishment, provoked by breaking a taboo or religious law, or the work of witches or sorcerers. In any case, illness was regarded as a supernatural occurrence. Both diagnosis and treatment of diseases required magical or religious means and rites, and the people entrusted with patient care were priests or shamans. Treatment and diagnosis also drew from other magical and religious practices, such as observing crystals, throwing bones in the air, entering trance states to perform diagnoses, and a variety of ceremonies, prayers, and magical rituals. Patients were also therapeutically patted and touched with specific objects.

Diseases were understood to arise from different causes. Some of the more frequent included divine punishment, a foreign object such as a stone or bone entering the patient's body, possession by a spirit, loss of the soul, the 'evil eye', and fright. Traumatic lesions, pregnancy complications, and even animal bites (from jaguars or snakes, for example), were charged with magical or supernatural meaning in the primitive world.

Nevertheless, medicine in primitive societies was effective due to the positive psychological effect of the doctor-patient relationship. The patient and his family and friends, along with the doctor and his helpers, all belonged to the same social context and shared the same beliefs and ideas about illnesses. Many diseases did run their course naturally, and this spontaneous recovery was fundamentally promoted by the placebo effect. I might also point out that primitive medicine was reasonably effective at treating war wounds and other

traumatic lesions, managing complications of pregnancy and childbirth, and caring for many acute gynaecological and paediatric illnesses. On some occasions, however, the treatment provided by the priest or shaman was (and continues to be) catastrophic for the patient, owing both to the interventions that were performed and to those omitted.

#### Traditional Chinese medicine

Chinese medicine consists of a catalogue of traditional healing practices developed between the beginning of the Common Era and about the year 1600. Its theoret-

ical basis is that life force (Qi) regulates spiritual, emotional, mental, and physical balance, and that it is affected by the opposing forces of 'ying' (negative energy) and 'yang' (positive energy). Diseases arise when something disrupts the flow of Qi. Chinese medicine includes herbal treatments, diets and nutrient supplementation, physical exercise, meditation, acupuncture and moxibustion, therapeutic massage, prescriptions from the Chinese pharmacopoeia, and others.

Acupuncture was the most commonly employed treatment in China during 2500 years. Archaeological

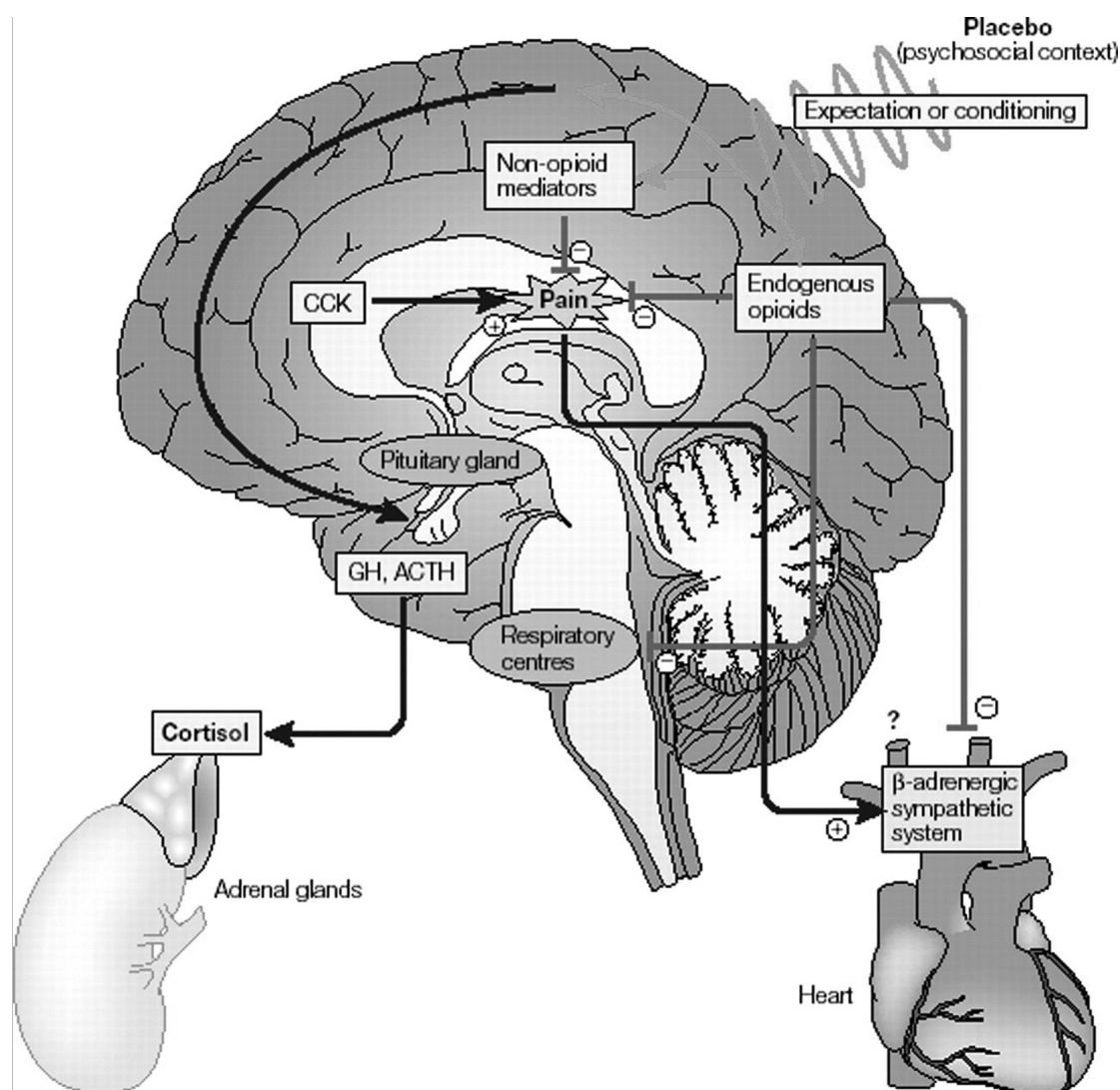


Figure 1. Neurochemical consequences of the placebo effect<sup>4</sup>

research dates the dawn of acupuncture to the Neolithic or Stone Age. A 'bian' was a sharp stone for skinning animals, and it was also used in those times to apply pressure to different parts of a sick person's body in an attempt to alleviate the discomfort in some way. Blood-letting, an intervention that was common to all traditional approaches to medicine, was another predecessor of acupuncture, which would be introduced to Europe in the seventeenth century by the Jesuits. In the twentieth century, the practice caught the eye of Soulié de Morant, the French ambassador to China. After his health problems had been cured by traditional Chinese medicine, he translated several texts and promoted their dissemination throughout Europe. The use of unsterilised needles was probably responsible for hepatitis B being endemic in China.

Randomised trials suggest that the efficacy of acupuncture is due to a placebo effect. Trials comparing verum acupuncture (the traditional Chinese method) to sham acupuncture (superficial insertion), no treatment, or usual treatment have shown this to be the case. Acupuncture has been tested for migraines, tension headaches, chronic lower back pain, and osteoarthritis of the knee.<sup>16-18</sup> Generally speaking, no differences were observed between verum and sham acupuncture, but benefits for patients treated with either intervention exceeded those in the untreated group.<sup>19</sup> The patient's expectations regarding pain relief was the most important prognostic factor, and the effect lasted one year.

#### Assyrian and Sumerian medicine

The Assyrians practised a magic and religion-based medicine according to which one of the main mechanisms of illness was possession, or presence of an evil spirit in the body.<sup>20</sup> The evil spirit responsible for pain in the neck was named Adad, whereas pain in the chest was caused by Ishtar, and pain in the temporal region was the work of Alu. These demons could be forced out by means of exorcism, accompanied by rites of purification, sacrifice, and penitence. The doctor, or 'asu', fulfilled a dual role as priest and healer. There were 250 substances recommended for use in ointments or medicines administered by other routes, and they included anise, asafoetida, belladonna, marijuana, cardamom, castor oil, cinnamon, garlic, mandrake, mustard, myrrh, and opium.

An important part of an asu's treatment plan was placing little statues of threatening-looking monsters around the sick person. This way, the demon causing the illness would see them and be frightened off. Another part of his task was to divine the prognosis, which was done by inspecting an animal's liver. Hepatoscopy was performed using sheep livers, and not only in cases of illness. It was also used before entering into business, contracting matrimony, waging war, and



Figure 2. Code of Hammurabi. The Louvre, Paris





Figure 3. Ebers Papyrus. Library of the University of Leipzig

engaging in other risky ventures. The Assyrians also used astrology as a form of divination.

The Sumerians (Mesopotamia, 3500 BCE) considered that diseases were caused by demonic spirits which could only be overcome using specific rites that incorporated empirical and spiritual medicine. Healers, who had a variety of names including 'ka-pirig' and 'mash-mash', had undergone special training and were normally priests. These healers held specific rites near the patient which included divination methods, repeating prayers, applying unguents, and many others.

The Code of Hammurabi listed ten basic rules stipulating the fees that had to be paid to healers and the consequences they would face in cases of malpractice. A few curious examples from this code are listed below<sup>21</sup>:

218. If a physician [Asu] uses a bronze knife to operate on a gravely wounded noble and kills him,

or if he opens an abscess with a bronze knife and destroys the eye, his hand shall be cut off.

219. If a physician uses a bronze knife to operate on a slave and kills him, he shall replace the slave with another of equal value.

221. If a physician sets a broken bone or relieves an intestinal disease for a noble, he shall give him five shekels of silver [some 150 g].

223. If the patient is a slave, his owner must pay two silver shekels.

#### Medicine in ancient Egypt

Egypt was home to a magical and religious system of medicine in which priests were doctors and diseases were caused by the entire pantheon of gods: Ra the sun god, Osiris god of the Nile, Isis his wife and sister and the mother to other gods, Ptah the Great Architect and god of health, and many others. The Egyptians believed in the immortality of the soul and in bodily resurrection. These

beliefs probably influenced their practice of mummification, which dates to the second dynasty (ca. 3000 BCE). The most distinguished figure in medicine was Imhotep, chancellor to King Djoser (third dynasty, ca. 2980 BCE). In 525 CE he was recognised as a god and a son of Ptah (although he was known to have been born to the architect Kanofer). Imhotep was later recognised as the god of medicine, and together with Ptah, he was the most revered deity in Memphis during the Hellenistic period. Various rites were celebrated in their temples, which were visited by the afflicted, many of whom slept there. Imhotep would appear to them in dreams and indicate the proper treatment. The Greeks equated him to Asclepius and adopted many traditions linked to the worship of Imhotep.<sup>22</sup>

The Ebers papyrus lists the incantations needed to cure specific diseases, as well as providing several practical remedies. This papyrus mentions three types of doctors according to the treatments they provided: remedies for physicians, operations for surgeons, and exorcisms for sorcerers or exorcists. One chapter in the Ebers papyrus addresses remedies for migraines. Dementia,

convulsions, and tetanus are briefly addressed in several rolls of papyrus.<sup>23</sup> Drug treatments included using castor oil as a laxative, and willow leaves and bark (containing acetylsalicylic acid) to promote scar formation. Faeces were used to ward off evil spirits; in fact, it was said that sick people would be made to eat faeces so that no spirits would come near them. The Edwin Smith papyrus describes numerous fractures (the assessment and structured description of craniovertebral trauma is especially interesting), dislocations, wounds, tumours, ulcers, and abscesses, including treatment plans for each lesion.<sup>23</sup> The text also recommends use of exorcism and incantations or prayers before or during treatment, but without placing much emphasis on this point.

Head wounds were routinely treated with trepanation, that is, opening the skull to relieve pressure.<sup>23</sup> Nevertheless, some of the Egyptian remedies are still popular; an example would be milk and honey as treatment for a sore throat. According to Shapiro, the list of the most famous historical remedies should include unicorn horn and bezoars for snake venom.<sup>24</sup>



**Figure 4.** Pre-Columbian medicine. Treatment for an epileptic seizure



## Pre-Columbian medicine

In pre-Columbian cultures, disease indicated an imbalance between favourable and unfavourable influences, and the reason for that imbalance had to be ascertained. Nothing was thought to be arbitrary in these cultures, not even death, since it was believed that a supernatural power was toying with humankind.<sup>25</sup> The shaman was usually both a sorcerer and a priest, and his magical power was more important than his medical knowledge. Shamans learned their craft after a trial of ascetic preparatory rites. Some inherited their roles, while others were initiated after disasters or accidents occurred. Only civilisations with relatively advanced levels of feudal and territorial organisation, such as the Incas, Aztecs, and possibly the Mayas, were said to have priests. In the case of Aztec city-dwellers, the functions of priest and doctor remained separate. The latter was a hereditary occupation that also required the acquisition of knowledge.

Medicine in pre-Columbian times evolved from a solemn and ritualised practice to a more magical-empir-

ical current.<sup>26</sup> Even when the shaman employed drugs, the liturgical pomp and circumstance and the melodramatics of priests and practitioners lingered on as a ceremonial relic. They used cinchona bark, coca leaf, Mexican tea, ayahuasca or yagé (a brew of vines containing MAOIs and *Psychotria viridis* with its DMT), and many other substances. Pre-Colombian medicines contained a wide variety of products extracted from snakes, worms, spiders, and the viscera of larger animals. Shamans were versed in the properties of many plants, including those used in treating parasites: Mexican tea, wild fig, achiote, guayaco, and otoba. They also employed sarsaparilla, ipecacuanha, four o'clocks, copaiba, and Jesuit's bark.<sup>27,28</sup>

These practitioners possessed extensive knowledge of the ichthyotoxic properties of curare and timbo.<sup>27</sup> The use of hallucinogenic drugs was very important and closely tied to the experience known as shamanic flight.<sup>28</sup> Indigenous people also used mushrooms of the *Psilocybe* genus and others, as well as parotid secretions of

## A CLINICAL TRIAL OF SANOCRY SIN IN PULMONARY TUBERCULOSIS<sup>1</sup>

J. BURNS AMBERSON, JR., B. T. McMAHON AND MAX PINNER

Obviously, the matching could not be precise, but it was as close as possible, each patient having previously been studied independently by two of us. Then, by a flip of the coin, one group became identified as group I (sanocrysin-treated) and the other as group II (control). The members of the separate groups were known only to the nurse in charge of the ward and to two of us. The patients themselves were not aware of any distinction in the treatment administered.

Figure 5. First placebo-controlled clinical trial<sup>65</sup>

the *Bufo marinus* toad, which contain very powerful hallucinogens. The active substance in angel's trumpet or *Datura arborea* is scopolamine, more commonly known as 'burundanga' and used by almost all indigenous groups. It causes mental, visual, and coordination disorders. The Muisca people used it for its hallucinogenic properties, and to anaesthetise the servants and courtesans who were buried alive when an important chief died.<sup>29</sup>

### Traditional medicine in India

Traditional medicine in India can be traced back to the Ayurvedic texts, a collection of ancient religious writings from the beginning of the first millennium of our era. The two most important texts are the *Charaka Samhita* and the *Sushruta Samhita*, supposedly written by the scholars Charaka and Sushruta. Both texts present a theoretical framework in which bodily tissues are the product of three humours. Kapha, or phlegm, is composed of the elements of earth and water. Pitta, or bile, represents fire and water. Vata, or wind, is the product of air and space. As in Chinese medicine, illness was considered to be the result of an imbalance of the humours, and the aim of treatment was to re-establish equilibrium.<sup>30</sup>

### Hippocrates

The Greek physician Hippocrates was born on Kos in 460 BCE and died in 377 BCE. He was considered the father of medicine because of his exhaustive scientific knowledge and his skill in healing. His writings comprise the *Corpus Hippocraticum*, a collection of 87 ancient Greek texts on medicine.<sup>31</sup> One of the factors with the most influence on the doctor's approach, and which would have the greatest historical transcendence, was belief in *Vis Curatrix Naturae*, or natural tendency to healing displayed by all living things. The doctor's task was thus to ensure that the body would be able to heal itself.

### Galen

Galen of Pergamon (Pergamon, 130 CE - Rome, ca. 216 CE) left behind more than 200 studies on anatomy, physiology, pathology, hygiene, pharmacology, and herbology. When he died, there was a movement to organise and systematically present his teachings so that they could be studied by doctors over a period of no more than four years. This practice continued in

Alexandria until the sixth century. Galen wrote, "I have had greater success with those patients who truly believed that they would be cured". He promoted the use of theriac, a mixture of many drugs and a variety of other ingredients (some blends contained more than 70 substances). The exact formula was given in numerous treatises, from Galen's own *Theriakà* in the second century to Johan Zwelfer's *Pharmacopoeia augustana* in 1653, the *Codex Medicamentarius*, a French text from 1758, or even Spanish pharmacopoeias from the early twentieth century. Galen maintained that an individual's health depended on the balance between the blood and a series of humours known as yellow bile, black bile, and phlegm. Galen was one of the first scholars to observe physiological phenomena scientifically, and he practised many dissections. Galen wrote, "[Physicians] behave despotically toward their colleagues and disciples, while letting their patients treat them like slaves. This behaviour contrasts with that of the ancient sons of Aesculapius, who taught that we should rule our patients as a general leads his soldiers, and as a monarch rules his possessions". In Galen's writings (139 CE - 201 CE), we find references showing that he knew that the patient's expectations could exert an influence on the outcome. Galen stated that the patient's trust in the doctor and in the medicine employed was more important than the treatment method itself.<sup>32</sup>

### Medicine in the Middle Ages

Ideas did not evolve in the Middle Ages; critical thinking and science made little progress during this time, and medical practices were based on empirical knowledge. Doctors were not concerned with the effectiveness of treatments until the sixteenth century. Paracelsus (1493-1541) chose his treatments according to their effect, but also keeping in mind their colour and other properties.<sup>33</sup>

### The Eighteenth Century

One of the first examples of a drug with proved effectiveness was quinine, as demonstrated by Sydenham. Nevertheless, James Lind<sup>34</sup> was the one known for performing the first controlled clinical trial in 1747, in which he concluded that oranges and lemons were the most effective treatment for scurvy.<sup>34,35</sup> Even so, his recommendation would not be accepted by the British



Navy for several years. Charles II of England had himself employed a type of placebo. He treated more than 90 000 patients using what was known as the 'royal touch'. This practice continued in England until the late eighteenth century, and even into the nineteenth century in France.<sup>35</sup>

#### Franz Mesmer and Elisha Perkins (18th century)

Franz Mesmer of Germany (1733-1815) believed that every person possessed the ability to cure others using the 'animal magnetism' supposedly found in electricity. His method was evaluated by a French Royal Committee, formed by Louis XVI in 1784, which concluded that there was no evidence of a magnetic field, and that the method's effects were the product of imagination, i.e. the placebo effect.<sup>36</sup> Elisha Perkins (1741-1799), an American doctor, invented his 'Perkins patent tractors' in 1798. These devices were rods or crooks that were pointed at one end and rounded at the other, and made of such different metal alloys as copper and zinc, gold and iron, or platinum and silver. John Haygarth (1740-1827) demonstrated that they produced a placebo effect when he used wooden rods instead of the metal ones.<sup>37</sup>

#### Homeopathy (18th century)

Samuel Hahnemann (1755-1843) created a new type of medicine that broke with the previous traditions. The theory in homeopathic medicine is that "like cures like", and that only a tiny amount of a substance is needed to produce the desired effect. Homeopathy aims to restore the balance between the life forces that have become altered in the patient's body by providing a minuscule amount of a substance that will elicit a chain of reactions within the body that will in turn cause it to heal.<sup>38</sup> A report drawn up by the Science and Technology Committee of the British House of Commons maintains that the effect of homeopathic remedies is similar to that of placebos.

#### Drugs in modern medicine

Active ingredients have made infrequent and erratic appearances throughout the history of medicine. Quinine first appeared as a fever treatment in 1632. At a later date, Sydenham used the drug to treat malaria. Digitalis as a treatment for dropsy was introduced by Withering in 1776; it would later be used to treat

hysteria and pneumonia as well. Edward Jenner observed in 1802 that milkmaids did not contract smallpox since the cowpox they caught instead offered protection. In 1899, Hoffman, a chemist working for Bayer, managed to develop a preparation containing mostly salicylic acid: aspirin.<sup>35</sup>

Ehrlich introduced Salvarsan in 1901 as treatment for syphilis. He developed it according to his 'magic bullet' concept, and it worked like a precursor of monoclonal antibodies and receptors themselves. In 1921, orthopaedic specialist Banting, with Best, a medical student, isolated insulin in a Toronto laboratory. Alexander Fleming, an English surgeon, discovered penicillin in 1929.<sup>35</sup>

In modern medicine, treatment always includes an active ingredient; the placebo effect itself occurs because some treatment has been given. The opposite would be the nocebo effect: patients who do not believe the treatment is beneficial will lose ground.

#### Placebos in modern medicine

Although descriptions of 19th century treatments show that doctors were aware of the placebo effect and used it intentionally, this practice was controversial. Charcot's school in Paris played a key role in establishing the foundations of modern neurology and the basis of hysteria.<sup>39</sup> The Madrid school of neurology (1885-1939), which was spearheaded by Cajal and Río-Hortega, managed to nurture both clinical practice and cutting-edge neuropathological research.<sup>40</sup> Luis Simarro, Gayarre, Achúcarro (the first doctor to detect a case of Alzheimer disease in the United States), and Rodríguez Lafora (who discovered progressive myoclonus epilepsy) were the top neurologists of this era,<sup>40,41</sup> and they laid the groundwork for a great Spanish school of neurology.

As Rosenberg indicated,<sup>42,43</sup> "Mid-19th-century doctors doubted that placebos had any effect". Meanwhile, Cabot wrote that he was "brought up, as I suppose every physician is, to use placebo, bread pills, water subcutaneously, and other devices for acting on a patient's symptom through his mind". Placebo use changed as the scientific method was developed and began to be applied to medicine. In 1916, Macht performed one of the first clinical trials in history when he compared the analgesic effects of morphine

to those of saline solution. In 1932, Paul Martini prescribed placebos as a means of controlling active ingredients,<sup>44,45</sup> and this was one of the first steps in the development of double-blind techniques. Martini believed that it was important to compare active treatment to a control, and this revelation would change the face of clinical pharmacology. Toward the middle years of the 20th century, the 'placebo effect' would become a controversial subject within the scientific community. In 1939, DuBois stated in a conference held in Cornell that placebos were used more often than any other class of drugs. He listed three types of placebos: firstly, simple inert substances, such as lactose; secondly, 'pseudo-drugs' such as herbal extracts; and thirdly, placebos in which a therapeutic agent is also present.<sup>46,47</sup> Without providing a concise definition of placebo as a concept, DuBois held that active ingredients could also exert a placebo effect.

Ten years later, Balint wrote in *The doctor, the patient and the illness* that "the most frequently-used drug in general practice was the doctor himself".<sup>48</sup> In the years that followed, the role of the placebo and of the placebo effect were to change. In the second half of the 20th century, placebos were seen from a different angle, and they came to be regarded as a methodological tool whose use was limited to clinical trials.<sup>49,50</sup> In 1955, Beecher described the placebo effect as 30% effective, and stated that it was to be found in all diseases, all patients, and all settings.<sup>47</sup> Several studies of the pharmacology of the placebo effect have been carried out to shed light on the characteristics and properties of this phenomenon.<sup>51-53</sup> These studies were performed to examine the constancy of the placebo effect, and not to question the existence of the effect itself.<sup>54</sup> Since that time, different authors have criticised Beecher's concept of the constancy of the placebo effect.<sup>54,55</sup> The main question is whether the total effect of any substance is equal to the sum of the effect of its active ingredient (specific effect) and its placebo effect.<sup>56</sup> Some authors hold that the placebo effect is secondary to other effects, including regression to the mean, the disease running its natural course, or even technical artefacts.<sup>57-59</sup> They have even stated that the placebo effect is just another of the myths that surround drugs.<sup>60</sup> Lastly, Moerman suggested replacing the term 'placebo effect' with his new term, 'placebo response'.<sup>61</sup> This idea is based on the hypothesis that the response obtained with treatment cannot be removed from the context of the patient or that of prior experience. The debate continues today.

Placebos are the gold standard treatment to which all other treatments are compared in clinical trials.<sup>6,62-64</sup> The purpose of placebo use is to distinguish between the pharmacological activity of the drug and other psychological or physical factors that may contribute to the observed outcome. Even today, placebos are a tool that doctors should be willing to consider, despite the presence of specific drugs; and furthermore, active drugs may too be used as placebos. Additionally, we find the 'doctor as medicine' phenomenon: the doctor should be aware that his or her mere presence exerts a placebo effect on the patient.<sup>46,62</sup>

### History of the placebo in clinical trials

The first placebo-controlled clinical trial was completed in 1931. The study focused on Sanocrysin, a drug to treat tuberculosis, and the placebo in this case was distilled water.<sup>65</sup> Questions about the ethical limitations on randomised clinical trials have less to do with the increased expectations of patients receiving placebos and more to do with the higher numbers of patients being included in those trials.<sup>66</sup> As stated by the Declaration of Helsinki (adopted by the World Medical Association in 1964) and the Belmont Report, patients should be included in clinical trials when no effective treatment is available, and trials should include as few subjects as possible.<sup>67,68</sup>

A meta-analysis examining 202 clinical trials in 60 different clinical situations found that, in general, clinical trials exhibited little influence by placebo-based interventions. In the presence of certain symptoms, such as pain and nausea, placebos affect the results reported by patients. Variations in the placebo effect can be explained in part by differences in how clinical trials are managed and in how the patients are informed.<sup>68</sup>

Analysis of natural therapy use (2011 Report by the Ministry of Health, Social Services, and Equality)

In Spain, 23.6% of the population has used alternative treatments at some point, mostly referring to yoga, acupuncture, and homeopathy. In the United States, 30% of the population uses alternative treatments. The 2011 report by the Ministry of Health documented the rise in these treatments and warns that no scientific studies support their effectiveness in most cases.<sup>69</sup> It reads,

Generally speaking, very few natural treatments have shown benefits in specific clinical situations in which the scientific method is applied. However, absence of evidence of efficacy cannot be considered evidence of absence of efficacy....in many cases, no studies are available that would allow us to determine if relief results from the specific effect of the treatment, or if it is caused by a placebo effect.<sup>70</sup>

It is believed that more than 90% of all alternative medicines are based on the placebo effect. More guidelines covering both alternative treatments and evidence-based medicine, like those recently published by the American Academy of Neurology for multiple sclerosis, are needed to clarify the questions that remain.<sup>71</sup>

## Conclusion

The history of medicine equates to the history of the placebo effect in treatment. In contrast with magic and religion-based medicine as practised by primitive societies, modern pharmaceutical treatments always include an active ingredient. The main question is whether the total effect of any substance is equal to the sum of the effect of its active ingredient (specific effect) and its placebo effect. Prescribing innocuous treatments to patients came to be a widespread practice beginning in the 18th century. Placebos are the gold standard treatment to which all other treatments are compared in clinical trials. They are used to distinguish between the pharmacological activity of the drug and other psychological or physical factors that may contribute to the observed outcome.

Some 23.6% of the Spanish population has used alternative treatments at some point, and more than 90% of all alternative medicines are thought to be based on the placebo effect. Guidelines are needed for both alternative medicine and evidence-based medicine so as to measure the impact of the placebo effect in either case.

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